National Institute for Health and Care Excellence

Draft for consultation

Stroke rehabilitation in adults (update)

[P] Evidence reviews for interventions for spasticity

NICE guideline GID-NG10175

Evidence reviews underpinning recommendations 1.15.1 to 1.15.8 and research recommendations in the NICE guideline

April 2023

Draft for Consultation

These evidence reviews were developed by the Guideline Development Team at NICE

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1 Management of spasticity after stroke

1.1 Review question

In people after stroke, what is the clinical and cost effectiveness of interventions (for example: oral baclofen, intrathecal baclofen, acupuncture and TENS [transcutaneous electrical nerve stimulation]), in reducing spasticity?

1.1.1 Introduction

Spasticity commonly develops in individuals after a stroke and can be very painful and debilitating. In severe cases, spasticity can impact seating, the ability to stand and transfer, maintenance of skin hygiene, and can lead to muscle shortening causing joints to become fixed requiring surgery to correct. Spasticity management has not been covered in previous NICE stroke guidelines, but the variability of current practice and access to specialist assessment and intervention among stroke and community teams makes this a timely and important addition to the guidance. In addition, there has been considerable research recently investigating less conventional interventions such as electroacupuncture and neuromuscular modulation. Alongside the more established albeit varied practice of oral and intramuscular pharmacological intervention, the area of spasticity management post-stroke warrants an up to date clinical guideline based upon the current evidence.

1.1.2 Summary of the protocol

Table 1: PICO characteristics of review question

Population	Inclusion:
	• Adults (age ≥16 years) who have had a stroke who have spasticity
	  ○ Stratification by site of spasticity:
	  – Focal spasticity (affecting one specific part of the body – for example: left arm)
	  – Multifocal spasticity (affecting multiple, but specific parts of the body – for example: left arm and right leg)
	  – Segmental spasticity (affecting a segment [for example: just the lower half of the body])
	  – Generalised spasticity (affecting multiple, widespread muscle groups)
	  – Mixed spasticity (both focal and generalised spasticity)
	
	Exclusion:
	• Children (age <16 years)
	• People with other conditions that cause spasticity
	• People who had a transient ischaemic attack

Interventions	• Oral medicine
	  ○ Baclofen (dose: 5mg is lowest dose, maximum dose: 100mg per day)
	  ○ Tinzanidine (dose: 2mg-36mg, maximum dose per day: 36mg per day)
	  ○ Dantrolene (dose: 25mg-225mg, maximum dose per day: 100mg four times a day)
	  ○ Gabapentin (as an adjunct treatment, dose: 900mg-3.6 grams)
	  ○ Pregabalin (as an adjunct treatment, dose: 50-300mg per day)
	  ○ Clonidine
	  ○ Benzodiazepines

	– Diazepam (dose: 2mg-60mg, maximum dose per day: 60mg) – Clonazepam (dose: 0.5mg-8mg) • Intramuscular medicine o Botulinum toxin type A – Onabotulinum toxin A (BOTOX®) (maximum recommended dose is 200-240 units in the arm, 300 units in the leg for a single injection) – Abobotulinum toxin A (Dysport®) (maximum recommended dose is 1500 units in the arm or leg in a single adult injection session)) – Incobotulinum toxin A (Xeomin®) (maximum recommended dose is 500 units in the arm and no more than 250 units in the shoulder muscles in a single adult injection session) • Intrathecal medicine o Baclofen (dose range = 22 micrograms/day-1.4mg/day) • Functional Electrical Stimulation • Neuromuscular electrical stimulation (NMES)Transcutaneous electrical nerve stimulation (TENS) • Acupuncture/dry needling • Electroacupuncture • Combinations of the above
Comparisons	• Each other • Placebo/sham • Usual care or no treatment Confounding factors (for non-randomised studies only): • Presence of comorbidities • Severity of spasticity • Age
Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical: At time periods: • ≤6 months • >6 months If multiple outcomes are reported before or after these time period then the latest time period that is ≤6 months or >6 months will be extracted and used in the analysis. • Person/participant generic health-related quality of life (continuous outcomes will be prioritised) • Carer generic health-related quality of life (continuous outcomes will be prioritised) • Spasticity outcome measures (continuous outcomes prioritised) • Physical function (continuous outcomes will be prioritised) o General o Physical function – upper limb o Physical function – lower limb • Pain (continuous outcomes will be prioritised) • Activities of daily living (continuous outcomes will be prioritised) • Stroke-specific Patient-Reported Outcome Measures (continuous outcomes will be prioritised)

	• Additional health care contacts (dichotomous outcome) • Hospitalisation (dichotomous outcome) • Stroke outcome – modified Rankin scale (continuous outcomes will be prioritised) • Withdrawal due to adverse events (dichotomous outcome)

Study design	• Systematic reviews of RCTs
	• Parallel RCTs
	• Non-randomised studies (if insufficient RCT evidence is available)
	  ○ Prospective cohort studies
	  ○ Retrospective cohort studies

For full details see the review protocol in Appendix A.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

Eighty nine randomised controlled trial studies (91 papers) were included in the review;[1-3, 5, 6, 8, 9, 11-15, 17, 19, 21, 22, 28, 30, 34, 35, 37, 38, 44-47, 53-56, 59-62, 64-68, 70, 73-82, 84, 85, 90, 91, 97-100, 102, 103, 105, 106, 110, 114, 116-120, 123-127, 131-135, 137, 138, 140-149] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summaries (section 1.1.6 Summary of the effectiveness evidence) and summary matrices (section 1.1.5.13 Summary matrices).

The majority of the evidence from randomised controlled trials was in people with focal spasticity, however this was not always clearly highlighted by the studies and some interpretation was required. There was a smaller amount of evidence available for people with generalised spasticity. No evidence was identified for multifocal spasticity, segmental spasticity or mixed spasticity.

The evidence from the randomised controlled trial studies investigated the follow stratifications and comparisons:

Focal Spasticity

- Oral baclofen compared to:
  - Incobotulinum Toxin A (Xeomin) – 1 study[127]
- Tizanidine compared to:
  - Onabotulinum toxin A (BOTOX) – 1 study[118]
  - Abobotulinum toxin A (Dysport) – 1 study[143]
  - Placebo/sham – 1 study[118]
- Onabotulinum toxin A (BOTOX) compared to:
  - Tizanidine – 1 study[118]
  - Combination therapy: Onabotulinum toxin A (BOTOX) and functional electrical stimulation (FES) – 1 study[21]
  - Placebo/sham – 20 studies[8, 11, 12, 30, 45, 55, 56, 60, 70, 74, 98, 117, 118, 123, 124, 131, 134, 137, 138]
  - Usual care or no treatment – 1 study[22, 62]
- Abobotulinum toxin A (Dysport) compared to:
  - Tizanidine – 1 study[143]
  - Neuromuscular electrical stimulation (NMES) – 1 study[45]
  - Combination therapy: Abobotulinum toxin A (Dysport) and neuromuscular electrical stimulation (NMES) – 1 study[45]
  - Placebo/sham – 7 studies[2, 37, 78, 99, 100, 102, 103]
  - Usual care or no treatment – 1 study[114]
- Incobotulinum Toxin A (Xeomin) compared to:
  - Oral baclofen – 1 study[127]
  - Placebo/sham – 4 studies[28, 59, 76, 77]
  - Usual care or no treatment – 1 study[44]
- Functional electrical stimulation (FES) compared to:
  - Placebo/sham – 2 studies[61, 141]
  - Usual care or no treatment – 7 studies[5, 17, 64, 85, 105, 141, 144]
- Neuromuscular electrical stimulation (NMES) compared to:
  - Abobotulinum toxin A (Dysport) – 1 study[45]
  - Transcutaneous electrical nerve stimulation (TENS) – 1 study[149]

  - Combination therapy: Abobotulinum toxin A (Dysport) and neuromuscular electrical stimulation – 1 study[45]
  - Placebo/sham – 3 studies[6, 19, 65]
  - Usual care or no treatment – 14 studies[3, 46, 47, 68, 73, 80, 84, 106, 110, 116, 133, 142, 145, 149]
- Transcutaneous electrical nerve stimulation (TENS) compared to:
  - Neuromuscular electrical stimulation (NMES) – 1 study[149]
  - Combination therapy: Abdobotulinum toxin A (Dysport) and transcutaneous electrical nerve stimulation (TENS) – 1 study[75]
  - Placebo/sham – 8 studies[53, 54, 81, 90, 91, 97, 126, 140]
  - Usual care or no treatment – 7 studies[38, 90, 91, 119, 120, 140, 149]
- Acupuncture compared to:
  - Placebo/sham – 4 studies[9, 34, 125, 147]
  - Usual care or no treatment – 4 studies[132, 146-148]
- Combination therapy: Abobotulinum toxin A (Dysport) and transcutaneous electrical nerve stimulation (TENS) compared to:
  - Transcutaneous electrical nerve stimulation (TENS) (and placebo injection) – 1 study[75]
- Combination therapy: Abobotulinum toxin A (Dysport) and neuromuscular electrical stimulation (NMES) compared to:
  - Abobotulinum toxin A (Dysport) only – 1 study[45]
  - Neuromuscular electrical stimulation (NMES) only – 1 study[45]
- Combination therapy: Onabotulinum toxin A (BOTOX) and functional electrical stimulation (FES) compared to:
  - Onabotulinum toxin A (BOTOX) only – 1 study[21]

Generalised Spasticity

- Oral baclofen compared to:
  - Tizanidine – 1 study[79]
- Tizanidine compared to:
  - Oral baclofen – 1 study[79]
- Intrathecal baclofen compared to:
  - Usual care or no treatment – 1 study (3 papers)[13-15]
- Acupuncture compared to:
  - Electroacupuncture – 1 study[82]
  - Placebo/sham – 3 studies[66, 67, 135]
  - Usual care or no treatment – 1 study[1]
- Electroacupuncture compared to:
  - Acupuncture – 1 study[82]
- Usual care or no treatment – 1 studies[35]

No relevant clinical studies were identified for the following oral interventions:

- Dantrolene
- Gabapentin
- Pregabalin
- Clonidine
- Benzodiazepines (including diazepam and clonazepam)

The studies represented a mixture of different time periods after stroke, including people in the acute/subacute and chronic phase, however the majority of studies included people who were in the chronic phase. The severity of the spasticity at baseline was not always reported but the studies included a mix of mild, moderate and severe spasticity on the Modified Ashworth Scale with different interventions typically including different populations. In the majority of studies, stroke severity and the type of stroke (using the Bamford scale) were not reported.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix C and GRADE tables in Appendix J

Indirectness

Some studies included indirect evidence. This led to several outcomes being downgraded for indirectness in the GRADE analysis. Indirect evidence included:

- Population indirectness - Three studies were downgraded for population indirectness as they included people with traumatic brain injury or Multiple Sclerosis and not a stroke only population.
- Intervention indirectness – one study was downgraded as they did not report a conventional control group so for the purpose of this review the mirror therapy group was used as a control group. Another study used a Chinese version of Onabotulinum Toxin A so this was downgraded for intervention indirectness.

Inconsistency

A number of outcomes showed significant heterogeneity. This was not resolved by subgroup analysis and so random effects models were used and the outcomes were downgraded for inconsistency.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

1.5.1.1 Oral Baclofen

Table 2: Summary of studies including oral baclofen as an intervention in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Medici 1989[79]	**Tizanidine** (n=15) 2 capsules tizanidine (8mg) per day, increased by 1 capsule every 3 days to a maximum of 5 capsules per day (20mg tizanidine) administered in three daily doses. Total duration of therapy: 52 weeks.	**People after a first or recurrent stroke** Mean age (range): 50 (22-73) years N = 30 Type of Spasticity: Generalised	Withdrawal due to adverse events at ≤6 months	Setting: Setting unclear. Conducted in Uruguay. Sources of funding: No additional information

	Baclofen (n=15) 2 capsules baclofen (20mg) per day, which increased by 1 capsule every 3 days to a maximum of 5 capsules per day (50mg baclofen) administered in three daily doses. For both treatments: The optimal dose achieved at the end of the titration phase was then continued during a 30-week maintenance phase. **Concomitant therapy:** Concomitant medication, other than drugs exhibiting muscle relaxing properties, were allowed and registered.	Severity of spasticity: Moderate/severe Time period since stroke mean (range) intervention and control: 2.47 (0.1 to 10), 4.5 (0.5 to 14) years		
Turcu-Stiolica 2021[127]	**Incobotulinum toxin A (Xeomin)** (n=17) Incobotulinum toxin 200 units. The injection was performed only on the upper spastic limb. Follow up at 6 months. **Baclofen** (n = 17) Baclofen (started from 10 mg up to 60 mg daily). **Concomitant therapy:** All people participated in a physiotherapy program.	**People after a first or recurrent stroke** Mean age (SD): 60.22 (11.10) years N = 34 Type of Spasticity: Focal Severity of spasticity: Mixed Time period since stroke range: Not stated/unclear	Person/participant generic health-related quality of life at ≤6 months Spasticity outcome measures at ≤6 months Physical function - upper limb at ≤6 months Activities of daily living at ≤6 months	Setting: Neurology Hospital of Craiova in Romania Sources of funding: This research received no external funding

1

1.5.1.2 Tizanidine

Table 3: Summary of studies including tizanidine as an intervention in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Medici 1989[79]	**Tizanidine** (n=15) 2 capsules tizanidine (8mg) per day, increased by 1 capsule every 3 days to a maximum of 5 capsules per day (20mg tizanidine) administered in three daily doses. Total duration of therapy: 52 weeks. **Baclofen** (n=15) 2 capsules baclofen (20mg) per day, which increased by 1 capsule every 3 days to a maximum of 5 capsules per day (50mg baclofen) administered in three daily doses. For both treatments: The optimal dose achieved at the end of the titration phase was then continued during a 30-week maintenance phase. **Concomitant therapy:** Concomitant medication, other than drugs exhibiting muscle relaxing properties, were allowed and registered.	**People after a first or recurrent stroke** Mean age (range): 50 (22-73) years N = 30 Type of Spasticity: Generalised Severity of spasticity: moderate/severe Time period since stroke mean (range) intervention and control: 2.47 (0.1 to 10), 4.5 (0.5 to 14) years	Withdrawal due to adverse events at ≤6 months	Setting: Setting unclear. Conducted in Uruguay. Sources of funding: No additional information
Simpson 2009[118]	**Onabotulinum toxin A (BOTOX)** (n=20) Onabotulinum toxin A 50 Units (1.0 cm3)/muscle into each of the wrist	**People after a first or recurrent stroke** Mean age (SD): 55.9 (13.5) years N = 60	Spasticity outcome measures at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Multi-centre trial in the United States of America Sources of funding: Mount Sinai School of Medicine is the

	flexors. In addition, oral placebo. Follow up at week 22 **Tinzanidine** (n=21) Tinzanidine (initiated at 2 mg/day to a maximum of 36 mg/day) and intramuscular placebo group (saline injection). **Placebo/sham** (n=19) Intramuscular and oral placebo. **Concomitant therapy:** Not reported	Type of Spasticity: Focal spasticity Severity of spasticity: Severe (or MAS 3) Time period since stroke: Mixed		sponsor of the study. The study was funded by an unrestricted grant by Allergan, Inc.
Yazdchi 2013[143]	**Abobotulinum Toxin A (Dysport)** (n=34) Injections into dominant spastic muscles of the upper extremities using 500 units of Dysport (maximum dosage 1000 units). Follow up at 24 weeks **Tizanidine** (n=34) Initiated dosage of 2mg and gradual increase of 2 mg weekly to reach 24 mg at week 12 and continued the same dosage until week 24 to the end of the study. **Concomitant therapy:** 45-60 min physiotherapy program three times a week.	**People after a first or recurrent stroke** Mean age (range): Intervention: 67.5 (35-70) years Control: 64.7 (51-68) years N= 68 Type of Spasticity: Focal Severity of spasticity: Severe (or MAS 3) Time period since stroke range: Not stated/unclear	Spasticity outcome measures at ≤6 months Physical function – upper limb at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Imam Reza University Hospital and Neurology Clinic Iran Sources of funding: Not reported

1.5.1.3 Onabotulinum toxin A (BOTOX)

Table 3: Summary of studies including onabotulinum toxin A (BOTOX) as an intervention in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Brashear 2002[7]	**Onabotulinum toxin A (BOTOX)** (n=64) 200-240 units delivered in one session. 50 units injected in each of four wrist and finger muscles (50 units per muscle) with optional injections in one or two thumb muscles (20 units per muscle). Follow up at 12 weeks. **Placebo/sham** (n=62) Botulinum toxin A vehicle only delivered identically to the botulinum toxin type A group. **Concomitant therapy:** No additional information	**People after a first or recurrent stroke** Age range: 23-88 years N = 126 Type of Spasticity: Focal upper limb Severity of spasticity: Severe Mean time period since stroke: 4.7 years	Spasticity outcome measures at ≤6 months Activities of daily living at ≤6 months	Setting: Outpatient follow up in the United States of America Sources of funding: Supported by Allergan.
Childers 2004[11]	**Onabotulinum toxin A (BOTOX)** (n=44) 100 units of onabotulinum toxin A with 0.5mg of human serum albumin and 0.9mg of sodium chloride in each vial. Injection volume was the same between all injections (4mL) by adding saline. Subjects were eligible for a second treatment cycle 12 weeks or more after the first. Follow up at 24 weeks **Placebo/sham** (n=26) Placebo injections that contained 0.5mg of serum albumin and 0.9mg of sodium chloride.	**People after a first or recurrent stroke** Age range: 30.4-79.4 years N = 70 Type of Spasticity: Focal upper limb Severity of spasticity: Not reported Time period since stroke (range): 0.9-226.9 months	Withdrawal due to adverse events at ≤6 months	Setting: 19 outpatient clinics across the United States Sources of funding: 'A commercial party with a direct financial interest in the results of the research supporting this article has conferred or will confer a financial benefit on the author or 1 or more of the authors'

	Concomitant therapy: Investigators could implement concurrent therapies after the first week after injection (with the exception of stabilisation devices such as splits, casts and orthotic devices). Use of antispasticity was not restricted and investigators were permitted to add, change the dose or stop the antispasticity medication at their discretion.			
Cousins 2010[12]	**Onabotulinum toxin A (BOTOX)** (n=19) Half (9 people) or a quarter (10 people) of the usual dose of botulinum toxin type A. The standard doses considered for this study were 50-100 units dependent on muscle site. **Placebo/sham** (n=11) Saline injections corresponding to the amount provided in the botulinum toxin groups. **Concomitant therapy:** No additional information	**People after a first or recurrent stroke** Mean age (SD): 69 (11.8) years N = 30 Type of Spasticity: focal upper limb Severity of spasticity: Not reported Mean time period since stroke (SD): 23 (9) days	Physical function - upper limb at ≤6 months Withdrawal due to adverse events at ≤6 months 20 weeks	Setting: Stroke unit of the University Hospital of North Staffordshire, a large teaching hospital in the United Kingdom. Sources of funding: The study received support from the North Staffordshire Medical Institute and an unrestricted educational grant from Allergan Ltd.
Ding 2015[22]	**Onabotulinum toxin A (BOTOX)** (n=35) 100 units/ampule, diluted with 4mL 0.9% saline into 25u/ml) drawn into 1mL syringes. Needle administered to	**People after a first or recurrent stroke** Mean age (SD): 63.5 (12.0) years N = 68 Type of Spasticity: Focal lower limb	Spasticity outcome measures at ≤6 months Physical function – lower limb at ≤6 months Activities of daily living at ≤6 months	Setting: No additional information. Conducted in China. Sources of funding: No additional information

	muscle where spasms were most obvious. Follow up at 6 months. **Usual care or no treatment** (n=33) A third study arm (n=35) received the same care as treatment group, with additional ankle brace was excluded due to incomparability with control group (no ankle brace given in control). **Concomitant therapy:** Conventional therapy and rehabilitation training including Bobath concept, range of motion training, walking, massage, physiotherapy and occupational therapy, activities of daily living training.	Severity of spasticity: Not reported Time period since stroke: Not reported		
Ding 2017[21]	**Combination therapy: Functional Electrical Stimulation (FES) and Onabotulinum Toxic A (BOTOX)** (n=41) Each target muscle was injected at 3-5 points, with a total dose of 350 units. FES for one treatment course was 10 days, with a total of three treatment courses. Follow up at 12 weeks. **Onabotulinum toxin A (BOTOX) alone** (n=39)	**People after a first or recurrent stroke** Mean age (SD): 61.9 (6.7) years N = 80 Type of Spasticity: Focal Mean severity of spasticity (SD) – Modified Ashworth Scale: 4.1 (0.6) Mean time period since stroke (SD): 126.6 (29.5) days	Spasticity outcome measures at ≤6 months Physical function – upper limb at ≤6 months Activities of daily living at ≤6 months	Setting: Xiangyang No. 1 People's Hospital, China. Sources of funding: No additional information.

	Botulinum toxin A injection alone (administered with same protocol as intervention group) **Concomitant therapy:** No additional information			
Esquenazi 2019[30]	**Onabotulinum toxin A (BOTOX)** (n=233) 400 units of onabotulinum toxin A or less at approximately 12 week intervals (the initial 12 week period was double blind, while time after that was a part of an open label trial. Only the evidence for the double blind period was included in this analysis). Follow up at 12 weeks. **Placebo/sham** (n=235) A matching placebo (0.9% sodium chloride solution only) was injected instead of onabotulinum toxin A. **Concomitant therapy:** People receiving muscle relaxants or oral medication for spasticity were on a stable dose for 2 months or more before study day 1. Those receiving antiepileptic medications were on a stable dose for 1 month or more before study day 1. People on a stable program of physical therapy including the use of static or dynamic splints 14	**People after a first or recurrent stroke** Mean age (SD): Not stated/unclear N = 468 Type of Spasticity: Focal lower limb Severity of spasticity: Severe (or MAS 3) Mean time period since stroke (SD): 64.3 (74.2) months	Spasticity outcome measure at ≤6 months Pain at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Multicenter trial, outpatient follow up. Conducted at 60 sites in North America, Europe and Asia. Sources of funding: Authors were funded by a pharmaceutical company (Allergan).

	days or more before study treatment could be enrolled if the program was not expected to change.			
Kaji 2010[56]	**Onabotulinum toxin A (BOTOX)** (n=72) Combination of higher dose (n=51) and lower dose (n=21) botulinum toxin type A. People were given either a single injection of 200 units (in 4mL solution, higher-dose) or 120units (in 2.4mL solution, lower-dose) that were injected into each of flexor carpi radialis, flexor carpi ulnaris, flexor digitorum profundus and flexor digitorum superficialis to improve wrist and finger flexion. For people with thumb spasticity, an additional 40 units (in 0.8mL, higher-dose) or 30 units (in 0.6mL, lower-dose) was injected into each of the flexor pollicis longus and adductor pollicis to improve thumb flexion. Follow up at 12 weeks. **Placebo/sham** (n=37) Placebo injections corresponding to the relevant doses of the botulinum toxin injections (higher dose n=26, lower dose n=11). Injection was with 0.9% normal saline	**People after a first or recurrent stroke** Mean age (SD): 63.3 (9.8) years N = 109 Type of Spasticity: Focal Severity of spasticity: Severe (or MAS 3) Mean time period since stroke (SD): Not stated/unclear.	Spasticity outcome measures at ≤6 months Activities of daily living at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: 19 Japanese medical institutions. Sources of funding: This study was sponsored by GlaxoSmithKline.

	using the same methods. **Concomitant therapy:** No additional information.			
Kaji 2010[55]	**Onabotulinum toxin A (BOTOX)** (n=58) A single injection of 300 units of botulinum toxin type A injected as 75 units into the following locations: medial head of gastrocnemius, lateral head of gastrocnemius and soleus muscle and tibialis posterior muscle (divided into three sites per muscle). Follow up at 12 weeks. **Placebo/sham** (n=62) Physiological saline of the same amount into the same locations. **Concomitant therapy:** No additional information.	**People after a first or recurrent stroke** Mean age (SD): 62.5 (9.0) years N = 120 Type of Spasticity: Focal Severity of spasticity: Severe – MAS 3.28 (0.45) Mean time period since stroke (SD): 76.3 (66.8) months	Spasticity outcome measures Withdrawal due to adverse events	Setting: People from 19 Japanese medical institutions. Sources of funding: This study was sponsored by GlaxoSmithKline K.K.
Kerzoncuf 2020[60]	**Onabotulinum toxin A (BOTOX)** (n=23) Maximum dose 300 units injected by intramuscular injection into the lower limb muscles. Follow up at 6 weeks. **Placebo/sham** (n=26) Placebo injection (physiologic serum). Otherwise, the same procedure. **Concomitant therapy:** The use	**People after a first or recurrent stroke** Mean age: 52.0 (13.9) years N = 49 Type of Spasticity: Focal Mean severity of spasticity (SD): Modified Ashworth scale 2.48 (1.31) Mean time period since stroke: 61.2 (53.7) months	Spasticity outcome measures at ≤6 months	Setting: Multicenter trial. Outpatient follow up in France. Sources of funding: Supported by the Protocole Hospitalier de Recherche Clinique (PHRC 2005/21).

	of any rehabilitation procedures, antispastic drugs, and orthoses were continued unchanged during botulinum toxin type A treatment.			
Lannin 2018[62]	**Onabotulinum toxin A (BOTOX)** (n=12) If indicated, participants received injections into both upper and lower limb muscles during the same injection session; a maximum dose of 500 units was given in one session. Follow up at 12 weeks. **Usual care or no treatment** (n=14) **Concomitant therapy:** Participants then undertook an intensive 8-week rehabilitation program delivered by physiotherapists and occupational therapists.	**People after a first or recurrent stroke** Mean age (SD): Not reported N = 23 Type of Spasticity: 70% upper limb focal spasticity but some with multifocal spasticity Severity of spasticity: Not reported Mean time period since stroke (SD): 37 (43) months	Spasticity outcome measures at ≤6 months Physical Function - Lower Limb at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Rehabilitation centre in Australia. Sources of funding: No additional information.
Lindsay 2021[70]	**Onabotulinum Toxin A (BOTOX)** (n=49) Intramuscular injections of Onabotulinum toxin-A were administered to all six muscles of the affected arm in predetermined doses. Follow up at 6 months. **Placebo/sham** (n=48) 0.9% sodium chloride solution placebo. **Concomitant therapy:** No	**People after a first or recurrent stroke** Mean age (SD): 67.5 (16.0) years N = 97 Type of Spasticity: Focal Severity of spasticity: Not reported Mean time period since stroke: 17.9 (9.3) days	Physical Function - upper limb at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Stroke unit in a tertiary care hospital in the United Kingdom. Sources of funding: This paper summarises independent research funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit Programme (PB-PG-0808-16319). Allergan provided the drug used and an unrestricted educational grant to support this study.

	additional information.			
Marciniak 2012[74]	**Onabotulinum Toxin A (BOTOX)** (n=10) Onabotulinum toxin A total of 100-150 units injected into the pectoralis major muscle and a total of 40-60 units were injected into the teres major muscle if the shoulder extensors exhibited spasticity of an Ashworth grade of 3 or 4. Follow up at 16 weeks. **Placebo/sham** (n=11) 2ml saline with no additional treatment. **Concomitant therapy:** No additional information	**People after a first or recurrent stroke** Mean age (SD): 60.0 (9.2) years N = 21 Type of Spasticity: Focal Severity of spasticity: Severe (or MAS 3) Time period since stroke: Chronic ≥6 months	Withdrawal due to adverse events at ≤6 months	Setting: Rehabilitation centre in the United States of America. Sources of funding: Funded by an unrestricted educational grant from Allergan Inc, for whom the main author has been a consultant.
Marco 2007[75]	**Onabotulinum Toxin A (BOTOX)** (n=14) Intramuscular injection, at 4 sites, of 500 units of onabotulinum toxin A in the pectoralis major muscle of the paretic side. Follow up at 6 months. **Placebo/sham** (n=15) Placebo in place of onabotulinum toxin A injection **Concomitant therapy:** All the patients were treated with conventional TENS, consisting of short pulses (250 μsec) of high frequency (75 megahertz) and low intensity for a 6-	**People after a first or recurrent stroke** Mean age (SD): 65.6 (9.2) years N = 31 Type of Spasticity: Focal Severity of spasticity: Severe (or MAS 3) Mean time period since stroke (range): Intervention: 174 (89-263) days Control: 133 (112 to 210) days	Spasticity outcome measures at ≤6 months Pain at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Rehabilitation unit in an acute-care general hospital in Spain. Sources of funding: Institut Municipal d'Investigacio Mèdica provided a grant.

	week period. All participants underwent training in daily living activities and different aspects of mobility.			
Patel 2020[98]	**Onabotulinum toxin A (BOTOX)** (n=233) 300 units into three sites each of the gastrocnemius (medial and lateral heads), soleus, and tibialis posterior muscles (i.e., mandatory ankle muscles. An optional dose of up to 100 units onabotulinum toxin A was injected into the flexor digitorum longus, flexor digitorum brevis, flexor hallucis longus, extensor hallucis, or rectus femoris if clinically indicated. Follow up at 12 weeks. **Placebo/sham** (n=235) Placebo (0.9 mg sodium chloride) **Concomitant therapy:** During the double-blind phase, the initiation of any medications for spasticity, muscle relaxants, or antiepileptic medications was prohibited. The initiation of physical therapy or the use of static or dynamic splints within 14 days of the first study visit was also prohibited.	**People after a first or recurrent stroke** Mean age (SD): 56.47 (12.23) years N = 468 Type of Spasticity: Focal lower limb Severity of spasticity: Severe (or MAS 3) Mean time period since stroke (SD): 5.34 (6.20) years	Withdrawal due to adverse events at ≤6 months	Setting: Conducted at 60 sites throughout Canada, the United States, Czech Republic, Germany, Hungary, Poland, Russia, the United Kingdom and South Korea. Sources of funding: This study was sponsored by Allergan plc (Dublin, Ireland). Writing and editorial assistance was provided to the authors by Dana Franznick, PharmD, of Complete Healthcare Communications, LLC, and was funded by Allergan plc; and by Karen Pemberton, PhD, of Evidence Scientifc Solutions, Inc, Philadelphia, PA, and funded by Allergan plc. All authors met the ICMJE authorship criteria. Neither honoraria nor payments were made for authorship.
Simpson 2009[118]	**Onabotulinum toxin A (BOTOX)** (n=20) Onabotulinum toxin A 50 units (1.0	**People after a first or recurrent stroke**	Spasticity outcome measures at ≤6 months	Setting: Multi-centre trial in the United States of America.

	cm^3)/muscle into each of the wrist flexors. In addition, oral placebo. Follow up at week 22 **Tinzanidine** (n=21) Tinzanidine (initiated at 2 mg/day to a maximum of 36 mg/day) and intramuscular placebo group (saline injection). **Placebo/sham** (n=19) Intramuscular and oral placebo. **Concomitant therapy:** Not reported	Mean age (SD): Intervention: 55.8 (13.6) years N = 60 Type of Spasticity: Focal spasticity Severity of spasticity: Severe (or MAS 3) Time period since stroke: Mixed	Withdrawal due to adverse events at ≤6 months	Sources of funding: Mount Sinai School of Medicine is the sponsor of the study. The study was funded by an unrestricted grant by Allergan, Inc.
Tan 2021[123]	**Onabotulinum toxin A (BOTOX)** (n=18) Onabotulinum toxin A (2mL 100 units/mL) was injected at 2 points, under direct ultrasound guidance, with each injection point receiving 50 units and the maximum total dose per patient was 100 units. Follow up at 4 weeks. **Placebo/sham** (n=18) The control group received 2.0mL saline injection at 2 points and a 1mL injection of saline at each point. **Concomitant therapy:** All patients received a standard course of exercise therapy (stretching, increasing active motion) and	**People after a first or recurrent stroke** Mean age (SD): 52.5 (12.3) years N = 36 Type of Spasticity: Focal Severity of spasticity: Severe (or MAS 3) Time period since stroke range: Subacute (7 days - 6 months)	Spasticity outcome measures at ≤6 months Physical function - upper limb at ≤6 months Pain at ≤6 months Stroke specific patient reported outcome measures at ≤6 months Discontinuation - due to adverse events at ≤6 months	Setting: Outpatients department of rehabilitation medicine in China. Sources of funding: Academic/goverment funding support.

	physiotherapy (hot pack and interferential current therapy).			
Tao 2015[124]	**Onabotulinum Toxin A (BOTOX)** (n=11) 200 units onabotulinum toxin A injected into the gastrocnemius (medial and lateral head of the gastrocnemius, 100 units), the soleus (50 units), and the posterior tibial muscle (50 units). Follow up at 8 weeks. **Placebo/sham** (n=12) The same volume of placebo solution was injected into the same muscles. **Concomitant therapy:** Both groups received comprehensive rehabilitation. This included physiotherapy (45 minutes every workday) and occupational therapy (30 minutes every workday).	**People after a first or recurrent stroke** Mean age (SD): 56.5 (13.2) years N = 23 Type of Spasticity: Focal spasticity Severity of spasticity: Mixed Time period since stroke range: Subacute (7 days - 6 months)	Physical Function - lower limb at ≤6 months Activities of daily living at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Stroke/neurology units or rehabilitation department of Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University in China. Sources of funding: Not reported.
Wallace 2020[131]	**Onabotulinum toxin A (BOTOX)** (n=14) 100 units in 2 mL of saline, injected into muscles identified by the multidisciplinary assessment. Follow up at 5 weeks. **Placebo/sham** (n=14) Saline. **Concomitant therapy:** Physiotherapy - 4 weeks, with each	**People after a first or recurrent stroke** Mean age (SD): 49 (16.2) years N = 28 Type of Spasticity: Focal Severity of spasticity: Not reported Time period since stroke range: Chronic (≥6 months)	Person/participant generic health-related quality of life at ≤6 months Physical function - upper limb at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Focal spasticity clinics at the National Hospital for Neurology and Neurosurgery in the United Kingdom. Sources of funding: Supported by UK Stroke Association (TSA 2008/01).

	session time ranging from 45 minutes up to 1.5 hours.			
Ward 2014[134]	**Onabotulinum toxin A (BOTOX)** (n=139) A single injection of onabotulinum toxin A with a second dose at a minimum of 12 weeks, if the treating physician thought they would benefit from a second treatment. Maximum dose 800 units. Follow up at 24 and 52 weeks. **Placebo/sham** (n=135) During the double-blind period, patients received a single injection of placebo, with a second dose at a minimum of 12 weeks, if the treating physician thought they would benefit from a second treatment. **Concomitant therapy**: All study participants received standard care.	**People after a first or recurrent stroke** Mean age (range): 63.0 (22.6 to 82.4) years N = 274 Type of Spasticity: Focal Severity of spasticity: Moderate (or MAS 2) Time period since stroke range: Chronic (≥6 months)	Spasticity outcome measures at ≤6 months and at >6 months Withdrawal due to adverse events at ≤6 months and at >6 months	Setting: rehabilitation centres in Germany, Sweden, the United Kingdom, and Canada. Sources of funding: Allergan.
Wein 2018[136]	**Onabotulinum toxin A (BOTOX)** (n=233) The dose for each muscle was evenly distributed across the number of specified injection sites for that muscle, including 3 sites for each of the mandatory ankle muscles. An optional total additional dose ≤100 units was injected into additional muscles (ie, flexor digitorum longus, brevis,	**People after a first or recurrent stroke** Mean age (SD): 56.5 (12.3) years N = 468 Type of Spasticity: Multifocal spasticity Severity of spasticity: Severe (or MAS 3) Time period since stroke: Chronic (≥6 months)	Spasticity outcome measures at ≤6 months Adverse events at ≤6 months	Setting: Sixty study centres in North America, Europe, Russia, the United Kingdom, and South Korea. Sources of funding: Funding source: Allergan plc (Dublin, Ireland).

	flexor hallucis longus, rectus femoris), if clinically indicated. Follow up at 6 weeks. **Placebo/sham** (n=235) **I**dentical process as with the onabotulinum toxin A but patients instead received the placebo injection. **Concomitant therapy:** not reported			
Wolf 2012[138]	**Onabotulinum toxin A (BOTOX)** (n=12) Up to 300 units injected into the wrist and finger muscles. Follow up at 15 weeks. **Placebo/sham** (n=13) Up to 300 units of saline injected into the wrist and finger muscles. **Concomitant therapy:** Exercise programme. Three sessions were scheduled per week beginning approximately 1 month after injections and continued until 12 to 16 treatment sessions were completed.	**People after a first or recurrent stroke** Mean age (SD): 49.3 (14.7) years N = 25 Type of Spasticity: Focal Severity of spasticity: Not stated/unclear Time period since stroke range: Mixed	Discontinuation at ≤6 months	Setting: Department of Rehabilitation Medicine, Emory University School of Medicine, Atlanta in the United States of America. Sources of funding: Supported by Allergan, Inc (grant no. IIT-000121).

1.5.1.4 Abobotulinum toxin A (Dysport)

Table 4: Summary of studies including abobotulinum toxin A (Dysport) as an intervention in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Bakheit 2000[2]	**Abobotulinum toxin type A (Dysport)** (n=63) Botulinum toxin type A (Dysport) delivered at three different doses: 500 units (n=22), 1000 units (n=22) and 1500 units (n=19). Follow up at 16 weeks. **Usual care or no treatment** (n=16) Conventional stroke rehabilitation care only. **Concomitant therapy:** No additional information	**People after a first or recurrent stroke** Mean age (SD): 62.5 (13.4) years N = 82 Type of Spasticity: Focal spasticity Severity of spasticity: Severe Time period since stroke: Subacute (7 days - 6 months)	Spasticity outcome measures at ≤6 months Physical function - upper limb at ≤6 months Activities of daily living at ≤6 months	Setting: Rehabilitation units in hospitals. Conducted in the United Kingdom, Germany and Austria. Sources of funding: The study was sponsored by Ipsen Limited, Maidenhead, Berkshire, UK, who also designed the study in consultation with the senior authors and was responsible for the recruitment of the researchers and monitoring of the data collection.
Gracies 2015[37]	**Abobotulinum toxin type A (Dysport)** (n=162) Abobotulinum toxin type A either 500 units or 1000 units. People received 5 mL of reconstituted treatment into the primary target muscle group and at least two other upper limb muscles in a single injection. After injecting the primary target muscle group, the remainder of the 5mL was injected in the additional upper limb muscles selected. Follow up at 4 weeks. **Placebo/sham** (n=81) Placebo injection only using the same methods. **Concomitant therapy:** Presence or absence of concomitant	**People after a first or recurrent stroke** Mean age (SD): 52.8 (13.5) years N = 243 Type of Spasticity: Focal upper limb Severity of spasticity – Mean modified Ashworth scale (SD): 3.9 (0.5) Mean time period since stroke mean (SD): 5.1 (4.4) years	Spasticity outcome measures at ≤6 months Activities of daily living at ≤6 months Withdrawal due to adverse event at ≤6 months	Setting: 34 centres, outpatient follow up. Conducted in Belgium, Czech Republic, France, Hungary, Italy, Poland, Russia, Slovakia and the United States of America. Sources of funding: Funded by Ipsen.

Study	Intervention and comparison	Population	Outcomes	Comments
	physiotherapy throughout the trial was recorded; if patients received physiotherapy before enrolment, the regimen was kept unchanged during the trial. Concomitant medications were to be maintained at a stable dose during the study.			
Hesse 1998[45]	**Combination therapy: Abobotulinum toxin type A (Dysport) and neuromuscular electrical stimulation (NMES)** (n=6) 1000 units of Botulinum Toxin type A (Dysport) into biceps brachii, brachialis (each 250 units), flexor carpi ulnaris, flexor carpi radialis, flexor digitorum profundus et superficialis (each 125 units) at two sites per muscle, close to the motor point. An IJS dual channel stimulator with continuous trains (3s) of charge-balanced constant current pulses (20 Hz, 200 microseconds, 50-90 milliamperes) was used for stimulation. Follow up at 12 weeks. **Abobotulinum toxin type A (Dysport)** (n=6) Abobotulinum toxin type A only. **Neuromuscular electrical**	**People after a first or recurrent stroke** Mean age: 52.3 years N = 24 Type of Spasticity: Focal Severity of spasticity: Not reported Mean time period since stroke: 7.45 months	Spasticity outcome measures at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Outpatient clinic in Germany. Sources of funding: This study was supported by a grant of Speywood Pharmaceuticals Ltd, UK, who supplied the botulinum toxin and placebo used in this study.

Study	Intervention and comparison	Population	Outcomes	Comments
	stimulation (NMES) (n=6) NMES and injection with 0.9% saline instead of abobotulinum toxin type A. **Placebo/sham** (n=6) 0.9% normal saline injection only. **Concomitant therapy:** All received an average of two physiotherapeutic treatment sessions for half an hour per week, which did not change during the course of the study. The amount of therapy did not differ across the groups and was unanimously applied by the Bobath techniques. None of the patients received a concomitant anti-spasticity medication during the study.			
McCrory 2009[78]	**Abobotulinum toxin A (Dysport)** (n=54) Total dose range 750–1000 units. Injected into the principal spastic muscles of the distal upper limb (restricted to muscles acting at elbow, wrist and finger joints) Patients received re-treatment with the same agent as their first cycle at week 12 with a total dose range of 500–1000 units according to the response in the initial cycle.	**People after a first or recurrent stroke** Mean age (SD): 59.1 (13.3) years N = 96 Type of Spasticity: Focal upper limb Severity of spasticity: Moderate (or MAS 2) Mean time period since stroke (SD): 5.9 (10.6) years	Person/participant generic health-related quality of life at ≤6 months Spasticity outcome measures at ≤6 months Pain at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: 6 outpatient spasticity clinics in Australia. Sources of funding: Fully funded by Ipsen Pty Ltd, Australia.

Study	Intervention and comparison	Population	Outcomes	Comments
	Follow up at 24 weeks. **Placebo/sham** (n = 42) **Concomitant therapy:** No additional information.			
Pittock 2003[99]	**Abobotulinum Toxin A (Dysport)** (n=179) 500, 1,000 or 1,500 units doses combined for this review. Injection into four lower limb sites. Follow up at 12 weeks. **Placebo/sham** (n=55) **Concomitant therapy:** No additional information.	**People after a first or recurrent stroke** Mean age (SD): 58.5 (12.2) years N = 234 Type of Spasticity: Focal Severity of spasticity: Not reported. Mean time period since stroke (SD): 3.35 (3.89) months	Physical function - lower limb at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Multicentre design. Sources of funding: Ipsen UK sponsored the study and designed the study in consultation with senior authors.
Prazeres 2018[100]	**Abobotulinum Toxin A (Dysport)** (n=20) Abobotulinum toxin A dose unclear. Follow up at 6 and 9 months. **Placebo/sham** (n=20) Saline placebo **Concomitant therapy:** Physical exercises twice a week for 30 minutes.	**People after a first or recurrent stroke** Mean age (SD): 52.28 (11.79) years N = 40 Type of Spasticity: Focal Severity of spasticity: Moderate (or MAS 2) Mean time period since stroke (SD): 33.1 (18.5) months	Spasticity outcome measures at ≤6 months and >6 months	Setting: Neurorehabilitation unit at a University Hospital in Northeastern Brazil. Sources of funding: This work was funded by Brazilian National Institutes of Science (CITECS/INNT/CNPq), CAPES, and UFBA.
Rosales 2018[103]	**Abobotulinum Toxin A (Dysport)** (n=28) Patients received intramuscular injections of abobotulinum toxin A 500 units into selected muscles. Follow up at 12 weeks.	**People after a first or recurrent stroke** Mean age (SD): 59.8 (12.4) years N = 42 Type of Spasticity: Focal	Withdrawal - due to adverse events at ≤6 months	Setting: Conducted at four centers in Malaysia, Thailand, Singapore, and the Philippines. Sources of funding: Ipsen Pharma.

Study	Intervention and comparison	Population	Outcomes	Comments
	Placebo/sham (n=14) Patients received intramuscular injections of equal volume placebo into selected muscles. **Concomitant therapy:** No further details.	Severity of spasticity: Moderate (or MAS 2) Time period since stroke range: Subacute (7 days - 6 months)		
Rosales 2012[102]	**Abobotulinum Toxin A (Dysport)** (n=80) The recommended dose distribution was 2 injections of 200 units in a 1mL volume for the biceps brachii, 1 injection of 100 units in a 0.5mL volume in the brachioradialis, 1 injection of 100 units in a 0.5-mL volume in the flexor carpi ulnaris, and 1 injection of 100 units in a 0.5mL volume in the flexor carpi radialis. Follow up at 24 weeks. **Placebo/sham** (n=83) Same constituents injected apart from abobotulinum toxin A. **Concomitant therapy:** People were permitted to continue any anti spasticity medication already in place, although dose adjustment was not permitted. All patients continued with their standard rehabilitation programs throughout the	**People after a first or recurrent stroke** Mean age (range): 55.1 (17-79) years N = 163 Type of Spasticity: Focal spasticity Severity of spasticity: Moderate (or MAS 2) Time period since stroke range: Subacute (7 days - 6 months)	Spasticity outcome measures at ≤6 months and >6 months Activities of daily living at ≤6 months and >6 months Pain at ≤6 months and >6 months Stroke-specific Patient-Reported Outcome Measures at ≤6 months and >6 months Withdrawal due to adverse events at ≤6 months and >6 months	Setting: 5 neurological and rehabilitation units in Hong Kong, Malaysia, the Philippines, Singapore, and Thailand. Sources of funding: Ipsen Pharma.

Study	Intervention and comparison	Population	Outcomes	Comments
	study, as deemed suitable by the attending physician.			
Shaw 2010[112] Subsidiary paper: Shaw 2011[115]	**Abobotulinum Toxin A (Dysport)** (n=170) Botulinum toxin type A (Dysport). The maximum dose that could be administered at any one time point was 1000 units. Follow up at 3 months and 12 months. **Usual care or no treatment** (n=163) (1 hour twice per week provided by study therapist) Upper limb therapy programme, tailored to limb function. **Concomitant therapy:** Participants in both groups received the upper limb therapy programme for 4 weeks. The use of aminoglycosides was prohibited during the study. Clinicians were advised to use muscle relaxants with caution.	**People after a first or recurrent stroke** Mean age (IQR) Intervention: 67 (58.8 to 72.3) years Control: 66 (59.8 to 72.3) years N = 333 Type of Spasticity: Focal upper limb Severity of spasticity: Moderate (or MAS 2) Time period since stroke range: Subacute (7 days - 6 months)	Person/participant generic health-related quality of life at ≤6 months and at >6 months Spasticity outcome measures at ≤6 months and at >6 months Physical function – upper limb at ≤6 months and at >6 months Pain at ≤6 months and at >6 months Stroke-specific Patient-Reported Outcome Measures at ≤6 months and at >6 months	Setting: Twelve stroke services in the north of England. Sources of funding: NIHR Health Technology Assessment programme.
Simpson 1996[117]	**Abobotulinum Toxin A (Dysport)** (n=27) Patients were randomly assigned to receive either a low (75 units), medium (150 units) or high (300 units) total dose of abobotulinum toxin A. Follow up at 16 weeks. **Placebo** (n=10)	**People after a first or recurrent stroke** Mean age (SD): 59 (12) years N = 39 Type of Spasticity: Focal spasticity Severity of spasticity: Moderate (or MAS 2) Time period since stroke range:	Spasticity outcome measures at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Outpatient multicentre trial in 3 sites in the United States of America. Sources of funding: Supported from a grant from Allergan, Inc.

Study	Intervention and comparison	Population	Outcomes	Comments
	Concomitant therapy: Not reported	Chronic (≥6 months)		
Yazdchi 2013[143]	**Abobotulinum Toxin A (Dysport)** (n=34) Injections into dominant spastic muscles of the upper extremities using 500 units of Dysport (maximum dosage 1000 units). Follow up at 24 weeks. **Tizanidine** (n=34) Initiated dosage of 2mg and gradual increase of 2 mg weekly to reach 24 mg at week 12 and continued the same dosage until week 24 to the end of the study. **Concomitant therapy:** 45-60 min physiotherapy program three times a week.	**People after a first or recurrent stroke** Mean age (range): 66.1 (35-70) years N = 68 Type of Spasticity: Focal Severity of spasticity: Severe (or MAS 3) Time period since stroke range: Not stated/unclear	Spasticity outcome measures at ≤6 months Physical function - upper limb at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Imam Reza University Hospital and Neurology Clinic Iran. Sources of funding: Not reported.

1.5.1.5 Incobotulinum toxin A (Xeomin)

Table 5: Summary of studies including incobotulinum toxin A (Xeomin) as an intervention in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Elovic 2014[28]	**Incobotulinum toxin A (Xeomin)** (n=171) The total dose was fixed at 400 units of incobotulinum toxin A (using a 2.0 mL per 100 units dilution). The maximum injection volume per injection site was 1.0 mL, corresponding to 50 units.	**People after a first or recurrent stroke** Mean age (SD): 56.0 (11.4) years N = 259 Type of Spasticity: Focal Severity of spasticity: Mixed Modified Ashworth score ≥2	Spasticity outcome measures at ≤6 months and >6 months Withdrawal due to adverse events at ≤6 and >6 months	Setting: No additional information. Conducted in 46 sites in the Czech Republic, Germany, Hungary, India, Poland, Russia, and the United States of America. Sources of funding: Supported in part by The Lucy Gonda Foundation.

Study	Intervention and comparison	Population	Outcomes	Comments
	Follow up at 4 weeks and 48 weeks. **Placebo/sham** (n=88) Same as intervention, with 8.0mL placebo in place of incobotulinum toxin A. **Concomitant therapy:** No additional information.	Time period since stroke: Chronic (28 months median)		
Hesse 2012[44]	**Incobotulinum toxin A (Xeomin)** (n=9) 150 units botulinum toxin type A (Xeomin) injected into the deep and superficial finger (100 units) and wrist flexors (50 units). Follow up at 6 months. **Usual care or no treatment** (n=9) No injections. **Concomitant therapy:** Multiprofessional motor rehabilitation programme, including physiotherapy (45 minutes every workday) and occupational therapy (30 minutes every workday). Speech therapy, neuropsychology and spa therapy were administered according to individual needs.	**People after a first or recurrent stroke** Mean age (SD): 61.5 (11.9) years N = 18 Type of Spasticity: Focal Mean severity of spasticity (SD): 1.7 (0.5) Mean time period since stroke (SD): 5.7 (1.2) weeks	Spasticity outcome measures at ≤6 months Physical function – upper limb at ≤6 months Activities of daily living at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: An inpatient rehabilitation centre focused on early stroke rehabilitation in Germany. Sources of funding: The Verein zur Forderung der Hirnforschung und Rehabilitation e.V. supported the study.
Kanovsky 2009[57]	**Incobotulinum toxin A (Xeomin)** (n=73) Up to a maximum of 400 units. The	**People after a first or recurrent stroke** Mean age (SD): 55.7 (12.1) years	Withdrawal due to adverse events at ≤6 months	Setting: 23 sites in 3 European countries, outpatient setting. Conducted in the

Study	Intervention and comparison	Population	Outcomes	Comments
	choice of muscle to be treated within the muscle groups of forearm, pronators and thumb flexors was based on the investigator's clinical judgement. Follow up at 12 weeks. **Placebo** (n=75) Injection with matching placebo administered in the same manner. **Concomitant therapy:** Antispasticity medications with centrally acting muscle relaxants and/or benzodiazepine medication and physical and occupational therapy regimens were permitted if they had been stable in the 2 weeks before screening.	N = 148 Type of Spasticity: Focal Severity of spasticity: Moderate (or MAS 2) Mean time period since stroke: 55.0 months		Czech Republic, Hungary and Poland. Sources of funding: This study was supported by Merz Pharmaceuticals GmbH, Frankfurt.
Masakado 2020[76]	**Incobotulinum toxin A (Xeomin)** (n=67) One injection cycle of incobotulinum toxin A 400 units or incobotulinum toxin A 250 units. Follow up at 12 weeks. **Placebo** (n=33) One injection cycle of a matching placebo (either high or low dose placebo). **Concomitant therapy:** No additional information	**People after a first or recurrent stroke** Mean age (SD): 59.7 (11.9) years N = 100 Type of Spasticity: Focal Severity of spasticity: Not reported Time period since stroke: Subacute (7 days - 6 months)	Withdrawal due to adverse events at ≤6 months	Setting: no additional information. Conducted in Japan. Sources of funding: Financial support for the study was provided by Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany.

Study	Intervention and comparison	Population	Outcomes	Comments
Masakado 2022[77]	**Incobotulinum toxin A (Xeomin)** (n=104) Incobotulinum toxin A 400 units injected into the pes equinus muscle and then observed over 12 weeks. **Placebo** (n=104) Matching placebo injection. **Concomitant therapy:** Medical, physiotherapy, occupational therapy and any other rehabilitation measures required were permitted. Some therapies were not permitted (see study description for more information).	**People after a first or recurrent stroke** Mean age (SD): 59.2 (11.1) years N = 208 Type of Spasticity: Focal Severity of spasticity: Not reported Mean time period since stroke (SD): 82.9 (67.4) months	Spasticity outcome measures at ≤6 months Physical function – lower limb at ≤6 months Pain at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: no additional information. Conducted in Japan. Sources of funding: Financial support for the study was provided by Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany.
Turcu-Stiolica 2021[127]	**Incobotulinum toxin A (Xeomin)** (n=17) Incobotulinum toxin 200 units. The injection was performed only on the upper spastic limb. Follow up at 6 months. **Baclofen** (n=17) Baclofen (started from 10 mg up to 60 mg daily). **Concomitant therapy:** All people participated in a physiotherapy program.	**People after a first or recurrent stroke** Mean age (SD): 60.22 (11.10) years N = 34 Type of Spasticity: Focal. Severity of spasticity: Mixed. Time period since stroke range: Not stated/unclear.	Person/participant generic health-related quality of life at ≤6 months Spasticity outcome measures at ≤6 months Physical function - upper limb at ≤6 months Activities of daily living at ≤6 months	Setting: Neurology Hospital of Craiova in Romania. Sources of funding: This research received no external funding.

1.5.1.6 Intrathecal baclofen

Table 6: Summary of studies including intrathecal baclofen as an intervention in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Creamer 2018[13]	**Intrathecal baclofen** (n=31) Lioresal Intrathecal (baclofen injection, Novartis (Europe)/Saol Therapeutics (US)) was used for intrathecal baclofen therapy. After implant, patients underwent a 6-week titration period during which the intrathecal baclofen dose was increased until the desired clinical effect was achieved or reduced for side-effect management. People randomised to intrathecal baclofen who were not implanted remained on oral antispastic medication and physiotherapy until the study end. Follow up at 6 months. **Usual care or no treatment** (n=29) This arm received a combination of oral antispastic medication (at least one of oral baclofen, tinzanidine, diazepam/other benzodiazepines, or dantrolene) and physiotherapy throughout the study. **Concomitant therapy:** No additional information.	**People after a first or recurrent stroke** Mean age (SD): 55.9 (10.0) years N = 60 Type of Spasticity: Generalised Severity of spasticity: Not reported Mean time period since stroke (SD): 4.8 (3.7) years	Person/participant generic health-related quality of life at ≤6 months Spasticity outcome measures at ≤6 months Pain at ≤6 months Activities of daily living at ≤6 months Stroke-specific Patient-Reported Outcome Measures at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Rehabilitation hospitals in 11 European centers (Austria, Belgium, Germany, Italy, the Netherlands, Spain, UK, Slovenia) and 7 United States of America centres. Sources of funding: This work was supported by Medtronic International Trading Sàrl.

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1.5.1.7 Functional electrical stimulation (FES)

Table 7: Summary of studies including function electrical stimulation (FES) as an intervention in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Bethoux 2014[5]	**Functional Electrical Stimulation (FES)** (n=242) Functional Electrical Stimulation for 6 months. Follow up at 6 months. **Usual care or no treatment** (n=253) Ankle-Foot Orthosis (AFO) for 6 months. **Concomitant therapy:** No additional information	**People after a first or recurrent stroke** Mean age (SD): 64.1 (11.7) years N = 495 Type of Spasticity: Focal Severity of spasticity: Not reported Mean time period since stroke (SD): 6.9 (6.5) years	Physical function - lower limb at ≤6 months Stroke-specific Patient-Reported Outcome Measures at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: 30 rehabilitation centers across the United States of America. Sources of funding: This study was sponsored by Innovative Neurotronics.
Daly 2011[17]	**Functional Electrical Stimulation (FES)** (n=20) Intramuscular functional electrical stimulation was administered through a V-40 stimulator worn on the belt with a custom pattern downloaded to each participants stimulator for gait practice. Follow up at 6 months. **Usual care or no treatment** (n=24) The programs were identical to the intervention group, with the comparison group receiving no intramuscular functional electrical stimulation.	**People after a first or recurrent stroke** Mean age: 61 years N = 44 Type of Spasticity: Focal. Median severity of spasticity (IQR): Intervention: 21.5 (18.75 to 24.25) Control: 19.5 (17.13 to 21.88). Time period since stroke: Chronic (≥6 months)	Physical function – lower limb at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: No additional information. Conducted in the United States of America. Sources of funding: Funding from the Department of Veterans Affairs, Office of Rehabilitation Research and Development (grant numbers: B2226R, A3102R, B5080S).

Study	Intervention and comparison	Population	Outcomes	Comments
	Concomitant therapy: Four exercise sessions per week (1.5 hours each) for 12 weeks.			
Lairamore 2014[61]	**Functional Electrical Stimulation (FES)** (n=16) Electrical stimulation was delivered using a continuous, biphasic symmetric waveform with a pulse width of 200 microseconds with a pulse rate of 30 Hz. Follow up at 11 days **Placebo/sham** (n=16) The same unit was used but only sensory stimulation was applied. **Concomitant therapy:** All people were enrolled in an inpatient rehabilitation program and received 1.5 hour of physical therapy 5 days per week.	**People after a first or recurrent stroke** Mean age (SD): 51.3 (16.6) years N = 32 Type of Spasticity: Focal Severity of spasticity: Not reported Mean time period since stroke (SD): 14.2 (7.3) days	Physical function – lower limb at ≤6 months Activities of daily living at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Outpatient follow up in the United States of America. Sources of funding: No additional information. 12.5% of the population had a condition other than stroke. Therefore, outcomes reported from this study were considered to include population indirectness.
Lee 2013[64]	**Functional Electrical Stimulation (FES)** (n=15) A portable two-channel neurotransmitter was used for delivery of electrical stimulation. Follow up at 4 weeks. **Usual care or no treatment** (n=15) **Concomitant therapy:** Body weight supported	**People after a first or recurrent stroke** Mean age (SD): 54.6 (8.7) years N = 30 Type of Spasticity: Focal Severity of spasticity: Not reported Mean time period since stroke (SD): 4.04 (0.79) months	Physical function - lower limb at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Rehabilitation centre in the Republic of Korea. Sources of funding: No additional information.

Study	Intervention and comparison	Population	Outcomes	Comments
	treadmill training for 30 minutes a day, 5 days a week for 4 weeks.			
Nakipoglu Yuzer 2017[85]	**Functional electrical stimulation (FES)** (n=15) Functional Electrical Stimulation was applied 30 minutes per day for 5 days a week for a total of 20 sessions per patient. Follow up at 4 weeks. **Usual care or no treatment** (n=15) **Concomitant therapy:** Conventional treated consisting of passive ROM exercises, stretching exercises, and a wrist-hand static splint was also used and provided to both study groups.	**People after a first or recurrent stroke** Mean age (SD): 58.9 (11.5) years N = 30 Type of Spasticity: Focal Severity of spasticity: Severe (or MAS 3) Mean time period since stroke (SD): 3.2 (2.8) months	Physical function - upper limb at ≤6 months Activities of daily living at ≤6 months	Setting: Rehabilitation hospital inpatients in Turkey. Sources of funding: Not additional information.
Sabut 2010[105]	**Functional electrical stimulation (FES)** (n=27) Electrical stimulation was given for 20-30 minutes to the tibialis anterior muscle of the paretic limb. The stimulation current applied with 0.28 ms pulses, at 35 Hz in the constant mode. Follow up at 12 weeks. **Usual care or no treatment** (n=24)	**People after a first or recurrent stroke** Mean age (SD): 49.6 (9.6) years N = 51 Type of Spasticity: Focal Severity of spasticity: Moderate (or MAS 2) Time period since stroke range: Chronic (≥6 months)	Spasticity outcome measures at ≤6 months Physical function – lower limb at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Inpatient/outpatient department of National Institute for the orthopedically handicapped, Kolkata, India. Sources of funding: Not reported.

Study	Intervention and comparison	Population	Outcomes	Comments
	Concomitant therapy: All patients received the same conventional rehabilitation programme including neurodevelopmental techniques, physiotherapy and occupational therapy, 1 hours per day, 5 days per week, for 12 weeks.			
Yan 2005[141]	**Function electrical stimulation (FES)** (n=13) Functional electrical stimulation was delivered to quadriceps, hamstring, tibialis anterior, and medial gastrocnemius with 0.3-ms pulses at 30 Hz, maximum tolerance intensity (20 to 30 mA). 30 minutes per day, 5 days per week for 3 weeks. **Placebo/sham** (n=15) The placebo group received stimulation from an electrical stimulation device with disconnected circuit. **Usual care or no treatment** (n=13) **Concomitant therapy:** All participants received the same therapy including 60 minutes each of physiotherapy and occupational	**People after a first or recurrent stroke** Mean age (SD): 70.8 (8.1) years N= 46 Type of Spasticity: Focal Severity of spasticity: Mild (or MAS 1) Time period since stroke range: Subacute (7 days - 6 months)	Spasticity outcome measures at ≤6 months Physical function – lower limb at ≤6 months 8 weeks	Setting: Department of Rehabilitation Sciences in China. Sources of funding: supported by an Area of Strategic Development grant from the Hong Kong Polytechnic University.

Study	Intervention and comparison	Population	Outcomes	Comments
	therapy focused on activities of daily living, given once per day, 5 days per week for 3 weeks.			
You 2014[144]	**Functional electrical stimulation (FES)** (n=19) Functional electrical stimulation was given using a dual-channel stimulator. Follow up at 3 weeks. **Usual care or no treatment** (n=18) **Concomitant therapy:** Patients in both groups received necessary drugs and the standard rehabilitation programme including 60 minutes of physiotherapy (5 days per week).	**People after a first or recurrent stroke** Mean age (SD): 62.4 (10.4) years N = 37 Type of Spasticity: Focal. Severity of spasticity: Not stated/unclear. Time period since stroke range: Subacute (7 days - 6 months)	Spasticity outcome measures at ≤6 months Physical function –lower limb at ≤6 months Activities of daily living at ≤6 months	Setting: Stroke rehabilitation department, Department of Rehabilitation Medicine, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou China. Sources of funding: Supported by grants from the Guangdong Provincial Department of Science and Technology.

1.5.1.8 Neuromuscular electrical stimulation (NMES)

Table 8: Summary of studies including neuromuscular electrical stimulation (NMES) as an intervention in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Bakhtiary 2008[3]	**Neuromuscular electrical stimulation (NMES)** (n=20) Fifteen minutes of inhibitory Bobath techniques in combination with 9 minutes of electrical stimulation on the dorsiflexor muscles for 20 sessions daily. Follow up at 4 weeks.	**People after a first or recurrent stroke** Mean age (SD): Not reported. N = 40 Type of Spasticity: Focal. Severity of spasticity: Severe (or MAS 3). Time period since stroke: Not reported.	Spasticity outcome measures at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: The neurology clinic of the Semnan University of Medical Sciences in Iran. Sources of funding: No additional information.

Study	Intervention and comparison	Population	Outcomes	Comments
	Usual care or no treatment (n=20) Bobath technique exercises only. **Concomitant therapy:** In both groups, before starting treatment the subject's lower limbs were exposed to 10 minutes of infrared at a distance of 50 cm to warm up the limbs.			
Boyaci 2013[6]	**Neuromuscular electrical stimulation (NMES)** (n=20) A combination of active NMES (n=10) and passive NMES (n=10). Each treatment regimen was applied five times per week for 45 minutes for 3 weeks. Follow up at 3 weeks. **Placebo/sham** (n=10) The electrodes were placed away from all motor points and people received cutaneous stimulation just above the sensory threshold without motor activation. **Concomitant therapy:** All people performed the same neurophysiologic exercise program for 45 minutes five times per week for 3 weeks.	**People after a first or recurrent stroke** Mean age (SD): 59.4 (12.2) years N = 30 Type of Spasticity: Focal Severity of spasticity: Mild (or MAS 1) Mean time period since stroke (SD): 16.5 (17.3) weeks	Spasticity outcome measures at ≤6 months Physical function –upper limb at ≤6 months Activities of daily living at ≤6 months	Setting: An inpatient rehabilitation program in Turkey Sources of funding: No additional information.

Study	Intervention and comparison	Population	Outcomes	Comments
De Jong 2013[19]	**Neuromuscular electrical stimulation (NMES)** (n=23) Arm stretching positioning with simultaneous four-channel motor amplitude neuromuscular electrical stimulation. Follow up at 20 weeks. **Placebo/sham** (n=23) Sham stretch procedure with simultaneous sham neuromuscular electrical stimulation (achieved as transcutaneous electrical nerve stimulation with no motor effect) with minimal sensory stimulation. **Concomitant therapy:** All patients received multidisciplinary stroke rehabilitation (daily training of daily living by rehabilitation nurses, occupational therapists, physiotherapists and speech therapists).	**People after a first or recurrent stroke** Mean age (SD): 57.5 (12.2) years N = 46 Type of Spasticity: Focal. Severity of spasticity: Not reported. Mean time period since stroke (SD): 43.5 (14.4) days	Spasticity outcome measures at ≤6 months Physical function – upper limb at ≤6 months Pain at ≤6 months Hospitalisation at ≤6 months Additional health care contacts (prescription of pain medication) at ≤6 months Additional health care contacts (prescription of spasticity medication) at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Neurological unit of rehabilitation centres in the Netherlands. Sources of funding: Financial support from Fonds NutsOhra [SNO-T-0702-72] and Stichting Beatrixoord Noord-Nederland.
Hesse 1998[45]	**Combination therapy: Abobotulinum toxin type A (Dysport) and neuromuscular electrical stimulation (NMES)** (n=6) 1000 units of Botulinum Toxin type A (Dysport) into biceps brachii, brachialis (each	**People after a first or recurrent stroke** Mean age: 52.3 years N = 24 Type of Spasticity: Focal Severity of spasticity: Not reported	Spasticity outcome measures at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: outpatient clinic in Germany Sources of funding: This study was supported by a grant of Speywood Pharmaceuticals Ltd, UK, who supplied the botulinum toxin and placebo used in this study.

Study	Intervention and comparison	Population	Outcomes	Comments
	250 units), flexor carpi ulnaris, flexor carpi radialis, flexor digitorum profundus et superficialis (each 125 units) at two sites per muscle, close to the motor point. An IJS dual channel stimulator with continuous trains (3s) of charge-balanced constant current pulses (20 Hz, 200 microseconds, 50-90 mA) was used for stimulation. Follow up at 12 weeks. **Abobotulinum toxin type A (Dysport)** (n=6) Abobotulinum toxin type A only. **Neuromuscular electrical stimulation (NMES)** (n=6) NMES and injection with 0.9% saline instead of abobotulinum toxin type A. **Placebo/sham** (n=6) 0.9% normal saline injection only. **Concomitant therapy:** All received an average of two physiotherapeutic treatment sessions for half an hour per week, which did not change during the course of the study. The amount of therapy did not differ across the groups and was unanimously applied by the	Mean time period since stroke: 7.45 months		

Study	Intervention and comparison	Population	Outcomes	Comments
	Bobath techniques. None of the patients received a concomitant anti-spastic medication during the study.			
Hu 2015[46]	**Neuromuscular electrical stimulation (NMES)** (n=11) Electromyography (EMG)-driven NMES robot for seven weeks. The NMES group received the interactive assistance from both the motor and the NMES parts at the same time during the training. Follow up at 3 months. **Usual care or no treatment** (n=15) EMG-driven robot only (no NMES). **Concomitant therapy:** For both groups, each recruited subject received the wrist training with an intensity of 3 to 5 sessions/week for 20 sessions, finished within 7 weeks.	**People after a first or recurrent stroke** Mean age (SD): 47.7 (13.5) years N = 26 Type of Spasticity: Focal Mean severity of spasticity (SD) – Modified Ashworth scale: 1.39 (0.59) Mean time period since stroke (SD): 4.5 (4.6) years	Spasticity outcome measures at ≤6 months Physical function – upper limb at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Conducted in Hong Kong. Sources of funding: The study was financially supported by a GRF grant (PolyU 5318/09E) from the Research Grants Council and an ITF grant (ITS/033/12) from the Innovation and Technology Commission of the Hong Kong Special Administrative Region.
Huang 2020[47]	**Neuromuscular electrical stimulation (NMES)** (n=15) The NMES robot group. Synchronized support from the NMES and the robot were provided. Therapy delivered as 3-5 sessions/week for 20 sessions, finished within 7 consecutive weeks. Follow up at 3 months.	**People after a first or recurrent stroke** Mean age (SD): 58.7 (8.2) years N = 30 Type of Spasticity: Focal Severity of spasticity: Mild (or MAS 1) Mean time period since stroke (SD): 7.2 (4.0) years	Spasticity outcome measures at ≤6 months Physical function – upper limb at ≤6 months Activities of daily living at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: People from local districts in Hong Kong. Sources of funding: This project was funded by PolyU Central Fund1-ZE4R ITS/073/16 and NSFC81771959.

Study	Intervention and comparison	Population	Outcomes	Comments
	Usual care or no treatment (n=15) Robot group only. Therapy delivered as 3-5 sessions/week for 20 sessions, finished within 7 consecutive weeks. **Concomitant therapy:** Both groups received physical training by robot.			
Lee 2015[65]	**Neuromuscular electrical stimulation (NMES)** (n=20) The Bi-Manu-Track robotic arm training system and NMES. Each treatment session was 60–70 minutes. After the therapy, the participants received an additional 20 to 30 minutes of functional task training to facilitate transferring the acquired movements to daily activities. Follow up at 4 months. **Placebo/sham** (n=19) Sham NMES and robot therapy. **Concomitant therapy:** No additional information	**People after a first or recurrent stroke** Mean age (SD): 53.9 (10.6) years N = 39 Type of Spasticity: Focal Severity of spasticity: Mild (or MAS 1) Mean time period since stroke (SD): 26.6 (16.7) months	Spasticity outcome measures at ≤6 months Physical function – upper limb at ≤6 months Stroke-Specific Patient-Reported Outcome Measures at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Hospital in Taiwan. Sources of funding: This study was supported in part by the National Health Research Institutes (NHRI-EX104-10403PI), the Ministry of Science and Technology (102-2314-B002-154-MY2, 102-2628-B-182-005-MY3, and 103-2314-B-182-004-MY3), Healthy Ageing Research Center at Chang Gung University (EMRPD1E1711), and Chang Gung Memorial Hospital (CMRPD1B0332, CMRPD1C0403) in Taiwan.
Lin 2011[68]	**Neuromuscular electrical stimulation (NMES)** (n=19) The patients in the intervention group were given neuromuscular electrical	**People after a first or recurrent stroke** Mean age (SD): 64.1 (9.3) years. N = 37 Type of Spasticity: Focal.	Spasticity outcome measures at ≤6 months Activities of daily living at ≤6 months	Setting: Inpatient in China. Sources of funding: Financed by projects of GDSTC (No. 2007B031502005, 2010A040302002).

Study	Intervention and comparison	Population	Outcomes	Comments
	stimulation. Treatment lasted for 30 min, 5 days per week for 3 weeks. Follow up at 6 months. **Usual care or no treatment** (n=18) **Concomitant therapy:** All patients received the same standard treatment, including physical therapy and occupational therapy, for 30 min on 5 days each week for 3 weeks, respectively.	Severity of spasticity: Mild – mean MAS = 0.53 (0.5). Mean time period since stroke (SD): 42.4 (25.9) days		
Malhotra 2013[73]	**Neuromuscular electrical stimulation (NMES)** (n=45) 30-minute sessions of surface neuromuscular electrical stimulation to the wrist and finger extensors at least twice a day (a maximum of three times a day) for five days a week. Follow up at 36 weeks. **Usual care or no treatment** (n=45) **Concomitant therapy:** Patients in both the control and treatment arms were given a defined module of routine physiotherapy, with interventions which reflected local clinical practice, for a period of six weeks in addition to the usual clinical	**People after a first or recurrent stroke** Median age (range): Intervention: 74 (32 to 98) years Control: 74 (52 to 90) years N = 90 Type of Spasticity: Focal upper limb Severity of spasticity: Not reported Median time period since stroke (range): 3 (1 to 6) months	Pain at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Hospital and home-based in the United Kingdom. Sources of funding: This work was supported by Action Medical Research and Barnwood House Trust (grant number: AP0993). The surface neuromuscular stimulators were supplied by department of medical physics and biomedical engineering at Salisbury District Hospital. The equipment maintenance support was provided by Biometrics Ltd.

Study	Intervention and comparison	Population	Outcomes	Comments
	treatment on the stroke unit.			
Mesci 2009[80]	**Neuromuscular electrical stimulation (NMES)** (n=20) Neuromuscular electrical stimulation for hemiplegic foot dorsiflexor muscles for 4 weeks, 5 days a week for a total of 20 sessions. Follow up at 4 weeks. **Usual care or no treatment** (n=20) **Concomitant therapy:** All patients received a 4-week inpatient treatment with a conventional exercise program.	**People after a first or recurrent stroke** Mean age (SD): 60.9 (8.3) years N = 40 Type of Spasticity: Focal Mean severity of spasticity (SD) – Modified Ashworth scale: 1.7 (1.0) Mean time period since stroke (SD): 8.4 (4.7) months	Spasticity outcome measures at ≤6 months Physical function – lower limb at ≤6 months	Setting: Inpatient treatment centre in Turkey. Sources of funding: No additional information.
Morone 2012[84]	**Neuromuscular electrical stimulation (NMES)** (n=10) 20 sessions of 40 minutes, 5 times per week of walking training with NMES. Follow up at 1 month. **Usual care or no treatment** (n=10) Conventional neuromotor therapy 20 sessions of 40 minutes, 5 times per week of walking training with an ankle-foot orthosis. **Concomitant therapy:** Both groups undertook 40 minutes with a physiotherapist dedicated to improve activity of daily living and/or exercise for hand recovery.	**People after a first or recurrent stroke** Mean age (SD): 57.3 (15.9) years N = 20 Type of Spasticity: Focal Severity of spasticity: Not reported Mean time period since stroke (SD): 20 (21) days	Physical function – lower limb at ≤6 months	Setting: No additional information. Conducted in Italy. Sources of funding: No funding declared.

Study	Intervention and comparison	Population	Outcomes	Comments
Sahin 2012[106]	**Neuromuscular electrical stimulation (NMES)** (n=22) NMES treatment for a duration of 5 days a week, 20 sessions in total. Follow up at 4 weeks. **Usual care or no treatment** (n=22) **Concomitant therapy:** Patients received stretching with PNF applied to the upper extremity after 15 minutes of hot treatment with infrared on the extensor muscles, 5 days a week for 20 sessions.	**People after a first or recurrent stroke** Mean age (SD): 59.8 (7.9) years N = 44 Type of Spasticity: Focal Severity of spasticity: Severe (or MAS 3) Time period since stroke range: Chronic (≥6 months)	Spasticity outcome measures at ≤6 months Physical function –upper limb at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Outpatient in Turkey. Sources of funding: Not reported.
Sentandreu-Mano 2021[110]	**Neuromuscular electrical stimulation (NMES)** (n=46) Training was conducted for 3 days per week (a total of 24 sessions). Follow up at 3 months. **Usual care or no treatment** (n=23) **Concomitant therapy:** A standard physical therapy intervention was provided to all.	**People after a first or recurrent stroke** Mean age (SD): 71.0 (7.3) years N = 69 Type of Spasticity: Focal Severity of spasticity: Mild (or MAS 1) Time period since stroke range: Subacute (7 days - 6 months)	Spasticity outcome measures at ≤6 months Activities of daily living at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Outpatients in Spain. Sources of funding: This research was supported by a Grant from the Regional Ministry of Education (ACIF/2012/017) and from Regional Ministry of Health (004/2010).
Shin 2008[116]	**Neuromuscular electrical stimulation (NMES)** (n = 7) Patients received the EMG-stim treatment on the extensor digitorum communis with the walking man II EMG FES 3000 as	**People after a first or recurrent stroke** Mean age (SD): 57.6 (6.9) years N = 14 Type of Spasticity: Not reported	Physical function - upper limb at ≤6 months	Setting: Outpatient in Korea Sources of funding: Supported by the Korea Science and Engineering foundation (KOSEF) grant funded by the Korean government

Study	Intervention and comparison	Population	Outcomes	Comments
	one channel electrical stimulator. EMG treatment was performed for 2 sessions (30 minute session) a day, five times per week over 10 weeks. Follow up for 10 weeks. **Usual care or no treatment** (n = 7) **Concomitant therapy:** Both groups were allowed to perform low - intensity physical activities.	Severity of spasticity: Not reported Time period since stroke range: Not reported		
Wang 2016[133]	**Neuromuscular electrical stimulation (NMES)** (n=54) 3 levels of NMES combined for the purpose of this review (sensory threshold, motor threshold and full movement threshold stimulation). Follow up at 6 weeks. **Usual care or no treatment** (n=18) **Concomitant therapy**: All patients participated in conventional rehabilitation therapy, which included exercise of the ankle joint (range of movement), stretch of the spastic plantar flexors, and neurodevelopment facilitation techniques.	**People after a first or recurrent stroke** Age range: 30.4-79.4 years N = 70 Type of Spasticity: Focal Severity of spasticity: Moderate (or MAS 2) Time period since stroke range: Subacute (7 days - 6 months)	Spasticity outcome measures at ≤6 months Physical function - lower limb at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Rehabilitation hospital in China. Sources of funding: The study was supported by the Rehabilitation Center of Qilu hospital of Shandong University. This work was founded by the National Natural Science Foundation of China [grant No. 81000855 and No. 81272155] and the Natural Science Foundation of Shandong [grant No. ZR2010HQ021].

Study	Intervention and comparison	Population	Outcomes	Comments
Yang 2018[142]	**Neuromuscular electrical stimulation (NMES)** (n=17) Participants in the NMES groups received 20 minutes of NMES on either the tibialis anterior muscle or medial gastrocnemius muscle and then 15 minutes of ambulation training. All training sessions occurred 3 times per week for 7 weeks. Follow up at 7 weeks. **Usual care or no treatment** (n=8) 20 minutes of range of motion and stretching exercises, followed by 15 minutes of ambulation training. **Concomitant therapy:** Both groups received the 15 minutes of ambulation training focused on ankle movement and ankle control with verbal cues.	**People after a first or recurrent stroke** Mean age (SD): Intervention: 53.1 (4.4) years Control: 50.8 (3.8) years N = 25 Type of Spasticity: Focal. Severity of spasticity: Moderate (or MAS 2) Time period since stroke range: Chronic (≥6 months)	Spasticity outcome measures at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Taipei Veterans General Hospital in Taiwan. Sources of funding: supported by grants from the National Science Council (NSC 100-2314-B010-022-MY2).
Yun 2011[145]	**Neuromuscular electrical stimulation (NMES)** (n=40) 2 treatment groups combined for the purposes of this review (neuromuscular electrical stimulation alone, or neuromusucular electrical stimulation with mirror therapy).	**People after a first or recurrent stroke** Mean age (SD): 63.3 (9.9) years N = 60 Type of Spasticity: Focal Severity of spasticity: Mild (or MAS 1)	Spasticity outcome measures at ≤6 months Physical function – upper limb at ≤6 months	Setting: Department of Rehabilitation Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul in Korea Sources of funding: Not reported

Study	Intervention and comparison	Population	Outcomes	Comments
	Follow up at 3 weeks. **Usual care or no treatment** (n=20) Mirror therapy only. **Concomitant therapy:** All three groups received the same conventional rehabilitation programs and additionally, had each of their own therapies for thirty minutes, five days a week for three weeks.	Time period since stroke range: Subacute (7 days - 6 months)		
Zhou 2018[149]	**Neuromuscular electrical stimulation (NMES)** (n=36) The 4-week treatment consisted of 20 sessions, each session composed of 1 hour of stimulation per day. Follow up at 8 weeks. **Transcutaneous electrical nerve stimulation (TENS)** (n=36) TENS for the same frequency and duration. **Usual care or no treatment** (n=18) Conventional rehabilitation only. **Concomitant therapy:** Patients in all groups underwent a standardised rehabilitation programme.	**People after a first or recurrent stroke** Mean age (SD): 59.9 (10.4) years N = 90 Type of Spasticity: Focal Severity of spasticity: Mild (or MAS 1) Time period since stroke range: Subacute (7 days - 6 months)	Spasticity outcome measures at ≤6 months Physical function – upper limb at ≤6 months Pain at ≤6 months Activities of daily living at ≤6 months Stroke-specific Patient-Reported Outcome at ≤6 months	Setting: Hospital rehabilitation centre in China. Sources of funding: Research fund of the Baoshan district committee of science and technology, Shanghai, China.

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1.5.1.9 Transcutaneous electrical nerve stimulation (TENS)

Table 9: Summary of studies including transcutaneous electrical nerve stimulation (TENS) as an intervention in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Gurcan 2015[38]	**Transcutaneous electrical nerve stimulation (TENS)** (n=19) TENS for 20 minutes per day for 15 days (5 days per week for 3 weeks) in additional to conventional treatment. Follow up at 3 weeks. **Usual care or no treatment** (n=13) **Concomitant therapy:** All people were administered conventional treatment methods (range of joint motion, progressive resistive, stretching and neurophysiological exercises).	**People after a first or recurrent stroke** Mean age (SD): 57.8 (12.6) years N = 32 Type of Spasticity: Focal Mean severity of spasticity (SD): 2.53 (2.05) Mean time period since stroke (SD): 13.7 (18.9) months	Spasticity outcome measures at ≤6 months Physical function – lower limb at ≤6 months Activities of daily living at ≤6 months	Setting: Inpatients (people hospitalised and enrolled in a rehabilitation program) in Turkey. Sources of funding: No financial support.
Jung 2017[53]	**Transcutaneous electrical nerve stimulation (TENS)** (n=20) TENS for 30 minutes (5 times a week for 6 weeks) before each rehabilitation session. Follow up at 6 weeks. **Placebo/sham** (n=21) Sham TENS. The same protocol as the TENS group. However, the electrodes did not provide any electrical current when attached. **Concomitant therapy:** Sit-to-stand training for	**People after a first or recurrent stroke** Mean age (SD): 56.3 (10.3) years N = 41 Type of Spasticity: Focal Severity of spasticity: Moderate (or MAS 2) Mean time period since stroke (SD): 6.6 (2.6) months	Spasticity outcome measures at ≤6 months	Setting: Rehabilitation centers (outpatient follow up) in the Republic of Korea. Sources of funding: This work was supported by the 2016 Gimcheon University Research Grant, and also this work was supported by the Gachon University research fund of 2015 (GCU-2015-0060).

Study	Intervention and comparison	Population	Outcomes	Comments
	15 minutes a day, five times a week for six weeks. Otherwise, all people received conventional therapy for an additional hour a day, five times a week for six weeks.			
Jung 2020[54]	**Transcutaneous electrical nerve stimulation (TENS)** (n=20) Electrical stimulation for 30 minutes before the heel-raise-lower exercise training. Follow up at 6 weeks. **Placebo/sham** (n=20) The TENS apparatus and gave the subject a very fine electrical stimulation that they could feel. When the person could feel the stimulation, the research turned off power to the apparatus while hiding the TENS in the box and explained that a microcurrent of TENS was being applied to the subject. **Concomitant therapy:** Both groups received training 5 times a week for 6 weeks.	**People after a first or recurrent stroke** Mean age (SD): 52.9 (9.9) years N = 40 Type of Spasticity: Focal Severity of spasticity: Moderate (or MAS 2) Mean time period since stroke (SD): 6.9 (2.6) months	Spasticity outcome measures at ≤6 months Physical function – lower limb at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Inpatient in The K Hospital in South Korea. Sources of funding: This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (No. 2017R1C1B5075810).
Moon 2021[81]	**Transcutaneous Electrical Nerve Stimulation (TENS)** (n=22) TENS was applied for 30 min before occupational therapy. Follow up at 4 weeks.	**People after a first or recurrent stroke** Mean age (SD): 61.4 (7.8) years N = 48 Type of Spasticity: Focal	Spasticity outcome measures at ≤6 months Activities of daily living at ≤6 months Withdrawal due to adverse	Setting: No additional information. Conducted in Korea. Sources of funding: No external funding.

Study	Intervention and comparison	Population	Outcomes	Comments
	Placebo (n=21) In the placebo-TENS group, electrodes were attached to the same locations as the TENS group, and a transient current was delivered for 30s, then ramped down to zero over 15s. **Concomitant therapy:** Occupational and physical therapy were each performed for 30 min a day, 5 times a week, for 4 weeks.	Mean severity of spasticity (SD) – Modified Ashworth Scale: 1.26 (0.50) Mean time period since stroke (SD): 161.0 (102.0) days	events ≤6 months	
Ng 2007[91]	**Transcutaneous electrical nerve stimulation (TENS)** (n=44) Two groups. The TENS group received 60 minutes of TENS. The TENS and task related training group received 60 minutes of TENS followed by 60 minutes of task related training. Follow up at 8 weeks. **Placebo/sham** (n = 22) This group received 60 minutes of placebo-TENS from identical-looking TENS devices with the electrical circuit disconnected inside followed by 60 minutes of task related training. **Usual care or no treatment** (n=22)	**People after a first or recurrent stroke** Mean age (SD): 57.4 (8.2) years N = 88 Type of Spasticity: Focal Severity of spasticity: Moderate (or MAS 2) Mean time period since stroke (SD): 5.3 (3.6) years	Spasticity outcome measures at ≤6 months Withdrawal due to adverse event at ≤6 months	Setting: Community rehabilitation network in China. Sources of funding: This study was supported by the Health Service Research Fund (K-ZK34) from the Hong Kong Government (SAR) and a scholarship from The Hong Kong Polytechnic University to S.S.M.N.

Study	Intervention and comparison	Population	Outcomes	Comments
	The control group received no treatment. **Concomitant therapy:** Subjects were required to perform the home program daily 5 days a week for 4 weeks. During this period, they attended 8 instruction sessions to ensure they could complete the exercise program.			
Ng 2009[90]	**Transcutaneous electrical stimulation (TENS)** (n=55) Two groups: The TENS group received 60 minutes of TENS. The TENS + exercise group received 60 minutes of the same TENS protocol followed by 60 minutes of task-related exercises recommended for stroke rehabilitation. Follow up at 8 weeks. **Placebo/sham** (n=25) The placebo stimulation + exercise group performed 60 minutes of the same exercise after receiving 60 minutes of placebo stimulation from identical looking stimulation devices, but with the electrical circuit disconnected inside.	**People after a first or recurrent stroke** Mean age (SD): 56.7 (8.1) years N = 109 Type of Spasticity: Focal Severity of spasticity: Moderate to Severe Mean time period since stroke (SD): 4.7 (3.4) years	Physical function –lower limb at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Outpatient setting in China. Sources of funding: This study was supported by the Health Service Research Fund (# K-ZK34) from the Hong Kong Government (SAR), and a scholarship from The Hong Kong Polytechnic University to S. Ng.

Study	Intervention and comparison	Population	Outcomes	Comments
	Usual care or no treatment (n=29) The control group received no treatment, and they just attended four assessment sessions. **Concomitant therapy:** No additional information			
Park 2014[97]	**Transcutaneous electrical nerve stimulation (TENS)** (n=17) TENS plus therapeutic exercise group. Stimulation was 30 min, and the patient perceived no sensation. TENS was used with the general exercise program. Follow up at 6 weeks. **Placebo/sham** (n=17) Placebo TENS plus therapeutic exercise group. Stimulation was not applied and patients were informed that the treatment would be imperceptible. **Concomitant therapy:** Participants in the 2 groups engaged in the same 30-min therapeutic exercise 5 days per week for 6 weeks.	**People after a first or recurrent stroke** Mean age (SD): 71.2 (3.6) years N = 29 Type of Spasticity: Focal Mean severity of spasticity (SD): 2.6 (0.70) Mean time period since stroke (SD): 18.6 (2.13) months	Spasticity outcome measures at ≤6 months Physical function – lower limb at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: 4 rehabilitation hospitals in Seoul, South Korea. Sources of funding: This research was supported by a Sahmyook University Research Grant.
Sonde 1998[119] Subsidiary paper: Sonde 2000[120]	**Transcutaneous electrical nerve stimulation (TENS)** (n=24) The treatment group received low-TENS (frequency of 1.7hz in pulse	**People after a first or recurrent stroke** Mean age (SD): 72 (5) years N = 28 Type of Spasticity: Focal	Spasticity outcome measures at ≤6 months and >6 months Activities of daily living at ≤6 months and >6 months	Setting: Outpatients in Sweden. Sources of funding: Supported by funds from the Regional Social Insurance Office in collaboration with the

Study	Intervention and comparison	Population	Outcomes	Comments
	trains- eight pulses with an interval of 14ms) for 60 min, 5 days a week for 3 months. Follow up at 3 years. **Usual care or no treatment** (n=18) **Concomitant therapy**: Both groups received physiotherapy at the day centre, usually twice a week.	Severity of spasticity: Mild (or MAS 1) Time period since stroke range: Chronic (≥6 months)	Physical function – upper limb at ≤6 months and >6 months Withdrawal due to adverse events at ≤6 months and >6 months	Stockholm County Council, The committee for the Health and Caring sciences, Karolinska Institute and Foundation for Stroke Research.
Tekeoglu 1998[126]	**Transcutaneous electrical nerve stimulation (TENS)** (n=30) TENS stimulation: square pulses of 0.2 m s duration were delivered at a frequency of 100 per second. Follow up for 8 weeks. **Placebo/sham** (n=30) Sham TENS. **Concomitant therapy:** All the patients were treated using the Todd–Davies exercise programme. The study lasted eight weeks for total of 40 sessions. Both groups of patients received the same type of exercise programme every day in the morning.	**People after a first or recurrent stroke** Mean age (SD): 54.1 (6.5) years N = 60 Type of Spasticity: Focal spasticity Severity of spasticity: Mild (or MAS 1) Time period since stroke range: Subacute (7 days - 6 months)	Spasticity outcome measures at ≤6 months Activities of daily living at ≤6 months	Setting: Medical Faculty of Yüzüncü Yy'l University in Turkey. Sources of funding: Not reported.
Yan 2009[140]	**Transcutaneous electrical nerve stimulation (TENS)** (n=21) Treatment for TENS lasted 60 min per session, 5	**People after a first or recurrent stroke** Mean age (SD): 70.5 (8.5) years N = 56	Spasticity outcome measures at ≤6 months Physical function – lower limb at ≤6 months	Setting: Department of Rehabilitation Medicine in China. Sources of funding: supported by a grant from The Hong Kong

Study	Intervention and comparison	Population	Outcomes	Comments
	days a week for 3 weeks. Follow up at 8 weeks. **Placebo/sham** (n=21) Placebo stimulation was applied using the same electrodes, locations and device, with the circuit disconnected. **Usual care or no treatment** (n=20) **Concomitant therapy:** All participants received the same SR including both physiotherapy and occupational therapy, each lasting for 60 min.	Type of Spasticity: Focal Severity of spasticity: Mild (or MAS 1) Time period since stroke range: Subacute (7 days - 6 months)		Polytechnic University.
Zhou 2018[149]	**Neuromuscular electrical stimulation (NMES)** (n=36) The 4-week treatment consisted of 20 sessions, each session composed of 1 hour of stimulation per day. Follow up at 8 weeks. **Transcutaneous electrical nerve stimulation (TENS)** (n=36) TENS for the same frequency and duration. **Usual care or no treatment** (n=18) Conventional rehabilitation only. **Concomitant therapy:**	**People after a first or recurrent stroke** Mean age (SD): 59.9 (10.4) years N = 90 Type of Spasticity: Focal Severity of spasticity: Mild (or MAS 1) Time period since stroke range: Subacute (7 days - 6 months)	Spasticity outcome measures at ≤6 months Physical function – upper limb at ≤6 months Pain at ≤6 months Activities of daily living at ≤6 months Stroke-specific Patient-Reported Outcome at ≤6 months	Setting: Hospital rehabilitation centre in China. Sources of funding: Research fund of the Baoshan district committee of science and technology, Shanghai, China.

Study	Intervention and comparison	Population	Outcomes	Comments
	Patients in all groups underwent a standardised rehabilitation programme.			

1.5.1.10 Acupuncture/dry needling

Table 10: Summary of studies including acupuncture/dry needling as an intervention in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Alexander 2004[1]	**Acupuncture/dry needling** (n=16) 30 minutes of acupuncture therapy 7 days per week for 2 weeks. Follow up at 2 weeks. **Usual care or no treatment** (n=16) **Concomitant therapy:** Conventional stroke rehabilitation care included 3 hours of physical, occupational and/or speech therapy, 6 days per week for the duration of the inpatient stay.	**People after a first or recurrent stroke** Mean age (SD): 61.1 (11.8) years N = 32 Type of Spasticity: Generalised Severity of spasticity: Not reported Mean time period since stroke (SD): 22.1 (5.1) days	Physical function – general at ≤6 months Activities of daily living at ≤6 months Withdrawal due to adverse events ≤6 months	Setting: Stroke inpatient rehabilitation unit in the United States of America. Sources of funding: Supported in part by The Lucy Gonda Foundation.
Calvo 2022[9]	**Acupuncture/dry needling** (n=11) Dry needling for 60 minute sessions over 2 weeks. **Placebo/sham** (n=12) Sham dry needling with superficial placement of needles. **Concomitant therapy:** No additional information.	**People after a first or recurrent stroke** Mean age (SD): 60.8 (15.5) years N = 32 Type of Spasticity: Focal Severity of spasticity: Not reported Mean time period since stroke (SD): 6.0 (5.2) years	Person/participant generic health-related quality of life at ≤6 months Spasticity outcome measures at ≤6 months Physical function – upper limb at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Conducted in Spain. Sources of funding: No financial support.
Ghannadi 2020[34]	**Acupuncture/dry needling** (n=12)	**People after a first or recurrent stroke**	Spasticity outcome	Setting: Conducted in Iran.

Study	Intervention and comparison	Population	Outcomes	Comments
	Dry needling in three sessions spaced across one week, with at least 48 hours between treatment sessions. Follow up at 1 month. **Placebo/sham** (n=12) The sham treatment was applied exactly at the same area of the standard dry needling, with blunted dry needling. **Concomitant therapy:** No additional information	Mean age (SD): 57.0 (9.8) years N = 24 Type of Spasticity: Focal Severity of spasticity: Modified Ashworth Scale score ≥1 Mean time period since stroke (SD): 25.2 (12.7) months Severity: Not stated/unclear	measures at ≤6 months Physical function – lower limb at ≤6 months Activities of daily living at ≤6 months	Sources of funding: No additional information
Li 2014[6627]	**Acupuncture/dry needling** (n=121) Patients received 20 sessions of verum acupuncture in 4 weeks. Follow up at 12 weeks. **Sham acupuncture** (n=117) The points used in the sham acupuncture group located 0.1 cm lateral to the lower border of the 2nd, 4th, 6th, 8th, 10th, and 12th thoracic vertebra and the 2nd and 4th lumber vertebra. Piercing vertically, needles are inserted 5 mm in depth and remained for 30 minutes without moxibustion or electrical stimulation, with no needling sensation. **Concomitant therapy:** In	**People after a first or recurrent stroke** Mean age (SD): 63.7 (10.4) years N = 238 Type of Spasticity: Generalised Mean severity of spasticity (SD) – Modified Ashworth Scale: 12.7 (6.8) Mean time period since stroke (SD): 11.6 (7.2) days	Spasticity outcome measures at ≤6 months Physical function – general at ≤6 months Activities of daily living at ≤6 months Stroke-Specific Patient-Reported Outcome Measures at ≤6 months	Setting: Inpatient centre in China. Sources of funding: No additional information.

Study	Intervention and comparison	Population	Outcomes	Comments
	addition to acupuncture, the basic therapies for cerebrovascular disease were used in all the enrolled patients, including antiplatelet therapy, management of intracranial pressure and blood pressure, neuroprotective agents, treatment of complications, rehabilitation therapy.			
Liao 2017[67]	**Acupuncture/dry needling** (n=28) Manual acupuncture was carried out in patients in the supine position and comprised both body and scalp acupuncture for a total of 20 minutes per session 3 times per week for a total of 24 sessions. Follow up at 8 weeks. **Placebo/sham** (n=20) 24 sessions of acupuncture treatment; however, needling was performed 1 cm away from the real acupoints. In addition, none of the participants in the sham group received scalp acupuncture. No needle sensation (de qi) was elicited. **Concomitant therapy:** Patients in both groups also received conventional western rehabilitation with the same frequency	**People after a first or recurrent stroke** Mean age (SD): 59.4 (14.0) years N = 48 Type of Spasticity: Generalised Severity of spasticity: Not reported Mean time period since stroke: Not reported	Activities of daily living at ≤6 months Pain at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: No additional information. Conducted in China. Sources of funding: This study was supported by China Medical University under the Aim for Top University Plan of the Ministry of Education, Taiwan, and The Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW105-TDU-B-212-133019).

Study	Intervention and comparison	Population	Outcomes	Comments
	and received western medications as needed during inpatient admission and outpatient tracking.			
Tavakol 2021[125]	**Acupuncture/dry needling** (n=12) Dry needling was delivered for three sessions, separated by a 48-hours interval between sessions. Each muscle was needled for 1 minute. Follow up at 4 weeks. **Placebo/sham** (n=12) Sham needling was delivered for three sessions, separated by a 48-hours interval between sessions. **Concomitant therapy:** All patients were instructed not to have any other treatments during the study and follow up period, including other physical therapy treatments, medications, acupuncture, or dry needling.	**People after a first or recurrent stroke** Mean age (SD): 57 (9.6) years N = 24 Type of Spasticity: Focal Severity of spasticity: Mild (or MAS 1) Time period since stroke range: Chronic (≥6 months)	Physical function –upper limb at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Sports Medicine Research Center, Tehran University of Medical Sciences in Iran. Sources of funding: Supported by the Sports Medicine Research Center, Neuroscience Institute, Tehran University of Medical Sciences.
Wang 2019[132]	**Acupuncture/dry needling** (n=30) Patients received 6 consecutive sessions of acupuncture treatments for 4 weeks. Follow up at 4 weeks. **Usual care or no treatment**	**People after a first or recurrent stroke** Mean age (SD) 57.8 (7.4) years N = 59 Type of Spasticity: Focal Severity of spasticity: Moderate (or MAS 2)	Spasticity outcome measures at ≤6 months Physical function – lower limb at ≤6 months Activities of daily living at ≤6 months Withdrawal due to adverse	Setting: Department of Rehabilitation at Yueyang hospital in China. Sources of funding: Supported by the scientific research fund of Traditional Chinese Medicine of Shanghai Municipal Health and Family Planning

Study	Intervention and comparison	Population	Outcomes	Comments
	(n=29) **Concomitant therapy:** Both groups received standard routine internal medicine care, including blood pressure control and treatment of complications and exercise therapy 6 consecutive days per week for 4 weeks.	Time period since stroke range: Subacute (7 days - 6 months)	events at ≤6 months	Commission (no. 2018LP016).
Wayne 2005[135]	**Acupuncture/no treatment** (n=16) Treatments were administered twice weekly for 10 weeks. Both manual and electrostimulation were applied to the body points, while manual stimulation only was applied to the scalp points. Follow up at 3 months. **Sham acupuncture** (n=17) Administered twice weekly for 10 weeks. At each body treatment visit, 4 to 6 sham needles were placed at predetermined locations at least 1cm away from any acupuncture point. **Concomitant therapy:** Not reported	**People after a first or recurrent stroke** Mean age (SD): Not reported N = 33 Type of Spasticity: Generalised Severity of spasticity: Mild (or MAS 1) Time period since stroke range: Chronic (≥6 months)	Person/participant generic health-related quality of life at ≤6 months Spasticity outcome measures at ≤6 months Physical function – upper limb at ≤6 months Activities of daily living at ≤6 months	Setting: Spaulding Rehabilitation Hospital's Stroke Service in the United States of America. Sources of funding: Supported by an anonymous philanthropic foundation grant to the New England School of Acupuncture.
Zhang 2021[146]	**Acupuncture** (n=83) Two groups were combined, one receiving traditional acupuncture and one receiving staging	**People after a first or recurrent stroke** Mean age (SD): 65.1 (11.1) years N = 125	Physical function – general at ≤6 months Activities of daily living at ≤6 months	Reported in forest plots as Zhang 2021A Setting: Inpatients in the Second Affiliated Hospital of Nanjing

Study	Intervention and comparison	Population	Outcomes	Comments
	acupuncture lasting 20 minutes were performed once a day for 28 days. Follow up at 4 weeks. **Usual care or no treatment** (n=40) **Concomitant therapy:** Patients received basic rehabilitation exercises therapy, including comprehensive training of hemiplegic limbs, balance training and daily living ability training.	Type of Spasticity: Focal Severity of spasticity: Not stated/unclear Time period since stroke range: Subacute (7 days - 6 months)		Medical University in China. Sources of funding: Science and Development Fund of Nanjing Medical University (2016NJMU038).
Zhang 2021[147]	**Acupuncture** (n=70) Dry needling five times a week (30 minute each time) for 4 weeks. **Placebo/sham** (n=70) Sham dry needling for the same time and duration with insertion lateral to the myofascial trigger point without manual stimulation. **Usual care or no treatment** (n=70) **Concomitant therapy:** Patients received routine rehabilitation therapy including physiotherapy.	**People after a first or recurrent stroke** Mean age (SD): 64.7 (10.1) years N = 210 Type of Spasticity: Focal Severity of spasticity: Not stated/unclear Mean time period since stroke (SD): 12.9 (3.1) months	Withdrawal due to adverse events at ≤6 months	Reported in forest plots as Zhang 2021B Setting: Inpatients in China. Sources of funding: Government/academic grants.
Zhong 2002[148]	**Acupuncture** (n=48) Acupuncture therapy lasting 4 weeks. **Usual care or no treatment** (n=48)	**People after a first or recurrent stroke** Mean age (SD): Not reported N = 96 Type of Spasticity: Focal	Physical function – general at ≤6 months Activities of daily living at ≤6 months 4 weeks	Setting: Not reported. Conducted in China. Sources of funding: Not reported.

Study	Intervention and comparison	Population	Outcomes	Comments
	Concomitant therapy: All cases were given corresponding drugs regularly. After the condition was stable, cases of the 2 groups were performed basal rehabilitation therapy.	Severity of spasticity: Mild (or MAS 1) Time period since stroke range: Not reported		

1.5.1.11 Electroacupuncture

Table 11: Summary of studies including electroacupuncture as an intervention in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Gong 2009[25]	**Electroacupuncture** (n=124) Electroacupuncture was administered 5 times per week, once per day, 30 minutes per session and the intervention was 6 weeks in total. Follow up at 6 weeks. **Usual care or no treatment** (n=116) No acupuncture treatment. **Concomitant therapy:** Drugs related to motor function, such as muscle relaxants, were not administered to either group.	**People after a first or recurrent stroke** Mean age: 58.0 years N = 240 Type of Spasticity: Generalised Severity of spasticity: Not reported Time period since stroke: Not reported	Spasticity outcome measures at ≤6 months Physical function – lower limb at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: The Department of Neurological Rehabilitation, China Rehabilitation Research Centre (inpatient) in China. Sources of funding: Supported by the Foundation from China Rehabilitation Research Centre, No. 2007-15.
Moon 2003[82]	**Electroacupuncture** (n=15) All patients received the same routine acupuncture therapy for stroke and range of motion exercises once per day. Steel needles were used and were kept in place for 30	**People after a first or recurrent stroke** Mean age (SD): 61.0 (10.3) years N = 45 Type of Spasticity: Generalised Severity of spasticity: Severe (or MAS 3)	Spasticity outcome measures at ≤6 months	Setting: Inpatient in Korea. Sources of funding: Supported in part by The Lucy Gonda Foundation.

Study	Intervention and comparison	Population	Outcomes	Comments
	minutes at a time. Electrical stimulation was applied every other day for 15 days (8 sessions) with a frequency of 50Hz administered to the four needles on the Ch'u-Ch'ih-San-Li and Wai-Huan-Ho-Ku points of the paretic side for 30 minutes at a time. Follow up at 15 days. **Acupuncture** (n=10) All patients received the same routine acupuncture therapy for stroke and range of motion exercises once per day. **Concomitant therapy:** No additional information	Mean time period since stroke (SD): 3.3 (3.0) months		

1.5.1.12 Combination therapy

Table 12: Summary of studies including combination therapy as an intervention in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Ding 2017[21]	**Combination therapy: Functional Electrical Stimulation (FES) and Onabotulinum Toxic A (BOTOX)** (n=41) Normal saline (4 µl) was used to dilute 100 units BTX-A to reach 25 units/1 ml. Each target muscle was injected at 3-5 points, with a total dose of 350 units. FES for one	**People after a first or recurrent stroke** Mean age (SD): 61.9 (6.7) years N = 80 Type of Spasticity: Focal Mean severity of spasticity (SD) – Modified Ashworth Scale: 4.1 (0.56)	Spasticity outcome measures at ≤6 months Physical function – upper limb at ≤6 months Activities of daily living at ≤6 months	Setting: Xiangyang No. 1 People's Hospital, China. Sources of funding: No additional information.

Study	Intervention and comparison	Population	Outcomes	Comments
	treatment course was 10 days, with a total of three treatment courses. Follow up at 12 weeks. **Onabotulinum toxin A (BOTOX) alone** (n=39) Botulinum toxin A injection alone (administered with same protocol as intervention group). **Concomitant therapy:** No additional information.	Mean time period since stroke (SD): 126.6 (29.5) days		
Marco 2007[75]	**Combination therapy: Onabotulinum Toxin A (BOTOX) and Transcutaneous electrical nerve stimulation (TENS)** (n=14) 500 units of onabotulinum toxin A injected into four sites. Follow up at 6 months. **Placebo and TENS** (n=15) Placebo in place of onabotulinum toxin A injection. **Concomitant therapy:** Subsequently, all the patients were treated with conventional TENS, consisting of short pulses (250 μsec) of high frequency (75 megahertz) and low intensity for a 6-week period. People underwent training in activities of daily living.	**People after a first or recurrent stroke** Mean age (SD): 65.6 (9.2) years N = 31 Type of Spasticity: Focal Severity of spasticity: Severe (or MAS 3) Mean time period since stroke (range): Intervention: 153 (89 to 263) days	Spasticity outcome measures at ≤6 months Pain at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Rehabilitation unit in an acute-care general hospital in Spain. Sources of funding: Institut Municipal d'Investigacio Mèdica provided a grant.

Study	Intervention and comparison	Population	Outcomes	Comments
Hesse 1998[45]	**Combination therapy: Abobotulinum toxin type A (Dysport) and neuromuscular electrical stimulation (NMES)** (n=6) 1000 units of Botulinum Toxin type A (Dysport) into biceps brachii, brachialis (each 250 units), flexor carpi ulnaris, flexor carpi radialis, flexor digitorum profundus et superficialis (each 125 units) at two sites per muscle, close to the motor point. An IJS dual channel stimulator with continuous trains (3s) of charge-balanced constant current pulses (20 Hz, 200 microseconds, 50-90 mA) was used for stimulation. Follow up at 12 weeks. **Abobotulinum toxin type A (Dysport)** (n=6) Abobotulinum toxin type A only. **Neuromuscular electrical stimulation (NMES)** (n=6) NMES and injection with 0.9% saline instead of abobotulinum toxin type A. **Placebo/sham** (n=6) 0.9% normal saline injection only. **Concomitant therapy:** All	**People after a first or recurrent stroke** Mean age: 52.3 years N = 24 Type of Spasticity: Focal Severity of spasticity: Not reported Mean time period since stroke: 7.45 months	Spasticity outcome measures at ≤6 months Withdrawal due to adverse events at ≤6 months	Setting: Outpatient clinic in Germany. Sources of funding: This study was supported by a grant of Speywood Pharmaceuticals Ltd, UK, who supplied the botulinum toxin and placebo used in this study.

Study	Intervention and comparison	Population	Outcomes	Comments
	received an average of two physiotherapeutic treatment sessions for half an hour per week, which did not change during the course of the study. The amount of therapy did not differ across the groups and was unanimously applied by the Bobath techniques. None of the patients received a concomitant anti-spastic medication during the study.			

1 See Appendix D for full evidence tables.

1.1.5.13 Summary matrices

1.1.5.13.1 Focal spasticity

Table 13: Summary matrix of the protocol interventions compared to placebo for people with focal spasticity

		Tizanidine	Other oral medicine	Intrathecal medicine	Onabotulinum toxin A (BOTOX)	Abobotulinum toxin A (Dysport)	Incobotulinum toxin A (Xeomin)	Functional electrical stimulation (FES)	Neuromuscular electrical stimulation (NMES)	Transcutaneous electrical nerve stimulation (TENS)	Acupuncture	Electroacupuncture
Person/participant generic health-related quality of life	≤6 months	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=28 Low	1 outcome (1 study) N=96 Low	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=23 Moderate	No evidence identified
Person/participant generic health-related quality of life	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Carer generic health-related quality of life	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Carer generic health-	>6 months	No evidence	No evidence	No evidence	No evidence identified	No evidence identified	No evidence identified	No evidence	No evidence identified	No evidence identified	No evidence identified	No evidence identified

		Tizanidine	Other oral medicine	Intrathecal medicine	Onabotulinum toxin A (BOTOX)	Abobotulinum toxin A (Dysport)	Incobotulinum toxin A (Xeomin)	Functional electrical stimulation (FES)	Neuromuscular electrical stimulation (NMES)	Transcutaneous electrical nerve stimulation (TENS)	Acupuncture	Electroacupuncture
related quality of life		identified	identified	identified				identified				
Spasticity outcome measures	≤6 months	1 outcome (1 study) N=37 Very low	No evidence identified	No evidence identified	1 outcome (8 studies) N=1043 Moderate-very low	2 outcomes (7 studies) N=702 Very low	1 outcome (2 studies) N=467 High	1 outcome (1 study) N=28 Very low	1 outcome (3 studies) N=108 Moderate	1 outcome (5 studies) N=232 Low-very low	1 outcome (2 studies) N=47 Very low	No evidence identified
Spasticity outcome measures	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=40 Low	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Physical function – general	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Physical function – general	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Physical function – upper limb	≤6 months	No evidence	No evidence	No evidence	2 outcomes (4 studies) N=170	1 outcome (1 study)	No evidence identified	No evidence	1 outcome (3 studies) N=108	No evidence identified	2 outcome (2 studies) N=65	No evidence identified

		Tizanidine	Other oral medicine	Intrathecal medicine	Onabotulinum toxin A (BOTOX)	Abobotulinum toxin A (Dysport)	Incobotulinum toxin A (Xeomin)	Functional electrical stimulation (FES)	Neuromuscular electrical stimulation (NMES)	Transcutaneous electrical nerve stimulation (TENS)	Acupuncture	Electroacupuncture
		identified	identified	identified	Moderate/very low	N=82 Very low		identified	Low		Moderate-very low	
Physical function – upper limb	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Physical function – lower limb	≤6 months	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=23 Moderate	1 outcome (1 studies) N=218 Moderate	1 outcome (1 study) N = 116 Very low	2 outcomes (2 studies) N=54 Very low	No evidence identified	1 outcome (4 studies) N=181 Low-very low	1 outcome (1 study) N=24 Low	No evidence identified
Physical function – lower limb	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Pain	≤6 months	No evidence identified	No evidence identified	No evidence identified	1 outcome (2 studies) N=504 Very low	1 outcome (2 studies) N=259 Low	No evidence identified	1 outcome (1 study) N=208 Moderate	1 outcome (1 study) N=14 Very low	No evidence identified	No evidence identified	No evidence identified

		Tizanidine	Other oral medicine	Intrathecal medicine	Onabotulinum toxin A (BOTOX)		Abobotulinum toxin A (Dysport)	Incobotulinum toxin A (Xeomin)	Functional electrical stimulation (FES)	Neuromuscular electrical stimulation (NMES)	Transcutaneous electrical nerve stimulation (TENS)	Acupuncture	Electroacupuncture
Pain	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified		No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Activities of daily living	≤6 months	No evidence identified	No evidence identified	No evidence identified	2 outcome (3 studies) N=258 Moderate		1 outcome (3 studies) N=483 High	No evidence identified	1 outcome (1 study) N=26 Very low	1 outcome (1 study) N=30 Very low	1 outcome (2 studies) N=103 Very low	1 outcome (1 study) N=24 Very low	No evidence identified
Activities of daily living	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified		No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Stroke-specific Patient-Reported Outcome Measures	≤6 months	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=36 Moderate	11 outcomes (1 study) N=36 Moderate-Low	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=39 Low	No evidence identified	No evidence identified	No evidence identified
Stroke-specific Patient-Reported	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

		Tizanidine	Other oral medicine	Intrathecal medicine	Onabotulinum toxin A (BOTOX)		Abobotulinum toxin A (Dysport)	Incobotulinum toxin A (Xeomin)	Functional electrical stimulation (FES)	Neuromuscular electrical stimulation (NMES)	Transcutaneous electrical nerve stimulation (TENS)	Acupuncture	Electroacupuncture
Outcome Measures													
Additional health care contacts	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	2 outcomes (1 study) N=48 Low-Very low	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Additional health care contacts	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Hospitalisation	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=48 Very low	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Hospitalisation	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

		Tizanidine	Other oral medicine	Intrathecal medicine	Onabotulinum toxin A (BOTOX)		Abobotulinum toxin A (Dysport)	Incobotulinum toxin A (Xeomin)	Functional electrical stimulation (FES)	Neuromuscular electrical stimulation (NMES)	Transcutaneous electrical nerve stimulation (TENS)	Acupuncture	Electroacupuncture
Stroke outcome – modified Rankin scale	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=163 Very low	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Stroke outcome – modified Rankin scale	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Withdrawal due to adverse events	≤6 months	1 outcome (1 study) N=40 Very low	No evidence identified	No evidence identified	1 outcome (15 studies) N=2255 Very low	1 outcome (7 studies) N=859 Very low	No evidence identified	1 outcome (3 studies) N=456 Low	1 outcome (2 studies) N=87 Very low	1 outcome (8 studies) N=393 Very low	1 outcome (1 study) N=24 Low	1 outcome (3 studies) N=187 Very low	No evidence identified
Withdrawal due to adverse events	>6 months	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=274 Very low	No evidence identified	1 outcome (3 studies) N=507 Low	1 outcome (1 study) N=259 Moderate	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

Table 14: Summary matrix of the protocol interventions compared to usual care for people with focal spasticity

		Tizanidine	Other oral medicine	Intrathecal medicine	Onabotulinum toxin A (BOTOX)	Abobotulinum toxin A (Dysport)	Incobotulinum toxin A (Xeomin)	Functional electrical stimulation (FES)	Neuromuscular electrical stimulation (NMES)		Transcutaneous electrical nerve stimulation (TENS)	Acupuncture	Electroacupuncture
Person/participant generic health-related quality of life	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=283 Very low	No evidence identified	No evidence identified	No evidence identified		No evidence identified	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=174 Very low	No evidence identified	No evidence identified	No evidence identified		No evidence identified	No evidence identified	No evidence identified
Carer generic health-related quality of life	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified		No evidence identified	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified		No evidence identified	No evidence identified	No evidence identified
Spasticity outcome measures	≤6 months	No evidence identified	No evidence identified	No evidence identified	1 outcome (2 studies) N= 94 Very Low	1 outcome (1 study) N=314 Moderate	1 outcome (1 study) N=17 Very low	2 outcomes (3 studies) N=114 Very low	1 outcome (3 studies) N=134	1 outcome (7 studies) N=285	1 outcome (4 studies) N=161 Very low	1 outcome (1 study) N=59	No evidence identified

		Tizanidine	Other oral medicine	Intrathecal medicine	Onabotulinum toxin A (BOTOX)	Abobotulinum toxin A (Dysport)	Incobotulinum toxin A (Xeomin)	Functional electrical stimulation (FES)	Neuromuscular electrical stimulation (NMES)		Transcutaneous electrical nerve stimulation (TENS)	Acupuncture	Electroacupuncture
									Very low	Moderate		Moderate	
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=189 Moderate	No evidence identified	No evidence identified	No evidence identified		1 outcome (1 study) N=28 Very low	No evidence identified	No evidence identified
Physical function – general	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified		No evidence identified	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified		No evidence identified	No evidence identified	No evidence identified
Physical function – upper limb	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=314 Moderate	1 outcome (1 study) N=17 Low	1 outcome (1 study) N=30 Very low	1 outcome (5 studies) N=152 moderate	1 outcome (1study) N=54 Very low	2 outcomes (3 studies) N=114 Low-Very low	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=189 Moderate	No evidence identified	No evidence identified	No evidence identified		1 outcome (1 study) N=28 Very low	No evidence identified	No evidence identified

		Tizanidine	Other oral medicine	Intrathecal medicine	Onabotulinum toxin A (BOTOX)		Abobotulinum toxin A (Dysport)	Incobotulinum toxin A (Xeomin)	Functional electrical stimulation (FES)		Neuromuscular electrical stimulation (NMES)		Transcutaneous electrical nerve stimulation (TENS)		Acupuncture	Electroacupuncture
Physical function – lower limb	≤6 months	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N= 26 Very Low	1 outcome (1 study) N= 68 Very low	No evidence identified	No evidence identified	2 outcomes (4 studies) N=657 Very low	1 outcome (1 study) N=26 Low	3 outcomes (3 studies) N=126 High-Low		1 outcome (1 study) N=115 Very low	1 outcome (1 study) N=32 Very low	1 outcome (1 study) N=85 Moderate	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified		No evidence identified	No evidence identified	No evidence identified		No evidence identified		No evidence identified		No evidence identified	No evidence identified
Pain	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified		1 outcome (1 study) N=314 Low	No evidence identified	No evidence identified		2 outcomes (3 studies) N=123 Very low		1 outcome (1 study) N=54 Very low		No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified		1 outcome (1 study) N=189 Very low	No evidence identified	No evidence identified		No evidence identified		No evidence identified		No evidence identified	No evidence identified
Activities of daily living	≤6 months	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N= 68 Very low		1 outcome (1 study) N=314 Moderate	1 outcome (1 study) N=17 Very low	1 outcome (2 studies) N=67 Low		1 outcome (3 studies)	1 outcome (1 study) N= 54	1 outcome (3 studies) N=106 Low		1 outcome (1 study) N=59	No evidence identified

		Tizanidine	Other oral medicine	Intrathecal medicine	Onabotulinum toxin A (BOTOX)	Abobotulinum toxin A (Dysport)	Incobotulinum toxin A (Xeomin)	Functional electrical stimulation (FES)	Neuromuscular electrical stimulation (NMES)	Transcutaneous electrical nerve stimulation (TENS)	Acupuncture	Electroacupuncture
									N=128 Very low Very low		Low	
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=189 Moderate	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=28 Very low	No evidence identified	No evidence identified
Stroke-specific Patient-Reported Outcome Measures	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	10 outcomes (1 study) N=314 Low	No evidence identified	1 outcome (1 study) N=495 Low	1 outcome (1 study) N=54 Very low	1 outcome (1 study) N=41 Very low	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	10 outcomes (1 study) N=189 Low	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Additional health care contacts	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Hospitalisation	≤6 mo	No evide	No evide	No evide	No evidence identified	No evidence identified	No evidenc	No evidence identified	No evidence identified	No evidence identified	No evidenc	No evid

		Tizanidine	Other oral medicine	Intrathecal medicine	Onabotulinum toxin A (BOTOX)	Abobotulinum toxin A (Dysport)	Incobotulinum toxin A (Xeomin)	Functional electrical stimulation (FES)	Neuromuscular electrical stimulation (NMES)	Transcutaneous electrical nerve stimulation (TENS)	Acupuncture	Electroacupuncture
	nths	nce identified	nce identified	nce identified			e identified				e identified	ence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Stroke outcome – modified Rankin scale	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Withdrawal due to adverse events	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=18 Very low	1 outcome (4 studies) N=620 Very low	1 outcome (11 studies) N=500 Very low	1 outcome (5 studies) N=281 Very low	1 outcome (2 studies) N=199 Moderate	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=44 Very low	No evidence identified	No evidence identified

Table 15: Summary matrix of the protocol interventions compared to other protocol interventions for people with focal spasticity

		Onabotulinum toxin A (BOTOX) compared to Tizanidine	Abobotulinum toxin A (Dysport) compared to Tizanidine	Incobotulinum toxin A (Xeomin) compared to oral baclofen	Abobotulinum toxin A (Dysport) compared to neuromuscular electrical stimulation	Neuromuscular electrical stimulation (NMES) compared to transcutaneous electrical nerve stimulation (TENS)	Combination therapy: Abobotulinum toxin A (Dysport) and transcutaneous electrical nerve stimulation (TENS) compared to placebo and TENS	Combination therapy: Onabotulinum toxin A (BOTOX) and functional electrical stimulation compared to onabotulinum toxin A (BOTOX) alone	Combination therapy: Abobotulinum toxin A (Dysport) and NMES compared to abobotulinum toxin A (Dysport) alone	Combination therapy: Abobotulinum toxin A (Dysport) and NMES compared to NMES alone
Person/participant generic health-related quality of life	≤6 months	No evidence identified	No evidence identified	1 outcome (1 study) N=34 Very low	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Carer generic health-related quality of life	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Spasticity outcome measures	≤6 months	1 outcome (1 study) N=37	1 outcome (1 study) N=68	1 outcome (1 study) N=34	1 outcome (1 study) N=12	1 outcome (1 study) N=49	1 outcome (1 study) N=29	1 outcome (1 study) N=80	1 outcome (1 study) N=12	1 outcome (1 study) N=12

		Onabotulinum toxin A (BOTOX) compared to Tizanidine	Abobotulinum toxin A (Dysport) compared to Tizanidine	Incobotulinum toxin A (Xeomin) compared to oral baclofen	Abobotulinum toxin A (Dysport) compared to neuromuscular electrical stimulation	Neuromuscular electrical stimulation (NMES) compared to transcutaneous electrical nerve stimulation (TENS)	Combination therapy: Abobotulinum toxin A (Dysport) and transcutaneous electrical nerve stimulation (TENS) compared to placebo and TENS	Combination therapy: Onabotulinum toxin A (BOTOX) and functional electrical stimulation compared to onabotulinum toxin A (BOTOX) alone	Combination therapy: Abobotulinum toxin A (Dysport) and NMES compared to abobotulinum toxin A (Dysport) alone	Combination therapy: Abobotulinum toxin A (Dysport) and NMES compared to NMES alone
		Very low	Low	Very low	Very low	Low	Low	Very low	Very low	Very low
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Physical function – general	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Physical function – upper limb	≤6 months	No evidence identified	1 outcome (1 study) N=68 Low	1 outcome (1 study) N=34 Very low	No evidence identified	1 outcome (1 study) N=72 Very Low	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

		Onabotulinum toxin A (BOTOX) compared to Tizanidine	Abobotulinum toxin A (Dysport) compared to Tizanidine	Incobotulinum toxin A (Xeomin) compared to oral baclofen	Abobotulinum toxin A (Dysport) compared to neuromuscular electrical stimulation	Neuromuscular electrical stimulation (NMES) compared to transcutaneous electrical nerve stimulation (TENS)	Combination therapy: Abobotulinum toxin A (Dysport) and transcutaneous electrical nerve stimulation (TENS) compared to placebo and TENS	Combination therapy: Onabotulinum toxin A (BOTOX) and functional electrical stimulation compared to onabotulinum toxin A (BOTOX) alone	Combination therapy: Abobotulinum toxin A (Dysport) and NMES compared to abobotulinum toxin A (Dysport) alone	Combination therapy: Abobotulinum toxin A (Dysport) and NMES compared to NMES alone
Physical function – lower limb	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=80 Low	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Pain	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=72 Very low	1 outcome (1 study) N=29 Moderate	No evidence identified	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Activities of daily living	≤6 months	No evidence identified	No evidence identified	1 outcome (1 study) N=34 Very low	No evidence identified	1 outcome (1 study) N=72 Very low	No evidence identified	1 outcome (1 study) N=80 Low	No evidence identified	No evidence identified

		Onabotulinum toxin A (BOTOX) compared to Tizanidine	Abobotulinum toxin A (Dysport) compared to Tizanidine	Incobotulinum toxin A (Xeomin) compared to oral baclofen	Abobotulinum toxin A (Dysport) compared to neuromuscular electrical stimulation	Neuromuscular electrical stimulation (NMES) compared to transcutaneous electrical nerve stimulation (TENS)	Combination therapy: Abobotulinum toxin A (Dysport) and transcutaneous electrical nerve stimulation (TENS) compared to placebo and TENS	Combination therapy: Onabotulinum toxin A (BOTOX) and functional electrical stimulation compared to onabotulinum toxin A (BOTOX) alone	Combination therapy: Abobotulinum toxin A (Dysport) and NMES compared to abobotulinum toxin A (Dysport) alone	Combination therapy: Abobotulinum toxin A (Dysport) and NMES compared to NMES alone
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Stroke-specific Patient-Reported Outcome Measures	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=72 Very low	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Additional health care contacts	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Hospitalisation	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

		Onabotulinum toxin A (BOTOX) compared to Tizanidine	Abobotulinum toxin A (Dysport) compared to Tizanidine	Incobotulinum toxin A (Xeomin) compared to oral baclofen	Abobotulinum toxin A (Dysport) compared to neuromuscular electrical stimulation	Neuromuscular electrical stimulation (NMES) compared to transcutaneous electrical nerve stimulation (TENS)	Combination therapy: Abobotulinum toxin A (Dysport) and transcutaneous electrical nerve stimulation (TENS) compared to placebo and TENS	Combination therapy: Onabotulinum toxin A (BOTOX) and functional electrical stimulation compared to onabotulinum toxin A (BOTOX) alone	Combination therapy: Abobotulinum toxin A (Dysport) and NMES compared to abobotulinum toxin A (Dysport) alone	Combination therapy: Abobotulinum toxin A (Dysport) and NMES compared to NMES alone
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Stroke outcome – modified Rankin scale	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Withdrawal due to adverse events	≤6 months	1 outcome (1 study) N=41 Very low	1 outcome (1 study) N=68 Low	No evidence identified	1 outcome (1 study) N=12 Very low	1 outcome (1 study) N=72 Low	1 outcome (1 study) N=29 Low	No evidence identified	1 outcome (1 study) N=12 Very low	1 outcome (1 study) N=12 Very low
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

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1.1.5.13.2 Generalised spasticity

Table 16: Summary matrix of the protocol interventions compared to placebo for people with generalised spasticity

		Tizanidine	Other oral medicine	Intrathecal medicine	Onabotulinum toxin A (BOTOX)	Abobotulinum toxin A (Dysport)	Incobotulinum toxin A (Xeomin)	Functional electrical stimulation (FES)	Neuromuscular electrical stimulation (NMES)	Transcutaneous electrical nerve stimulation (TENS)	Acupuncture	Electroacupuncture
Person/participant generic health-related quality of life	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=19 Very low	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Carer generic health-related quality of life	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Spasticity outcome measures	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	2 outcomes (3 studies) N=278	1 outcome (1 study) N=240 Low

		Tizanidine	Other oral medicine	Intrathecal medicine	Onabotulinum toxin A (BOTOX)	Abobotulinum toxin A (Dysport)	Incobotulinum toxin A (Xeomin)	Functional electrical stimulation (FES)	Neuromuscular electrical stimulation (NMES)	Transcutaneous electrical nerve stimulation (TENS)	Acupuncture	Electroacupuncture
											Moderate-Low	
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Physical function – general	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=238 Moderate	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Physical function – upper limb	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=19 Moderate	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

		Tizanidine	Other oral medicine	Intrathecal medicine	Onabotulinum toxin A (BOTOX)	Abobotulinum toxin A (Dysport)	Incobotulinum toxin A (Xeomin)	Functional electrical stimulation (FES)	Neuromuscular electrical stimulation (NMES)	Transcutaneous electrical nerve stimulation (TENS)	Acupuncture	Electroacupuncture
Physical function – lower limb	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=240 Low
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Pain	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=48 Very low	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Activities of daily living	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 outcome (3 studies) N=305 Very low	No evidence identified

		Tizanidine	Other oral medicine	Intrathecal medicine	Onabotulinum toxin A (BOTOX)	Abobotulinum toxin A (Dysport)	Incobotulinum toxin A (Xeomin)	Functional electrical stimulation (FES)	Neuromuscular electrical stimulation (NMES)	Transcutaneous electrical nerve stimulation (TENS)	Acupuncture	Electroacupuncture
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Stroke-specific Patient-Reported Outcome Measures	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=238 High	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Additional health care contacts	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Hospitalisation	≤6 months	No evidence	No evidence	No evidence	No evidence identified	No evidence identified	No evidence identified	No evidence	No evidence identified	No evidence identified	No evidence identified	No evidence identified

		Tizanidine	Other oral medicine	Intrathecal medicine	Onabotulinum toxin A (BOTOX)	Abobotulinum toxin A (Dysport)	Incobotulinum toxin A (Xeomin)	Functional electrical stimulation (FES)	Neuromuscular electrical stimulation (NMES)	Transcutaneous electrical nerve stimulation (TENS)	Acupuncture	Electroacupuncture
		identified	identified	identified				identified				
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Stroke outcome – modified Rankin scale	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Withdrawal due to adverse events	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 outcome (2 studies) N=81 Very low	1 outcome (1 study) N=240 Low
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

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2 **Table 17: Summary matrix of the protocol interventions compared to usual care for people with generalised spasticity**

		Tizanidine	Other oral medicine	Intrathecal baclofen	Onabotulinum toxin A (BOTOX)	Abobotulinum toxin A (Dysport)	Incobotulinum toxin A (Xeomin)	Functional electrical stimulation (FES)	Neuromuscular electrical stimulation (NMES)	Transcutaneous electrical nerve stimulation (TENS)	Acupuncture	Electroacupuncture
Person/participant generic health-related quality of life	≤6 months	No evidence identified	No evidence identified	1 outcome (1 study) N=51 Very low	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Carer generic health-related quality of life	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Spasticity outcome measures	≤6 months	No evidence	No evidence	1 outcome (1 study)	No evidence identified	No evidence identified	No evidence identified	No evidence	No evidence identified	No evidence identified	No evidence identified	1 outcome (2 studies) N=262

		Tizanidine	Other oral medicine	Intrathecal baclofen	Onabotulinum toxin A (BOTOX)	Abobotulinum toxin A (Dysport)	Incobotulinum toxin A (Xeomin)	Functional electrical stimulation (FES)	Neuromuscular electrical stimulation (NMES)	Transcutaneous electrical nerve stimulation (TENS)	Acupuncture	Electroacupuncture
		identified	identified	N=51 Moderate				identified				Low
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Physical function – general	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 outcome (3 studies) N=244 Moderate-very low	1 outcome (1 study) N=23 Low
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Physical function – upper limb	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	>6 months	No evidence	No evidence	No evidence	No evidence identified	No evidence identified	No evidence identified	No evidence	No evidence identified	No evidence identified	No evidence identified	No evidence identified

		Tizanidine	Other oral medicine	Intrathecal baclofen	Onabotulinum toxin A (BOTOX)	Abobotulinum toxin A (Dysport)	Incobotulinum toxin A (Xeomin)	Functional electrical stimulation (FES)	Neuromuscular electrical stimulation (NMES)	Transcutaneous electrical nerve stimulation (TENS)	Acupuncture	Electroacupuncture
		identified	identified	identified				identified				
Physical function – lower limb	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 outcome (1 study) N=240 Low
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Pain	≤6 months	No evidence identified	No evidence identified	1 outcome (1 study) N=51 Low	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Activities of daily living	≤6 months	No evidence identified	No evidence identified	1 outcome (1 study) N=51	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	2 outcomes (3 studies) N=244	1 outcome (1 study) N=22 Very low

		Tizanidine	Other oral medicine	Intrathecal baclofen	Onabotulinum toxin A (BOTOX)	Abobotulinum toxin A (Dysport)	Incobotulinum toxin A (Xeomin)	Functional electrical stimulation (FES)	Neuromuscular electrical stimulation (NMES)	Transcutaneous electrical nerve stimulation (TENS)	Acupuncture	Electroacupuncture
				Low							Moderate-Very low	
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Stroke-specific Patient-Reported Outcome Measures	≤6 months	No evidence identified	No evidence identified	1 outcome (1 study) N=51 Low	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Additional health care contacts	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

		Tizanidine	Other oral medicine	Intrathecal baclofen	Onabotulinum toxin A (BOTOX)	Abobotulinum toxin A (Dysport)	Incobotulinum toxin A (Xeomin)	Functional electrical stimulation (FES)	Neuromuscular electrical stimulation (NMES)	Transcutaneous electrical nerve stimulation (TENS)	Acupuncture	Electroacupuncture
Hospitalisation	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Stroke outcome – modified Rankin scale	≤6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Withdrawal due to adverse events	≤6 months	No evidence identified	No evidence identified	1 outcome (1 study) N=60 Low	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 outcome (2 studies) N=157 Very low	1 outcome (2 studies) N=266 Low
	>6 months	No evidence	No evidence	No evidence	No evidence identified	No evidence identified	No evidence identified	No evidence	No evidence identified	No evidence identified	No evidence identified	No evidence identified

		Tizanidine	Other oral medicine	Intrathecal baclofen	Onabotulinum toxin A (BOTOX)	Abobotulinum toxin A (Dysport)	Incobotulinum toxin A (Xeomin)	Functional electrical stimulation (FES)	Neuromuscular electrical stimulation (NMES)	Transcutaneous electrical nerve stimulation (TENS)	Acupuncture	Electroacupuncture
		identified	identified	identified				identified				

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2 **Table 18: Summary matrix of the protocol interventions compared to other protocol interventions for people with generalised spasticity**

		Tizanidine compared to oral baclofen	Electroacupuncture compared to acupuncture
Person/participant generic health-related quality of life	≤6 months	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified
Carer generic health-related quality of life	≤6 months	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified
Spasticity outcome measures	≤6 months	No evidence identified	1 outcome (1 study) N=25 Low
	>6 months	No evidence identified	No evidence identified
Physical function – general	≤6 months	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified
Physical function – upper limb	≤6 months	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified
Physical function – lower limb	≤6 months	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified
Pain	≤6 months	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified
Activities of daily living	≤6 months	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified

		Tizanidine compared to oral baclofen	Electroacupuncture compared to acupuncture
Stroke-specific Patient-Reported Outcome Measures	≤6 months	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified
Additional health care contacts	≤6 months	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified
Hospitalisation	≤6 months	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified
Stroke outcome – modified Rankin scale	≤6 months	No evidence identified	No evidence identified
	>6 months	No evidence identified	No evidence identified
Withdrawal due to adverse events	≤6 months	No evidence identified	No evidence identified
	>6 months	1 outcome (1 study) N=30 Very low	No evidence identified

1.1.6 Summary of the effectiveness evidence

1.1.6.1 Focal spasticity

1.1.6.1.1 Tizanidine compared to placebo

Table 19: Clinical evidence summary: tizanidine compared to placebo

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Placebo	Risk difference with Focal spasticity - Tizanidine	
Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, change score) at ≤6 months	37 (1 RCT) follow-up: 21 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean spasticity outcome measures at ≤6 months was -0.47	MD **0.16 higher** (0.46 lower to 0.78 higher)	MID = 0.58 (0.5 x median baseline SD)
Withdrawal due to adverse events at ≤6 months	40 (1 RCT) follow-up: 21 weeks	⊕◯◯◯ Very low[a,b,c]	Peto OR 7.87 (1.02 to 60.71)	0 per 1,000	**190 more per 1,000** (10 more to 370 more) [d]	MID (precision) = Peto OR 0.8-1.25.

[a] Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias due to missing outcome data and bias in selection of the reported results)

[b] Downgraded by 1 or 2 increments because of population indirectness (as 10-20% of the population had a traumatic brain injury rather than a stroke)

[c] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

[d] Absolute effect calculated by risk difference due to zero events in at least one arm of one study

1.1.6.1.2 Onabotulinum toxin A (BOTOX) compared to tizanidine and placebo

Table 20: Clinical evidence summary: onabotulinum toxin A (BOTOX) compared to tizanidine

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Tizanidine	Risk difference with Focal spasticity - Onabotulinum toxin A (BOTOX)	
Spasticity outcome measures	37 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean spasticity outcome	MD **1.04 lower** (1.74 lower to 0.34 lower)	MID = 0.57 (0.5 x median baseline SD)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Tizanidine	Risk difference with Focal spasticity - Onabotulinum toxin A (BOTOX)	
(Modified Ashworth scale, 0-4, lower values are better, change scores) at ≤6 months	follow-up: 21 weeks			measures at ≤6 months was -0.31		
Withdrawal due to adverse events at ≤6 months	41 (1 RCT) follow-up: 21 weeks	⊕◯◯◯ Very low[a,b,c]	RR 0.79 (0.20 to 3.09)	190 per 1,000	**40 fewer per 1,000** (152 fewer to 398 more)	MID (precision) = RR 0.8-1.25.

[a.] Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias due to missing outcome data and bias in selection of the reported results)

[b.] Downgraded by 1 or 2 increments because of population indirectness (as 10-20% of the population had a traumatic brain injury rather than a stroke)

[c.] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 21: Clinical evidence summary: onabotulinum toxin A (BOTOX) compared to placebo

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Placebo	Risk difference with Focal spasticity - Onabotulinum toxin A (BOTOX)	
Person/participant generic health-related quality of life (EQ-5D, 0-1, higher values are better, final value) at ≤6 months	28 (1 RCT) follow-up: 5 weeks	⊕⊕◯◯ Low[a]	-	The mean person/participant generic health-related quality of life at ≤6 months was 0.68	MD **0.05 lower** (0.13 lower to 0.03 higher)	MID = EQ-5D 0.03 (established MID)
Spasticity outcome measures (Modified Ashworth scale, Resistance to passive	1007 (7 RCTs) follow-up: mean 11 weeks	⊕◯◯◯ Very low[a,b,c]	-	-	SMD **0.68 SD lower** (1.2 lower to 0.15 lower)	MID = 0.5 SD (SMD)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Placebo	Risk difference with Focal spasticity - Onabotulinum toxin A (BOTOX)	
movement (REPAS) [different scale ranges], lower values are better, change scores) at ≤6 months						
Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, final values) at ≤6 months	36 (1 RCTs) follow-up: mean 4 weeks	⨁⨁⨁◯ Moderate[a,e]	-	-	MD **0.22 SD lower** (0.67 lower to 0.23 higher)	MID = 0.4 0.5 x mean control SD
Physical function - upper limb (ARAT, FMA-UE [different scale ranges, higher values are better, final values) at ≤6 months	147 (3 RCTs) follow-up: mean 11 weeks	⨁⨁⨁◯ Moderat[a, e]	-	-	SMD **0.26 SD higher** (0.06 lower to 0.59 higher)	MID = 0.5 SD (SMD)
Physical function - upper limb (ARAT, 0-57, higher values are better, change score) at ≤6 months	23 (1 RCT) follow-up: 20 weeks	⨁◯◯◯ Very low[a,d]	-	The mean physical function - upper limb at ≤6 months was 12.8	MD **3.8 lower** (20.27 lower to 12.67 higher)	MID = 12 points dominant side (17 points non-dominant side) (ARAT established MID)
Physical function - lower limb (FMA-LE, 0-34, higher values are better, final value) at ≤6 months	23 (1 RCT) follow-up: 8 weeks	⨁⨁⨁◯ Moderate[b]	-	The mean physical function - lower limb at ≤6 months was 27.8	MD **1.2 higher** (2.47 lower to 4.87 higher)	MID = 3.4 (Fugl-Meyer lower extremity = Difference by 10% of the total scale)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Placebo	Risk difference with Focal spasticity - Onabotulinum toxin A (BOTOX)	
Pain (VAS, NRS, 0-10, lower values are better, change score and final value) at ≤6 months	504 (2 RCTs) follow-up: 9 weeks	⊕◯◯◯ Very low[a,c,f]	-	The mean pain at ≤6 months was 2.04	MD **0.24 lower** (1.45 lower to 0.97 higher)	MID = 1.0 (0.5 x median control group SD)
Activities of daily living (Disability assessment scale, 0-3, lower values are better, change scores) at ≤6 months	235 (2 RCTs) follow-up: 12 weeks	⊕⊕⊕◯ Moderate[a]	-	The mean activities of daily living at ≤6 months was -0.33	MD **0.45 lower** (0.63 lower to 0.26 lower)	MID = 0.34 (0.5 x median control group SD)
Activities of daily living (Barthel index, 0-100, higher values are better, final value) at ≤6 months	23 (1 RCT) follow-up: 8 weeks	⊕⊕⊕⊕ High	-	The mean activities of daily living at ≤6 months was 50.1	MD **15.4** higher (6.68 higher to 24.12 higher)	MID = 1.85 (Barthel index established MID)
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Upper extremity, 0-100, higher values are better, final value) at ≤6 months	36 (1 RCT) follow-up: 24 weeks	⊕⊕⊕◯ Moderate[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at ≤6 months was 16.33	MD **2.95 higher** (0.49 higher to 5.41 higher)	MID = 1.7 (0.5 x median baseline SD)
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Energy, 0-100, higher values are better, final value) at ≤6 months	36 (1 RCT) follow-up: 24 weeks	⊕⊕⊕◯ Moderate[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at ≤6 months was 9.33	MD **0.56 higher** (1.17 lower to 2.29 higher)	MID = 1.3 (0.5 x median baseline SD)
Stroke-specific Patient-	36 (1 RCT)	⊕⊕◯◯ Low[a]	-	The mean stroke-specific	MD **0.17 lower**	MID = 1.69 (0.5 x

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Placebo	Risk difference with Focal spasticity - Onabotulinum toxin A (BOTOX)	
Reported Outcome Measures (Stroke Impact Scale - Family, 0-100, higher values are better, final value) at ≤6 months	follow-up: 24 weeks			Patient-Reported Outcome Measures at ≤6 months was 7.11	(2.39 lower to 2.05 higher)	median baseline SD)
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Language, 0-100, higher values are better, final value) at ≤6 months	36 (1 RCT) follow-up: 24 weeks	⨁⨁⨁◯ Moderate[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at ≤6 months was 21	MD **0.61 higher** (2.63 lower to 3.85 higher)	MID = 2.9 (0.5 x baseline SD)
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Mobility, 0-100, higher values are better, final value) at ≤6 months	36 (1 RCT) follow-up: 24 weeks	⨁⨁◯◯ Low[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at ≤6 months was 20.94	MD **1.06 higher** (2.24 lower to 4.36 higher)	MID = 2.2 (0.5 x baseline SD)
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Mood, 0-100, higher values are better, final value) at ≤6 months	36 (1 RCT) follow-up: mean 24 weeks	⨁⨁⨁◯ Moderate[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at ≤6 months was 0	MD **1.05 higher** (2.26 lower to 4.36 higher)	MID = 2.5 (0.5 x baseline SD)
Stroke-specific Patient-Reported Outcome Measures	36 (1 RCT) follow-up: 24 weeks	⨁⨁◯◯ Low[a]	-	The mean stroke-specific Patient-Reported Outcome	MD **0.17 lower** (2.2 lower to 1.86 higher)	MID = 1.2 (0.5 x baseline SD)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Placebo	Risk difference with Focal spasticity - Onabotulinum toxin A (BOTOX)	
(Stroke Impact Scale - Personality, 0-100, higher values are better, final value) at ≤6 months				Measures at ≤6 months was 10.89		
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Social roles, 0-100, higher values are better, final value) at ≤6 months	36 (1 RCT) follow-up: 24 weeks	⨁⨁◯◯ Low[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at ≤6 months was 8.94	MD **0.16 lower** (1.2 lower to 0.88 higher)	MID = 0.76 (0.5 x baseline SD)
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Vision, 0-100, higher values are better, final value) at ≤6 months	36 (1 RCT) follow-up: 24 weeks	⨁⨁◯◯ Low[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at ≤6 months was 13.94	MD **0.11 lower** (0.85 lower to 0.63 higher)	MID = 0.6 (0.5 x baseline SD)
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Work, 0-100, higher values are better, final value) at ≤6 months	36 (1 RCT) follow-up: 24 weeks	⨁⨁◯◯ Low[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at ≤6 months was 7.78	MD **0.5 higher** (1.42 lower to 2.42 higher)	MID = 1.33 (0.5 x baseline SD)
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Self-care, 0-100,	36 (1 RCT) follow-up: 24 weeks	⨁⨁⨁◯ Moderate[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at ≤6	MD **1.04 higher** (1.54 lower to 3.62 higher)	MID = 1.80 (0.5 x baseline SD)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Placebo	Risk difference with Focal spasticity - Onabotulinum toxin A (BOTOX)	
higher values are better, final value) at ≤6 months				months was 18.4		
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Thinking, 0-100, higher values are better, final value) at ≤6 months	36 (1 RCT) follow-up: 24 weeks	⊕⊕◯◯ Low[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at ≤6 months was 10.39	MD **0.22 lower** (1.5 lower to 1.06 higher)	MID = 0.91 (0.5 x baseline SD)
Withdrawal due to adverse events at ≤6 months	2255 (15 RCTs) follow-up: mean 12 weeks	⊕◯◯◯ Very low[h,i]	RD 0.01 (-0.01 to 0.03)	33 per 1,000	**10 more per 1,000** (10 fewer to 30 more) [j]	Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.48 (0.8-0.9 = serious, <0.8 = very serious).
Withdrawal due to adverse events at >6 months	274 (1 RCT) follow-up: 52 weeks	⊕◯◯◯ Very low[a,f]	Peto OR 0.13 (0.03 to 0.56)	52 per 1,000	**50 fewer per 1,000** (90 fewer to 10 fewer) [j]	MID (precision) = Peto OR 0.8-1.25.

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

b. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias arising from the randomisation process, bias due to missing outcome data and bias in selection of reported result)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Placebo	Risk difference with Focal spasticity - Onabotulinum toxin A (BOTOX)	

c. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

d. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias arising from the randomisation process and bias due to missing outcome data)

e. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias arising from the randomisation process and bias due to deviations from the intended interventions)

f. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias in selection of reported result)

g. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias arising from the randomisation process, bias due to missing outcome data and bias in selection of reported result)

h. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

i. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

j. Absolute effect calculated by risk difference due to zero events in at least one study arm

Table 4: Clinical evidence summary: onabotulinum toxin A (BOTOX) compared to usual care

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Usual care	Risk difference with Focal spasticity - Onabotulinum toxin A (BOTOX)	
Spasticity outcome measures (Clinical spasticity influx, Tardieu scale [different scale ranges] lower values are better, final value) at ≤6 months	94 (2 RCTs) follow-up: 12 weeks	⨁◯◯◯ Very low[a,b,c,d]	-	-	SMD **1.43 SD higher** (4.46 lower to 1.61 higher)	MID = 0.5 SD (SMD)
Physical function - lower limb (6 minute walk test,	26 (1 RCT) follow-up: mean 12 weeks	⨁⨁◯◯ Low[d]	-	The mean physical function - lower limb at ≤6	MD **0.08 lower** (0.42 lower to 0.26 higher)	MID = 0.3 (0.5 x median control group SD)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Usual care	Risk difference with Focal spasticity - Onabotulinum toxin A (BOTOX)	
m/s, lower values are better, final value) at ≤6 months				months was 2.2		
Physical function - lower limb (Fugl-meyer assessment, 0-34, higher values are better, final value) at ≤6 months	68 (1 RCT) follow-up: 12 weeks	⨁◯◯◯ Very low[c,e]	-	The mean physical function - lower limb at ≤6 months was 7.65	MD **9.96** higher (8.56 higher to 11.36 higher)	MID = 3.4 (Fugl-Meyer lower extremity = Difference by 10% of the total scale)
Activities of daily living (FIM, 18-126, higher values are better, final values) at ≤6 months	68 (1 RCT) follow-up: 12 weeks	⨁◯◯◯ Very low[c,f]	-	The mean activities of daily living at ≤6 months was 60.3	MD **12.1** higher (7.03 higher to 17.7 higher)	MID = 22 (Functional independence measure established MID)

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias due to missing data and bias in the measurement of the outcome)

b. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

c. Downgraded by 1 or 2 increments because of population indirectness (where a mixed population of focal 70% and multifocal spasticity 30% were included)

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

e. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a bias arising from the randomisation process, bias due to deviation from intended intervention, bias due to missing outcome data and bias in measurement of the outcome)

f. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a bias arising from the randomisation process, bias due to missing outcome data and bias in measurement of the outcome)

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1.1.6.1.3 Abobotulinum toxin A (Dysport) compared to tizanidine, placebo and usual care

Table 22: Clinical evidence summary: abobotulinum toxin A (Dysport) compared to tizanidine

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Tizanidine	Risk difference with Focal spasticity - Abobotulinum toxin A (Dysport)	
Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, final value) at ≤6 months	68 (1 RCT) follow-up: 24 weeks	⊕⊕◯◯ Low[a]	-	The mean spasticity outcome measures at ≤6 months was 2.32	MD **0.64 lower** (0.89 lower to 0.39 lower)	MID = 0.36 (0.5 x baseline SD)
Physical function - upper limb (ARAT, 0-57, higher values are better, final value) at ≤6 months	68 (1 RCT) follow-up: 24 weeks	⊕⊕◯◯ Low[a]	-	The mean physical function - upper limb at ≤6 months was 11.35	MD **0.56 lower** (3.06 lower to 1.94 higher)	MID = 12 points dominant side (17 points non-dominant side) (ARAT established MID)
Withdrawal due to adverse events at ≤6 months	68 (1 RCT) follow-up: 24 weeks	⊕⊕◯◯ Low[a]	Peto OR 0.06 (0.02 to 0.17)	588 per 1,000	**590 fewer per 1,000** (760 fewer to 420 fewer) [b]	MID (precision) = Peto OR 0.8-1.25.

[a] Downgraded by 2 increments as the majority of the evidence was at very high risk of bias (due to bias arising from the randomisation process, bias due to deviations from the intended interventions and bias due to missing outcome data)

[b] Absolute effect calculated by risk difference due to zero events in at least one study arm

Table 23: Clinical evidence summary: abobotulinum toxin A (Dysport) compared to neuromuscular electrical stimulation

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with NMES	Risk difference with Focal spasticity - Abobotulinum toxin A (Dysport)	
Spasticity outcome measures (Modified Ashworth scale, 0-5, lower values are better, final value) at ≤6 months	12 (1 RCT) follow-up: 12 weeks	⊕◯◯◯ Very low[a,b]	-	The mean spasticity outcome measures at ≤6 months was 3.11	MD **0.11 higher** (1.2 lower to 1.42 higher)	MID = 0.57 (0.5 x median control SD)
Withdrawal due to adverse events at ≤6 months	12 (1 RCT) follow-up: 12 weeks	⊕◯◯◯ Very low[a,c,d]	RD 0.00 (-0.27 to 0.27)	0 per 1,000	**0 fewer per 1,000** (270 fewer to 270 more)	Sample size used to determine precision: 75-150 = serious imprecision, <75 = very serious imprecision.

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias arising from the randomisation process)
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c. Absolute effect calculated by risk difference due to zero events in at least one arm of one study
d. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

Table 24: Clinical evidence summary: abobotulinum toxin A (Dysport) compared to placebo

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Placebo	Risk difference with Focal spasticity - Abobotulinum toxin A (Dysport)	
Person/participant generic health-related quality of life (AQOL, 0-1, higher values are better, change score) at ≤6 months	96 (1 RCT) follow-up: 20 weeks	⊕⊕◯◯ Low[a,b]	-	The mean person/participant generic health-related quality of life at ≤6 months was 0.06	MD **0.03 lower** (0.09 lower to 0.03 higher)	MID = 0.06 (0.5 x median control group SD)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Placebo	Risk difference with Focal spasticity - Abobotulinum toxin A (Dysport)	
Spasticity outcome measures (Modified Ashworth scale, ROC analysis [different scale ranges], lower values are better, change scores) at ≤6 months	490 (4 RCTs) follow-up: 8 weeks	⊕◯◯◯ Very low[b,c,d]	-	-	SMD **0.8 SD lower** (1.17 lower to 0.43 lower)	MID = 0.5 SD (SMD)
Spasticity outcome measures (Modified Ashworth scale [different scale ranges] lower values are better, final value) at ≤6 months	212 (3 RCTs) follow-up: mean 8 weeks	⊕◯◯◯ Very low[b,d,e]	-	The mean spasticity outcome measures at ≤6 months was 2.13	SMD **0.5 SD lower** (1.1 lower to 0.04 lower)	MID = 0.5 0.5 SD (SMD)
Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, final value) at >6 months	40 (1 RCT) follow-up: 9 months	⊕⊕◯◯ Low[b,f]	-	The mean spasticity outcome measures at >6 months was 1.9	MD **0.5 lower** (1.04 lower to 0.04 higher)	MID = 0.21 (0.5 x baseline SD)
Physical function - upper limb (Rivermead motor assessment arm, scale range unclear, lower values are better, change score) at ≤6 months	82 (1 RCT) follow-up: mean 4 weeks	⊕◯◯◯ Very low[b,g]	-	-	MD **0** (0.37 lower to 0.37 higher)	MID = 0.34 (0.5 x median control group)
Physical function - lower limb (2 min walk test, meters, higher values are better, final	218 (1 RCT) follow-up: 12 weeks	⊕⊕⊕◯ Moderate[f]	-	The mean physical function - lower limb at ≤6 months was 50.5	MD **0.84 lower** (9.56 lower to 7.88 higher)	MID = 11.14 (0.5 x baseline SD)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Placebo	Risk difference with Focal spasticity - Abobotulinum toxin A (Dysport)	
value) at ≤6 months						
Pain (VAS, Global pain scale, 0-100, lower values are better, change score) at ≤6 months	259 (2 RCTs) follow-up: mean 12 weeks	⊕⊕◯◯ Low[a,b]	-	-	MD **7.57 lower** (13.69 lower to 1.44 lower)	MID = 2.9 (0.5 x SD for mean differences)
Activities of daily living (Barthel index, disability assessment scale [different scale ranges], higher values are better, change scores) at ≤6 months	483 (3 RCTs) follow-up: mean 5 weeks	⊕⊕⊕⊕ High	-	-	SMD **0.06 SD** higher (0.21 lower to 0.33 higher)	MID = 0.5 SD (SMD)
Stroke outcome - Modified Rankin scale (Modified Rankin scale, 0-6, higher values are better, change score) at ≤6 months	163 (1 RCT) follow-up: 4 weeks	⊕◯◯◯ Very low[a,b]	-	-	MD **0.09 higher** (0.14 lower to 0.32 higher)	MID = 0.06 (0.5 x SD for mean differences)
Withdrawal due to adverse events at ≤6 months	859 (7 RCTs) follow-up: mean 14 weeks	⊕◯◯◯ Very low[h,i,j]	RD 0.02 (-0.01 to 0.04)	27 per 1,000	**20 fewer per 1,000** (10 fewer to 40 more)	Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.67 (0.8-0.9 = serious, <0.8 =

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Placebo	Risk difference with Focal spasticity - Abobotulinum toxin A (Dysport)	
						very serious).

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias in selection of the reported result)
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias arising from the randomisation process and bias in selection of the reported result)
d. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis
e. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias due to missing outcome data and bias in selection of the reported result)
f. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias due to missing outcome data)
g. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a bias arising from the randomisation process and bias in selection of the reported result)
h. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
i. Absolute effect calculated by risk difference due to zero events in at least one arm of one study
j. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

Table 25: Clinical evidence summary: abobotulinum toxin A (Dysport) compared to usual care

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with usual care	Risk difference with Focal spasticity - Abobotulinum toxin A (Dysport)	
Person/participant generic health-related quality of life (EQ5D, -0.11-1, higher values are better, final value) at ≤6 months	283 (1 RCT) follow-up: 3 months	⨁◯◯◯ Very low[a,b]	-	The mean Person/participant generic health-related quality of life at ≤6 months was 0.32	MD **0.03** (0.04 lower to 0.1 higher)	MID = EQ-5D 0.03 (established MID)
Person/participant generic health-related quality of life (EQ5D, -0.11-1, higher values are better, final value) at >6 months	174 (1 RCT) follow-up: 12 months	⨁◯◯◯ Very low[a,b]	-	The mean Person/participant generic health-related quality of life at >6 months was 0.27	MD **0.05** (0.04 lower to 0.14 higher)	MID = EQ-5D 0.03 (established MID)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with usual care	Risk difference with Focal spasticity - Abobotulinum toxin A (Dysport)	
Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, final value) at ≤6 months	314 (1 RCT) follow-up: 3 months	⊕⊕⊕◯ Moderate[c]	-	The mean spasticity outcome measures at ≤6 months was -0.1	MD **0.2 lower** (0.42 lower to 0.02 higher)	MID = 0.62 (0.5 x median control group SD)
Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, final value) at >6 months	189 (1 RCT) follow-up: 12 months	⊕⊕⊕◯ Moderate[c]	-	The mean spasticity outcome measures at >6 months was -0.10	MD **0.1 lower** (0.46 lower to 0.26 higher)	MID = 0.74 (0.5 x median control group SD)
Physical function - upper limb (ARAT, 0-57, higher values are better, final values) at ≤6 months	314 (1 RCT) follow-up: 3 months	⊕⊕⊕◯ Moderate[c]	-	The mean physical function - upper limb at ≤6 months was 11.4	MD **1.1 higher** (2.06 lower to 4.26 higher)	MID = 12 points dominant side (17 points non-dominant side) (ARAT established MID)
Physical function - upper limb (ARAT, 0-57, higher values are better, final value) at >6 months	189 (1 RCT) follow-up: 12 months	⊕⊕⊕◯ Moderate[c]	-	The mean physical function - upper limb at >6 months was 11.9	MD **1.7 higher** (2.42 lower to 5.82 higher)	MID = 12 points dominant side (17 points non-dominant side) (ARAT established MID)
Pain (VAS, 0-10, lower values are better, final value) at ≤6 months	314 (1 RCT) follow-up: 3 months	⊕⊕◯◯ Low[a]	-	The mean pain at ≤6 months was -1.2	MD **0.4 lower** (1.24 lower to 0.44 higher)	MID = 1.85 (0.5 x median control group SD)
Pain (VAS, 0-10, lower values are better, final value) at >6 months	189 (1 RCT) follow-up: 12 months	⊕◯◯◯ Very low[a,b]	-	The mean pain at >6 months was -0.8	MD **1.4 lower** (2.38 lower to 0.42 lower)	MID = 1.85 (0.5 x median control group SD)
Activities of daily living (Barthel index, 0-100, higher values are	314 (1 RCT) follow-up: 12 months	⊕⊕⊕◯ Moderate[c]	-	The mean activities of daily living at ≤6 months was 13.4	MD **0** (1.6 lower to 1.6 higher)	MID = Barthel Index 1.85

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with usual care	Risk difference with Focal spasticity - Abobotulinum toxin A (Dysport)	
better, final value) at ≤6 months						(established MID)
Activities of daily living (Barthel index, 0-100, higher values are better, final value) at >6 months	189 (1 RCT) follow-up: 3 months	⊕⊕⊕◯ Moderate[c]	-	The mean activities of daily living at >6 months was 13.7	MD **0.3 lower** (1.63 lower to 1.03 higher)	MID = Barthel Index 1.85 (established MID)
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Strength, 0-100, higher values are better, final values) at ≤6 months	314 (1 RCT) follow-up: 3 months	⊕⊕◯◯ Low[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at ≤6 months was 31.2	MD **0.9 higher** (4.31 lower to 6.11 higher)	MID = 12.4 (0.5 x median control group SD)
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Memory, 0-100, higher values are better, final values) at ≤6 months	314 (1 RCT) follow-up: 3 months	⊕⊕◯◯ Low[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at ≤6 months was 73.6	MD **1.5 higher** (4.39 lower to 7.39 higher)	MID = 14.9 (0.5 x median control group SD)
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Emotion, 0-100, higher values are better, final values) at ≤6 months	314 (1 RCT) follow-up: 3 months	⊕⊕◯◯ Low[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at ≤6 months was 67.3	MD **3.4 lower** (7.26 lower to 0.46 higher)	MID = 8.7 (0.5 x median control group SD)
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Communication, 0-100, higher values are better, final values) at ≤6 months	314 (1 RCT) follow-up: 3 months	⊕⊕◯◯ Low[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at ≤6 months was 76.4	MD **3.1 higher** (2.95 lower to 9.15 higher)	MID = 14.3 (0.5 x median control group SD)
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - ADL, 0-100, higher	314 (1 RCT) follow-up: 3 months	⊕⊕◯◯ Low[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at	MD **0** (4.71 lower to 4.71 higher)	MID = 10.85 (0.5 x median control group SD)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with usual care	Risk difference with Focal spasticity - Abobotulinum toxin A (Dysport)	
values are better, final values) at ≤6 months				≤6 months was 43		
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Mobility, 0-100, higher values are better, final values) at ≤6 months	314 (1 RCT) follow-up: 3 months	⨁⨁◯◯ Low[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at ≤6 months was 50.4	MD **1.3 lower** (7.41 lower to 4.81 higher)	MID = 14.3 (0.5 x median control group SD)
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Hand function, 0-100, higher values are better, final values) at ≤6 months	314 (1 RCT) follow-up: 3 months	⨁⨁◯◯ Low[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at ≤6 months was 12.2	MD **1.2 higher** (3.65 lower to 6.05 higher)	MID = 11.1 (0.5 x median control group SD)
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Participation/handicap, 0-100, higher values are better, final values) at ≤6 months	314 (1 RCT) follow-up: 3 months	⨁⨁◯◯ Low[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at ≤6 months was 40.4	MD **0.4 higher** (6.2 lower to 7 higher)	MID = 14.6 (0.5 x median control group SD)
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Physical domains, 0-100, higher values are better, final values) at ≤6 months	314 (1 RCT) follow-up: 3 months	⨁⨁◯◯ Low[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at ≤6 months was 33.9	MD **0.1 higher** (4.18 lower to 4.38 higher)	MID = 10.0 (0.5 x median control group SD)
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Stroke recovery, 0-100, higher values are better, final	314 (1 RCT) follow-up: 3 months	⨁⨁◯◯ Low[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at ≤6 months was 43.8	MD **0.3 lower** (5.08 lower to 4.48 higher)	MID = 11.2 (0.5 x median control group SD)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with usual care	Risk difference with Focal spasticity - Abobotulinum toxin A (Dysport)	
values) at ≤6 months						
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Strength, 0-100, higher values are better, final values) at >6 months	189 (1 RCT) follow-up: 12 months	⊕⊕◯◯ Low[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at >6 months was 29.7	MD **1.8 higher** (5.8 lower to 9.4 higher)	MID = 13.0 (0.5 x median control group SD)
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Memory, 0-100, higher values are better, final values) at >6 months	189 (1 RCT) follow-up: 12 months	⊕⊕◯◯ Low[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at >6 months was 71.1	MD **3.9 higher** (5.13 lower to 12.93 higher)	MID = 16.5 (0.5 x median control group SD)
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Emotion, 0-100, higher values are better, final values) at >6 months	189 (1 RCT) follow-up: 12 months	⊕⊕◯◯ Low[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at >6 months was 64.7	MD **1 lower** (7.5 lower to 5.5 higher)	MID = 11.8 (0.5 x median control group SD)
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Communication, 0-100, higher values are better, final values) at >6 months	189 (1 RCT) follow-up: 12 months	⊕⊕◯◯ Low[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at >6 months was 77.9	MD **1.2 higher** (8.56 lower to 10.96 higher)	MID = 17.4 (0.5 x median control group SD)
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - ADL, 0-100, higher values are better, final values) at >6 months	189 (1 RCT) follow-up: 12 months	⊕⊕◯◯ Low[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at >6 months was 41.8	MD **2.5 higher** (5 lower to 10 higher)	MID = 13.4 (0.5 x median control group SD)
Stroke-specific Patient-Reported Outcome	189 (1 RCT)	⊕⊕◯◯ Low[a]	-	The mean stroke-specific Patient-	MD **1 lower** (10.41 lower	MID = 16.2 (0.5 x median

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with usual care	Risk difference with Focal spasticity - Abobotulinum toxin A (Dysport)	
Measures (Stroke Impact scale - Mobility, 0-100, higher values are better, final values) at >6 months	follow-up: 12 months			Reported Outcome Measures at >6 months was 49.1	to 8.41 higher)	control group SD)
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Hand function, 0-100, higher values are better, final values) at >6 months	189 (1 RCT) follow-up: 12 months	⨁◯◯◯ Very low[a,b]	-	The mean stroke-specific Patient-Reported Outcome Measures at >6 months was 8.3	MD **6.8 higher** (0.68 lower to 14.28 higher)	MID = 10.0 (0.5 x median control group SD)
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Participation/handicap, 0-100, higher values are better, final values) at >6 months	189 (1 RCT) follow-up: 12 months	⨁⨁◯◯ Low[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at >6 months was 41.4	MD **0.4 higher** (10.66 lower to 11.46 higher)	MID = 18.7 (0.5 x median control group SD)
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Physical domains, 0-100, higher values are better, final values) at >6 months	189 (1 RCT) follow-up: 12 months	⨁⨁◯◯ Low[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at >6 months was 31.9	MD **2.6 higher** (3.85 lower to 9.05 higher)	MID = 10.6 (0.5 x median control group SD)
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Stroke recovery, 0-100, higher values are better, final values) at >6 months	189 (1 RCT) follow-up: 12 months	⨁⨁◯◯ Low[a]	-	The mean stroke-specific Patient-Reported Outcome Measures at >6 months was 40.6	MD **3.4 higher** (4.83 lower to 11.63 higher)	MID = 14.3 (0.5 x median control group SD

a. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias due to deviations from the intended intervention and bias in measurement of the outcome)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with usual care	Risk difference with Focal spasticity - Abobotulinum toxin A (Dysport)	
c. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias due to deviations from the intended intervention)						

1.1.6.1.4 Incobotulinum toxin A (Xeomin) compared to oral baclofen, placebo and usual care

Table 26: Clinical evidence summary: incobotulinum toxin A (Xeomin) compared to oral baclofen

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Baclofen (oral)	Risk difference with Focal spasticity - Incobotulinum Toxin A (Xeomin)	
Person/participant generic health-related quality of life (Romanian version of the general instrument 15D, 0-1, higher values are better, final value) at ≤6 months	34 (1 RCT) follow-up: 6 months	⨁◯◯◯ Very low[a,b]	-	The mean person/participant generic health-related quality of life at ≤6 months was 0.68	MD **0.04 higher** (0.05 lower to 0.13 higher)	MID = 0.05 (0.5 x baseline SD)
Spasticity outcome measures (Tardieu scale, 0-4, lower values are better, final value) at ≤6 months	34 (1 RCT) follow-up: 6 months	⨁◯◯◯ Very low[a,b]	-	The mean spasticity outcome measures at ≤6 months was 2.21	MD **0.03 lower** (0.52 lower to 0.46 higher)	MID = 0.29 (0.5 x baseline SD)
Physical function - upper limb (muscle strength, 0-5, higher values are better, final value) at ≤6 months	34 (1 RCT) follow-up: 6 months	⨁◯◯◯ Very low[a,b]	-	The mean physical function - upper limb at ≤6 months was 2.74	MD **0.26 higher** (0.1 lower to 0.62 higher)	MID = 0.38 (0.5 x baseline SD)
Activities of daily living	34 (1 RCT)	⨁◯◯◯	-	The mean activities of	MD **5.59 higher**	MID = Barthel

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Baclofen (oral)	Risk difference with Focal spasticity - Incobotulinum Toxin A (Xeomin)	
(Barthel Index, 0-100, higher values are better, final value) at ≤6 months	follow-up: 6 months	Very low[a,b]		daily living at ≤6 months was 47.35	(4.51 lower to 15.69 higher)	Index 1.85 (established MID)

a. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a mixture of bias arising from the randomisation process, bias due to deviations from the intended interventions, bias due to missing outcome data and bias in measurement of the outcome)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 27: Clinical evidence summary: incobotulinum toxin A (Xeomin) compared to placebo

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Placebo	Risk difference with Focal spasticity - Incobotulinum toxin A (Xeomin)	
Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, change scores) at ≤6 months	467 (2 RCTs) follow-up: mean 6 weeks	⊕⊕⊕⊕ High[a]	-	The mean spasticity outcome measures at ≤6 months was -0.45	MD **0.3 lower** (0.5 lower to 0.1 lower)	MID = 0.05 (0.5 x median control group SD for change scores)
Physical function - lower limb (10 meter walk test, seconds, lower values are better, change score) at ≤6 months	116 (1 RCT) follow-up: 12 weeks	⊕◯◯◯ Very low[b,c]	-	The mean physical function - lower limb at <6 months was 0.7	MD **1.9 lower** (5.78 lower to 1.98 higher)	MID = 5.4 (0.5 x median control group SD)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Placebo	Risk difference with Focal spasticity - Incobotulinum toxin A (Xeomin)	
Pain (Ankle pain score, scale range unclear, lower values are better, change score) at ≤6 months	208 (1 RCT) follow-up: 12 weeks	⨁⨁⨁◯ Moderate[d]	-	The mean pain at <6 months was -0.5	MD **0.1 lower** (0.65 lower to 0.45 higher)	MID = 1.0 (0.5 x median control group SD)
Withdrawal due to adverse events at ≤6 months	456 (3 RCTs) follow-up: 12 weeks	⨁⨁◯◯ Low[c]	RR 0.40 (0.12 to 1.29)	33 per 1,000	**20 fewer per 1,000** (29 fewer to 10 more)	MID (precision) = RR 0.8-1.25.
Withdrawal due to adverse events at >6 months	259 (1 RCT) follow-up: 48 weeks	⨁⨁⨁◯ Moderate[e]	RD 0.00 (-0.02 to 0.02)	0 per 1,000	**0 fewer per 1,000** (20 fewer to 20 more) [f]	Sample size used to determine precision: 75-150 = serious imprecision, <75 = very serious imprecision.

a. While there is significant heterogeneity in the forest plot, all effect sizes are in the same direction and confidence intervals after the minimally important difference. Therefore, any inconsistency has been thought to not be important, and so this has not been downgraded for in this case

b. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias arising from the randomisation process, bias due to deviations from the intended interventions and bias due to missing outcome data)

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias arising from the randomisation process)

e. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

f. Absolute effect calculated by risk difference due to zero events in at least one study arm

1

Table 28: Clinical evidence summary: incobotulinum toxin A (Xeomin) compared to usual care

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Usual care	Risk difference with Focal spasticity - Incobotulinum toxin A (Xeomin)	
Spasticity outcome measures (Modified Ashworth scale, 0-5, lower values are better, change score and final value) at ≤6 months	17 (1 RCT) follow-up: 14 weeks	⨁◯◯◯ Very low[a,b]	-	The mean spasticity outcome measures at ≤6 months was 1.05	MD **1 lower** (1.77 lower to 0.23 lower)	MID = 0.25 (0.5 x median baseline SD)
Physical function - upper limb (Fugl-Meyer score, 0-66, higher values are better, final value) at ≤6 months	17 (1 RCT) follow-up: 6 months	⨁⨁◯◯ Low[a]	-	The mean physical function - upper limb at ≤6 months was 12.8	MD **0.3 higher** (4.84 lower to 5.44 higher)	MID = 6.6 (Fugl-Meyer upper extremity = Difference by 10% of the total scale)
Activities of daily living (disability scale, 0-24, lower values are better, final value) at ≤6 months	17 (1 RCT) follow-up: 6 months	⨁◯◯◯ Very low[a,b]	-	The mean activities of daily living at ≤6 months was 10.9	MD **5.2 lower** (8.9 lower to 1.5 lower)	MID = 0.25 (0.5 x baseline SD)
Withdrawal due to adverse events at ≤6 months	18 (1 RCT) follow-up: 6 months	⨁◯◯◯ Very low[a,c]	RD 0.00 (-0.19 to 0.19)	0 per 1,000	**0 fewer per 1,000** (190 fewer to 190 more)	Sample size used to determine precision: 75-150 = serious imprecision, <75 = very serious imprecision.

a. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a mixture of bias due to deviations from the intended interventions, bias due to missing outcome data and bias in measurement of the outcome)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

d. Absolute effect calculated by risk difference due to zero events in at least one study arm

1.1.6.1.5 Functional electrical stimulation compared to placebo and usual care

Table 29: Clinical evidence summary: functional electrical stimulation compared to placebo

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Placebo	Risk difference with Focal spasticity - Functional electrical stimulation	
Spasticity outcome measures (Composite spasticity scale, 0-100, lower values are better, final value) at ≤6 months	28 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b]	-	The mean spasticity outcome measures at ≤6 months was 56	MD **14.2 lower** (82.85 lower to 54.45 higher)	MID = 32.4 (0.5 x median control group SD)
Physical function - lower limb (Timed up and go, seconds, lower values are better, final value) at ≤6 months	28 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b]	-	The mean physical function - lower limb at ≤6 months was 31.7	MD **3.3 lower** (21.46 lower to 14.86 higher)	MID = 13.1 (0.5 x median baseline SD)
Physical function - lower limb (walking speed, m/s, higher values are better, change score) at ≤6 months	26 (1 RCT) follow-up: 14 days	⊕◯◯◯ Very low[b,c]	-	The mean physical function - lower limb at ≤6 months was 0.11	MD **0.02 higher** (0.07 lower to 0.11 higher)	MID = 0.058 (0.5 x median baseline SD)
Activities of daily living (FIM, 1-7, higher values are better, final value) at ≤6 months	26 (1 RCT) follow-up: 11 days	⊕◯◯◯ Very low[b,c]	-	The mean activities of daily living at ≤6 months was 2.1	MD **0.1 higher** (0.72 lower to 0.92 higher)	MID = 0.55 (0.5 x median baseline SD)
Withdrawal due to adverse events at ≤6 months	32 (1 RCT) follow-up: 11 days	⊕◯◯◯ Very low[c,d]	RD 0.00 (-0.11 to 0.11)	0 per 1,000	**0 fewer per 1,000** (110 fewer to 110 more) [e]	Sample size used to determine precision: 75-150 = serious imprecision, <75 = very serious imprecision.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Placebo	Risk difference with Focal spasticity - Functional electrical stimulation	
a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias arising from the randomisation process) b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs c. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias due to missing outcome data) d. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size e. Absolute effect calculated by risk difference due to zero events in at least one arm of one study						

Table 30: Clinical evidence summary: functional electrical stimulation compared to usual care

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Usual care	Risk difference with Focal spasticity - Functional electrical stimulation	
Spasticity outcome measures (Modified Ashworth scale, Composite spasticity scale [different scale ranges], lower values are better, final values) at ≤6 months	88 (2 RCTs) follow-up: mean 8 weeks	⨁◯◯◯ Very low[a,b,c]	-	-	SMD **0.99 SD lower** (2.1 lower to 0.11 higher)	MID = 0.5 SD (SMD)
Spasticity outcome measures (Composite spasticity scale, %, 0-100, lower values are better, change score) at ≤6 months	26 (1 RCT) follow-up: 8 weeks	⨁⨁◯◯ Low[c,d]	-	The mean spasticity outcome measures at ≤6 months was 78.6	MD **36.8 lower** (98.61 lower to 25.01 higher)	MID = 32.4 (0.5 x control group SD)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Usual care	Risk difference with Focal spasticity - Functional electrical stimulation	
Physical function - upper limb (Rivermead motor assessment hand, 0-13, higher values are better, final value) at ≤6 months	30 (1 RCT) follow-up: 4 weeks	⨁◯◯◯ Very low[a,c]	-	The mean physical function - upper limb at ≤6 months was 2.2	MD **0.66 higher** (0.06 lower to 1.38 higher)	MID = 0.29 (0.5 x median baseline SD)
Physical function - lower limb (Berg Balance Scale, FMA-LE [different scale ranges], higher values are better, final values) at ≤6 months	613 (4 RCTs) follow-up: mean 6 weeks	⨁◯◯◯ Very low[b,c,e]	-	-	SMD **0.54 SD higher** (0.02 lower to 1.1 higher)	MID = 0.5 SD (SMD)
Physical function - lower limb (6 min walk, meters, higher values are better, final value) at ≤6 months	44 (1 RCT) follow-up: 12 weeks	⨁◯◯◯ Very low[c,f]	-	The mean physical function - lower limb at ≤6 months was 171.37	MD **47.52 higher** (21.21 lower to 116.25 higher)	MID = 43.3 (0.5 x median baseline SD)
Physical function - lower limb (timed up and go, seconds, lower values are better, final value) at ≤6 months	26 (1 RCT) follow-up: 8 weeks	⨁⨁◯◯ Low[c,d]	-	The mean physical function - lower limb at ≤6 months was 39.7	MD **11.3 lower** (31.25 lower to 8.65 higher)	MID = 12.8 (0.5 x median baseline SD)
Activities of daily living (Barthel index, 0-100, higher values are better, final values) at ≤6 months	67 (2 RCTs) follow-up: mean 4 weeks	⨁⨁◯◯ Low[a]	-	The mean activities of daily living at ≤6 months was 61.3	MD **8.46 higher** (3.36 higher to 13.57 higher)	MID = Barthel Index 1.85 (established MID)
Stroke-specific	495 (1 RCT)	⨁⨁◯◯ Low[g]	-	The mean stroke-	MD **2.4 lower**	MID = 18.9 (0.5 x

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Usual care	Risk difference with Focal spasticity - Functional electrical stimulation	
Patient-Reported Outcome Measures (Stroke-Specific Quality of Life, 49-245, higher values are better, final values) at ≤6 months	follow-up: mean 6 months			specific Patient-Reported Outcome Measures at ≤6 months was 184	(9.47 lower to 4.67 higher)	median baseline SD)
Withdrawal due to adverse events at ≤6 months	620 (4 RCTs) follow-up: mean 13 weeks	⨁◯◯◯ Very low[h,i,j]	RD 0.01 (-0.02 to 0.04)	19 per 1,000	**10 more per 1,000** (20 fewer to 40 more) [k]	Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.24 (0.8-0.9 = serious, <0.8 = very serious).

a. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a mixture of bias arising from the randomisation process and bias due to missing outcome data)

b. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. Downgraded by 2 increments as the majority of the evidence was of high risk of bias (due to bias due to missing outcome data)

e. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a mixture of bias arising from the randomisation process, bias due to missing outcome data and bias in measurement of the outcome)

f. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a mixture of bias arising from the randomisation process and bias due to deviations from the intended intervention)

g. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias due to deviations from the intended intervention, bias due to missing outcome data and bias in measurement of the outcome)

h. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a mixture of bias arising from the randomisation process, bias due to deviations from the intended intervention and bias due to missing outcome data)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Usual care	Risk difference with Focal spasticity - Functional electrical stimulation	

i. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
j. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size
k. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

1.1.6.1.6 Neuromuscular electrical stimulation compared to transcutaneous electrical nerve stimulation, placebo and usual care

Table 31: Clinical evidence summary: neuromuscular electrical stimulation compared to transcutaneous electrical nerve stimulation

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with TENS	Risk difference with Focal spasticity - Neuromuscular electrical stimulation	
Spasticity outcome measures measure (modified Ashworth scale, 0-6, lower values are better, change score) at ≤6 months	72 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b]	-	The mean spasticity outcome measures measure at ≤6 months was 0.16	MD **0.08 lower** (0.93 lower to 1.09 higher)	MID = 0.47 (0.5 x median baseline SD)
Physical function - upper limb (Fugl-meyer-Upper limb, 0-66, higher values are better, change score) at ≤6 months	72 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b]	-	The mean physical function - upper limb at ≤6 months was 5.46	MD **0.6 lower** (21.57 lower to 20.37 higher)	MID = 6.6 (Fugl-Meyer upper extremity = Difference by 10% of the total scale)
Pain (Numeric rating scale, 0-10, lower values are better, change score) at ≤6 months	72 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[b,c]	-	The mean pain at ≤6 months was -1.57	MD **0.67 lower** (3.72 lower to 2.38 higher)	MID = 0.63 (0.5 x median baseline SD)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with TENS	Risk difference with Focal spasticity - Neuromuscular electrical stimulation	
Activities of daily living (Barthel index, 0-100, higher values are better, change score) at ≤6 months	72 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b]	-	The mean activities of daily living at ≤6 months was 14.82	MD **3.15 higher** (40.7 lower to 34.4 higher)	MID = Barthel Index 1.85 (established MID)
Stroke-specific Patient-Reported Outcome Measures (SS-QOL, 49-245, higher values are better, change score) at ≤6 months	72 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[b,c]	-	The mean stroke-specific Patient-Reported Outcome Measures at ≤6 months was 12.68	MD **5.13 higher** (44.55 lower to 54.81 higher)	MID = 12.3 (0.5 x median baseline SD)
Withdrawal due to adverse events at ≤6 months	72 (1 RCT) follow-up: 8 weeks	⊕⊕◯◯ Low[a,b]	RR 1.88 (0.91 to 3.86)	222 per 1,000	**196 more per 1,000** (20 fewer to 636 more)	MID (precision) = RR 0.8-1.25.

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias due to missing outcome data)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias due to missing outcome data and bias in measurement of the outcome)

Table 32: Clinical evidence summary: neuromuscular electrical stimulation compared to placebo

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with Focal Spasticity - Neuromuscular electrical stimulation	
Spasticity outcome measures (Modified Ashworth scale, Leeds	108 (3 RCTs) follow-up: mean 9 weeks	⊕⊕⊕◯ Moderate[a]	-	-	SMD **0.02 SD lower** (0.41 lower to 0.36 higher)	MID = 0.5 SD (SMD)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with Focal Spasticity - Neuromuscular electrical stimulation	
adult/arm spasticity impact scale [different scale ranges], lower values are better, final values) at ≤6 months						
Physical function - upper limb (Fugl Meyer Assessment - Upper Extremity, 0-66, higher values are better, final values) at ≤6 months	108 (3 RCTs) follow-up: mean 9 weeks	⊕⊕◯◯ Low[a,b]	-	The mean physical function - upper limb at ≤6 months was 28.5	MD **2.91 higher** (1.76 lower to 7.58 higher)	MID = 6.6 (Fugl-Meyer upper extremity = Difference by 10% of the total scale)
Pain (Visual analogue scale, 0-10, lower values are better, final value) at ≤6 months	14 (1 RCT) follow-up: 20 weeks	⊕◯◯◯ Very low[b,c]	-	The mean pain at ≤6 months was 4.4	MD **1.3 higher** (1.4 lower to 4 higher)	MID = 1.2 (0.5 x median baseline SD)
Activities of daily living (Functional Independence Measure Self-Care subscale, 0-100, higher values are better, final value) at ≤6 months	30 (1 RCT) follow-up: 3 weeks	⊕◯◯◯ Very low[b,d]	-	The mean activities of daily living at ≤6 months was 22	MD **5.81 higher** (0.89 lower to 12.51 higher)	MID = 4.1 (0.5 x median baseline SD)
Stroke-specific Patient-Reported Outcome Measures (Stroke impact scale, 0-100, higher values are better,	39 (1 RCT) follow-up: 4 months	⊕⊕◯◯ Low[b,e]	-	The mean stroke-specific Patient-Reported Outcome Measures at ≤6 months	MD **3.26 higher** (3.41 lower to 9.93 higher)	MID = 5.2 (0.5 x median baseline SD)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with Focal Spasticity - Neuromuscular electrical stimulation	
final value) at ≤6 months				was 54.17		
Additional health care contacts (prescription of spasticity medication) at ≤6 months	48 (1 RCT) follow-up: 10 weeks	⊕◯◯◯ Very low[b,e]	RR 2.50 (0.54 to 11.65)	83 per 1,000	**125 more per 1,000** (38 fewer to 888 more)	MID (precision) = RR 0.8-1.25.
Additional health care contacts (prescription of pain medication) at ≤6 months	48 (1 RCT) follow-up: 10 weeks	⊕⊕◯◯ Low[b,e]	RR 1.45 (0.87 to 2.44)	458 per 1,000	**206 more per 1,000** (60 fewer to 660 more)	MID (precision) = RR 0.8-1.25.
Hospitalisation at ≤6 months	48 (1 RCT) follow-up: 20 weeks	⊕◯◯◯ Very low[b,e]	Peto OR 0.14 (0.00 to 6.82)	42 per 1,000	**40 fewer per 1,000** (150 fewer to 70 more) [f]	MID (precision) = Peto OR 0.8-1.25.
Withdrawal due to adverse events at ≤6 months	87 (2 RCTs) follow-up: mean 18 weeks	⊕◯◯◯ Very low[e,g,h]	RD 0.02 (-0.11 to 0.15)	93 per 1,000	**20 more per 1,000** (110 fewer to 150 more) [f]	Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.07 (0.8-0.9 = serious, <0.8 = very serious).

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias arising from the randomisation process and bias due to deviations from the intended interventions)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias due to deviations from the intended interventions and bias due to missing outcome data)

d. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias arising from the randomisation process and bias in selection of the reported result)

e. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias due to deviations from the intended interventions)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with Focal Spasticity - Neuromuscular electrical stimulation	
f. Absolute effect calculated by risk difference due to zero events in at least one arm of one study g. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies) h. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size						

Table 33: Clinical evidence summary: neuromuscular electrical stimulation compared to usual care

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with usual care	Risk difference with Focal Spasticity - Neuromuscular electrical stimulation	
Spasticity outcome measures (modified Ashworth scale [different scale ranges], lower values are better, change score) at ≤6 months	134 (3 RCTs) follow-up: mean 6 weeks	⊕◯◯◯ Very low[a,b,c]	-	-	MD **0.96 lower** (2.12 lower to 0.2 higher)	MID = 0.5 (0.5 x median baseline SD)
Spasticity outcome measures (modified Ashworth scale, composite spasticity scale [different scale ranges], lower values are better, final values) at ≤6 months	285 (7 RCTs) follow-up: mean 10 weeks	⊕⊕⊕◯ Moderate[d]	-	-	SMD **0.22 SD lower** (0.47 lower to 0.02 higher)	MID = 0.5 SD (SMD)
Physical function - upper limb (Fugl-meyer UE, 0-66, higher values are better,	54 (1 RCT) follow-up: mean 8 weeks	⊕◯◯◯ Very low[c,d]	-	The mean physical function - upper limb at ≤6 months was 5.31	MD **0.45 lower** (22.96 lower to 22.06 higher)	MID = 6.6 (established MID)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with usual care	Risk difference with Focal Spasticity - Neuromuscular electrical stimulation	
change scores) at ≤6 months						
Physical function - upper limb (FMA shoulder/elbow, UE, FIM, Box and block test [different scale ranges], higher values are better, final values) at ≤6 months	152 (5 RCTs) follow-up: mean 7.5 weeks	⨁⨁⨁◯ Moderate[e]	-	-	SMD **0.89 SD higher** (0.55 higher to 1.23 higher)	MID = 0.5 SD (SMD)
Physical function - lower limb (Rivermead motor assessment scale, 0-23, higher values are better, change score) at ≤6 months	40 (1 RCT) follow-up: 4 weeks	⨁⨁◯◯ Low[c,d]	-	The mean physical function - lower limb at ≤6 months was 2.05	MD **0.9 higher** (0.6 lower to 2.4 higher)	MID = 1.1 (0.5 x median control group SD)
Physical function - lower limb (timed up and go, seconds, lower values are better, final value) at ≤6 months	66 (1 RCT) follow-up: 6 weeks	⨁⨁⨁⨁ High	-	The mean physical function - lower limb at ≤6 months was 16.04	MD **0.97 lower** (4.07 lower to 2.13 higher)	MID = 4.3 (0.5 x median baseline SD)
Physical function - lower limb (walking speed, m/s, higher values are better, final value) at ≤6 months	20 (1 RCT) follow-up: 4 weeks	⨁⨁◯◯ Low[f]	-	The mean physical function - lower limb at ≤6 months was 0.49	MD **0.01 higher** (0.18 lower to 0.2 higher)	MID = 0.088 (0.5 x median baseline SD)
Pain (numeric rating scale, 0-10, lower values are better, change score) at ≤6 months	54 (1 RCT) follow-up: mean 8 weeks	⨁◯◯◯ Very low[c,g]	-	The mean Pain at ≤6 months was -1.25	MD **1.01 lower** (3.36 lower to 1.34 higher)	MID = 0.58 (0.5 x median baseline SDs)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with usual care	Risk difference with Focal Spasticity - Neuromuscular electrical stimulation	
Pain (verbal rating scale, 0-5, lower values are better, final values) at ≤6 months	69 (1 RCT) follow-up: mean 36 weeks	⨁⨁◯◯ Low[c,d]	-	-	MD **0.7 lower** (1.33 lower to 0.07 lower)	MID = 0.53 (0.5 x median baseline SD)
Activities of daily living (Barthel index, 0-100, higher values are better, change score) at ≤6 months	54 (1 RCT) follow-up: mean 8 weeks	⨁◯◯◯ Very low[c,d]	-	The mean activities of daily living at ≤6 months was 13.08	MD **1.41 lower** (25.65 lower to 22.83 higher)	MID = 1.85 (established MID)
Activities of daily living (FIM, Barthel index [different scale ranges], higher values are better, final values) at ≤6 months	128 (3 RCTs) follow-up: mean 12 weeks	⨁◯◯◯ Very low[c,h]	-	-	SMD **0.61 SD higher** (0.19 lower to 1.41 higher)	MID = 0.5 SD (SMD)
Stroke-specific Patient-Reported Outcome Measures (SS-QOL, 49-245, higher values are better, change score) at ≤6 months	54 (1 RCT) follow-up: 8 weeks	⨁◯◯◯ Very low[c,g]	-	The mean stroke-specific Patient-Reported Outcome Measures at ≤6 months was 10.77	MD **7.04 higher** (33.37 lower to 47.45 higher)	MID = 12.5 (0.5 x median baseline SD)
Withdrawal due to adverse events at ≤6 months	500 (11 RCTs) follow-up: mean 10 weeks	⨁◯◯◯ Very low[h,i,k]	RD 0.03 (-0.04 to 0.09)	137 per 1,000	**30 more per 1,000** (30 fewer to 90 more) [j]	Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.23

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with usual care	Risk difference with Focal Spasticity - Neuromuscular electrical stimulation	
						(0.8-0.9 = serious, <0.8 = very serious).

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias arising from the randomisation process, bias due to deviation from the intended interventions, bias due to missing outcome data and bias in selection of the reported result)

b. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias arising from the randomisation process)

e. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias arising from the randomisation process, bias due to deviation from the intended interventions, bias due to missing outcome data and bias in measurement of the outcome)

f. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias arising from the randomisation process, bias due to deviation from the intended interventions and bias due to missing outcome data)

g. Downgraded by 2 increments as the majority of the evidence was of high risk of bias (due to bias arising from the randomisation process and bias in the measurement of reported result)

h. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias arising from the randomisation process, bias due to deviation from the intended interventions and bias due to missing outcome data)

i. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

j. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

k. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

1.1.6.1.7 Transcutaneous electrical nerve stimulation compared to placebo and usual care

Table 34: Clinical evidence summary: transcutaneous electrical nerve stimulation compared to placebo

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with Focal spasticity - TENS	
Spasticity outcome measures (Composite spasticity score. 0-16, lower values	100 (2 RCTs) follow-up: mean 7 weeks	⊕◯◯◯ Very low[a,b]	-	The mean spasticity outcome measures at ≤6 months was 5.9	MD **0.88 lower** (2.34 lower to 0.59 higher)	MID = 0.95 (0.5 x median baseline SD)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with Focal spasticity - TENS	
are better, final value and change score) at ≤6 months						
Spasticity outcome measures (Modified Ashworth Scale, 0-5, lower values are better, final values and change scores) at ≤6 months	132 (3 RCTs) follow-up: mean 6 weeks	⨁⨁◯◯ Low[c,d]	-	The mean spasticity outcome measures at ≤6 months was 1.2	MD **0.53 lower** (0.78 lower to 0.29 lower)	MID = 0.53 (0.5 x median baseline SD)
Physical function - lower limb (Timed up and go, seconds, lower values are better, final values) at ≤6 months	141 (3 RCTs) follow-up: 7 weeks	⨁◯◯◯ Very low[b,d,e]	-	The mean physical function - lower limb at ≤6 months was 29.0	MD **6.73 lower** (12.23 lower to 1.22 lower)	MID = 9.2 (0.5 x median baseline SD)
Physical function - lower limb (10m walk, seconds, lower values are better, change score) at ≤6 months	40 (1 RCT) follow-up: 6 weeks	⨁⨁◯◯ Low[a,d]	-	The mean physical function - lower limb at ≤6 months was -2.7	MD **2.6 lower** (3.41 lower to 1.79 lower)	MID = 2.2 (0.5 x median baseline SD)
Activities of daily living (Barthel index, 0-100, higher values are better, change score and final value) at ≤6 months	103 (2 RCTs) follow-up: mean 6 weeks	⨁◯◯◯ Very low[b,d,f]	-	The mean activities of daily living at ≤6 months was 37.1	MD **12.57 higher** (2.03 lower to 27.17 higher)	MID = Barthel Index 1.85 (established MID)
Withdrawal due to adverse events at ≤6 months	393 (8 RCTs) follow-up: mean 8 weeks	⨁◯◯◯ Very low[c,g,h]	RD -0.00 (-0.06 to 0.05)	76 per 1,000	**0 fewer per 1,000** (60 fewer to 50 more) [i]	Precision calculated through Optimal Information

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with Focal spasticity - TENS	
						Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.06 (0.8-0.9 = serious, <0.8 = very serious).

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias arising from the randomisation process)
b. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis
c. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias arising from the randomisation process, bias due to deviation from the intended intervention and bias due to missing outcome data)
d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
e. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias due to missing outcome data)
f. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a mixture of bias arising from the randomisation process, bias due to deviation from the intended intervention and bias due to missing outcome data)
g. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
h. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size
i. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

Table 35: Clinical evidence summary: transcutaneous electrical nerve stimulation compared to usual care

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with usual care	Risk difference with Focal spasticity - TENS	
Spasticity outcome measures (Modified Ashworth scale, composite spasticity score, 0-4, lower values are better, change scores) at ≤6 months	54 (1 RCT) follow-up: mean 8 weeks	⨁◯◯◯ Very low[a,b,c]	-	The mean spasticity outcome at ≤6 months was 0	**MD 0.16 higher** (1.47 higher to 1.79 higher)	MID = 0.29 (0.5 x median baseline SD)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with usual care	Risk difference with Focal spasticity - TENS	
Spasticity outcome measures (Modified Ashworth scale, composite spasticity score [different scale ranges], lower values are better, final values) at ≤6 months	161 (4 RCTs) follow-up: mean 8 weeks	⊕◯◯◯ Very low[c,d]	-	-	SMD **0.14 SD higher** (0.3 lower to 0.57 higher)	MID = 0.5 SD (SMD)
Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, final value) at >6 months	28 (1 RCT) follow-up: 3 years	⊕◯◯◯ Very low[c,e]	-	The mean spasticity outcome measures at >6 months was 1.4	MD **0.8 higher** (0.16 lower to 1.76 higher)	MID = 0.53 (0.5 x median baseline SD)
Physical function - upper limb (Fugl-meyer, 0-66, higher values are better, change score and final value) at ≤6 months	83 (2 RCTs) follow-up: mean 10 weeks	⊕◯◯◯ Very low[b,e]	-	The mean physical function - upper limb at ≤6 months was 15.8	**MD 1.60 lower** (-13.54 lower to 10.34 higher)	MID = 6.6 (Fugl-Meyer upper extremity = Difference by 10% of the total scale)
Physical function - upper limb (Fugl-meyer, 0-50, higher values are better, change score) at ≤6 months	44 (1 RCT) follow-up: 8 weeks	⊕⊕◯◯ Low[b,f]	-	The mean physical function - upper limb at ≤6 months was 0.7	MD **3.06 higher** (1.07 higher to 5.05 higher)	MID = 5.0 (Fugl-Meyer upper extremity = Difference by 10% of the total scale)
Physical function - upper limb (Fugl-meyer, 0-66, higher values are better, final value) at >6 months	28 (1 RCT) follow-up: 3 years	⊕◯◯◯ Very low[b,e]	-	The mean physical function - upper limb at >6 months was 24.2	MD **4 lower** (16.55 lower to 8.55 higher)	MID = 6.6 (Fugl-Meyer upper extremity = Difference by 10% of the total scale)
Physical function - lower limb (Timed up and go,	115 (2 RCTs) follow-up:	⊕◯◯◯ Very low[b,d]	-	-	MD **10.70 lower** (29.56 lower to	MID = 7.1 (0.5 x median baseline SD)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with usual care	Risk difference with Focal spasticity - TENS	
seconds, lower values are better, final values) at ≤6 months	mean 8 weeks				8.15 higher)	
Physical function - lower limb (10m walking scale, seconds, lower values are better, final value) at ≤6 months	32 (1 RCT) follow-up: 3 weeks	⊕◯◯◯ Very low[b,g]	-	The mean physical function - lower limb at ≤6 months was 29.69	MD **5.32 lower** (18.71 lower to 8.07 higher)	MID = 10.2 (0.5 x median baseline SD)
Pain (Numeric rating scale, 0-10, lower values are better, change score) at ≤6 months	54 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[b,h]	-	The mean pain at ≤6 months was -1.23	MD **0.34 lower** (3.34 lower to 2.66 higher)	MID = 0.57 (0.5 x median baseline SD)
Activities of daily living (Barthel index 0-100, higher values are better, change score) at ≤6 months	54 (1 RCT) follow-up: mean 8 weeks	⊕◯◯◯ Very low[a,b]	-	The mean activities of daily living at ≤6 months was 66.5	MD **1.74 lower** (39.53 lower to 43.01 higher)	MID = Barthel Index 1.85 (established MID)
Activities of daily living (functional independence measure, Barthel index [different scale ranges], higher values are better, final values) at ≤6 months	60 (2 RCTs) follow-up: mean 8 weeks	⊕⊕◯◯ Low[c]	-	-	SMD **0.03 SD higher** (0.49 lower to 0.55 higher)	MID = 0.5 SD (SMD)
Activities of daily living (Barthel index, 0-100, higher values are better, final values) at >6 months	28 (1 RCT) follow-up: 3 years	⊕◯◯◯ Very low[b,e]	-	The mean activities of daily living at >6 months was 66.5	MD **11.6 higher** (4.26 lower to 27.46 higher)	MID = Barthel Index 1.85 (established MID)
Stroke-specific Patient-Reported Outcome	54 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[b,h]	-	The mean stroke-specific Patient-	MD **1.91 lower** (43.34	MID = 12.6 (0.5 x median baseline SD)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with usual care	Risk difference with Focal spasticity - TENS	
Measures (SS-QOL, 49-245, higher values are better, change score) at ≤6 months				Reported Outcome Measures at ≤6 months was 10.77	lower to 47.16 higher)	
Withdrawal due to adverse events at ≤6 months	244 (4 RCTs) follow-up: 9 weeks	⊕◯◯◯ Very low[b,i,j]	RR 1.08 (0.53 to 2.20)	103 per 1,000	**8 more per 1,000** (49 fewer to 124 more)	MID (precision) = RR 0.8-1.25.
Withdrawal due to adverse events at >6 months	44 (1 RCT) follow-up: 3 years	⊕◯◯◯ Very low[b,e]	RR 0.52 (0.22 to 1.24)	444 per 1,000	**213 fewer per 1,000** (347 fewer to 107 more)	MID (precision) = RR 0.8-1.25.

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias due to missing outcome data)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a mixture of bias arising from the randomisation process, bias due to missing outcome data and bias in measurement of the outcome)

d. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

e. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a mixture of bias arising from the randomisation process and bias due to missing outcome data)

f. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias due to missing outcome data)

g. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias arising from the randomisation process and bias in measurement of the outcome)

h. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias due to missing outcome data and bias in measurement of the outcome)

i. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias arising from the randomisation process and bias due to missing outcome data)

j. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

1

1.1.6.1.8 Acupuncture compared to placebo and usual care

Table 36: Clinical evidence summary: acupuncture compared to placebo

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with Focal spasticity - Acupuncture	
Person/participant generic health-related quality of life (EQ-5D, -0.11-1, higher values are better, change score) at ≤6 months	23 (1 RCT) follow-up: 2 weeks	⨁⨁⨁◯ Moderate[a]	-	-	MD **0.09 higher** (0.03 higher to 0.15 higher)	MID = 0.03 (EQ-5D established MID)
Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, final value) at ≤6 months	47 (2 RCTs) follow-up: mean 3 weeks	⨁◯◯◯ Very low[b,c,d]	-	The mean spasticity outcome measures at ≤6 months was 1.29	MD **0.58 lower** (1.25 lower to 0.2 higher)	MID = 0.5 (0.5 x median baseline SD)
Physical function - upper limb (Fugl Meyer Assessment Upper Extremity, 0-66, higher values are better, change score) at ≤6 months	23 (1 RCT) follow-up: 2 weeks	⨁⨁◯◯ Low[a,d]	-	-	MD **4.18 higher** (0.34 lower to 8.7 higher)	MID = 6.6 (Fugl-Meyer upper extremity = Difference by 10% of the total scale)
Physical function - upper limb (Box and block test, 0-150, higher values are better, final value) at ≤6 months	24 (1 RCT) follow-up: 5 weeks	⨁⨁⨁◯ Moderate[d]	-	The mean physical function - upper limb at ≤6 months was 3.25	MD **3.59 higher** (2.03 lower to 9.21 higher)	MID = 3.1 (0.5 x median baseline SD)
Physical function - lower limb (10m walk, seconds, lower values are better, final value) at ≤6 months	24 (1 RCT) follow-up: 4 weeks	⨁⨁◯◯ Low[d,e]	-	The mean physical function - lower limb at ≤6 months was 18.42	MD **6.15 lower** (17.19 lower to 4.89 higher)	MID = 8.3 (0.5 x median baseline SD)
Activities of daily living (Barthel Index, 0-100, higher values are better, final	24 (1 RCT) follow-up: 4 weeks	⨁◯◯◯ Very low[d,e]	-	The mean activities of daily living at	MD **5.41 higher** (3.29 lower to 14.11 higher)	MID = Barthel Index 1.85

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with Focal spasticity - Acupuncture	
values) at ≤6 months				≤6 months was 73.34		(established MID)
Withdrawal due to adverse events at ≤6 months	187 (3 RCTs) follow-up: mean 4 weeks	⨁◯◯◯ Very low[f,g]	RD -0.01 (-0.05 to 0.03)	0 per 1,000	**10 fewer per 1,000** (50 fewer to 30 more) [h]	Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.30 (0.8-0.9 = serious, <0.8 = very serious).

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias arising from the randomisation process)

b. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias arising from the randomisation process and bias due to deviations from the intended interventions)

c. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

e. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias due to deviations from the intended interventions)

f. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

g. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

h. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

Table 37: Clinical evidence summary: acupuncture compared to usual care

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with usual care	Risk difference with Focal spasticity - Acupuncture	
Spasticity outcome	59 (1 RCT)	⨁⨁⨁◯ Moderate[a]	-	The mean spasticity	MD **0.37 lower**	MID = 0.39 (0.5 x

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with usual care	Risk difference with Focal spasticity - Acupuncture	
measures (Modified Ashworth scale, 0-4, lower values are better, final value) at ≤6 months	follow-up: 28 days			outcome measures at ≤6 months was 1.92	(0.73 lower to 0.01 lower)	median baseline SD)
Physical function - lower limb (Fugl-Meyer lower extremity, 0-34, higher values are better, final value) at ≤6 months	85 (1 RCT) follow-up: 28 days	⊕⊕⊕◯ Moderate[a]	-	The mean physical function - lower limb at ≤6 months was 19.57	MD **5.76 higher** (1.88 higher to 9.64 higher)	MID = 3.4 (Fugl-Meyer lower extremity = Difference by 10% of the total scale)
Activities of daily living (Barthel Index, 0-100, higher values are better, final value) at ≤6 months	59 (1 RCT) follow-up: 28 days	⊕⊕◯◯ Low[a]	-	The mean activities of daily living at ≤6 months was 66.55	MD **4.12 higher** (8.35 lower to 16.59 higher)	MID = Barthel Index 1.85 (established MID)
Withdrawal due to adverse events at ≤6 months	199 (2 RCTs) follow-up: mean 4 weeks	⊕⊕⊕◯ Moderate[b]	RD 0.00 (-0.03 to 0.03)	0 per 1,000	**0 fewer per 1,000** (30 fewer to 30 more) [c]	Sample size used to determine precision: 75-150 = serious imprecision, <75 = very serious imprecision.

[a]. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

[b]. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

[c]. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

1.1.6.1.9 Combination therapy: Abobotulinum toxin A (Dysport) and neuromuscular electrical stimulation (NMES) compared to abobotulinum toxin A (Dysport) alone

Table 38: Clinical evidence summary: Abobotulinum toxin A (Dysport) and functional electrical stimulation compared to abobotulinum toxin A (Dysport) only

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Abobotulinum toxin A (Dysport) only	Risk difference with Abobotulinum toxin A (Dysport) + Neuromuscular Electrical Stimulation	
Spasticity outcome measures (Modified Ashworth scale, 0-5, lower values are better, final value) at ≤6 months	12 (1 RCT) follow-up: 12 weeks	⨁⨁◯◯ Low[a,b]	-	The mean spasticity outcome measures at ≤6 months was 3.22	MD **0.78 lower** (1.86 lower to 0.3 higher)	MID = 0.59 (0.5 x median control SD)
Withdrawal due to adverse events at ≤6 months	12 (1 RCT) follow-up: 12 weeks	⨁◯◯◯ Very low[a,c,d]	RD 0.00 (-0.27 to 0.27)	0 per 1,000	**0 fewer per 1,000** (270 fewer to 270 more)	Sample size used to determine precision: 75-150 = serious imprecision, <75 = very serious imprecision.

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias arising from the randomisation process)
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c. Absolute effect calculated by risk difference due to zero events in at least one arm of one study
d. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

1.1.6.1.10 Combination therapy: Abobotulinum toxin A (Dysport) and neuromuscular electrical stimulation (NMES) compared to neuromuscular electrical stimulation (NMES) alone

Table 39: Clinical evidence summary: Abobotulinum toxin A (Dysport) and neuromuscular electrical stimulation compared to neuromuscular electrical stimulation only

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with functional electrical stimulation only	Risk difference with Abobotulinum toxin A (Dysport) + Neuromuscular Electrical Stimulation	
Spasticity outcome measures (Modified Ashworth scale, 0-5, lower values are better, final value) at ≤6 months	12 (1 RCT) follow-up: 12 weeks	⨁⨁◯◯ Low[a,b]	-	The mean spasticity outcome measures at ≤6 months was 3.11	MD **0.67 lower** (1.72 lower to 0.38 higher)	MID = 0.57 (0.5 x median control SD)
Withdrawal due to adverse events at ≤6 months	12 (1 RCT) follow-up: 12 weeks	⨁◯◯◯ Very low[a,c,d]	RD 0.00 (-0.27 to 0.27)	0 per 1,000	**0 fewer per 1,000** (270 fewer to 270 more)	Sample size used to determine precision: 75-150 = serious imprecision, <75 = very serious imprecision.

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias arising from the randomisation process)
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c. Absolute effect calculated by risk difference due to zero events in at least one arm of one study
d. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

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1.1.6.1.11 Combination therapy: Abobotulinum toxin A (Dysport) and transcutaneous electrical nerve stimulation (TENS) compared to placebo and transcutaneous electrical nerve stimulation

Table 40: Clinical evidence summary: abobotulinum toxin A (Dysport) and transcutaneous electrical nerve stimulation compared to placebo and transcutaneous electrical nerve stimulation

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Placebo + TENS	Risk difference with Focal spasticity - Abobotulinum toxin A (Dysport) + TENS	
Spasticity outcome measures (Modified Ashworth scale, 0-5, lower values are better, final value) at ≤6 months	29 (1 RCT) follow-up: 6 months	⨁⨁◯◯ Low[a]	-	The mean spasticity outcome measures at ≤6 months was 3.2	MD **0.3 lower** (1.08 lower to 0.48 higher)	MID = 0.33 (0.5 x median baseline SD)
Pain (VAS, 0-100, lower values are better, final value) at ≤6 months	29 (1 RCT) follow-up: 6 months	⨁⨁⨁◯ Moderate[a]	-	The mean pain at ≤6 months was 48.3	MD **18.2 lower** (35.37 lower to 1.03 lower)	MID = 7.7 (0.5 x median baseline SD)
Withdrawal due to adverse events at ≤6 months	29 (1 RCT) follow-up: 6 months	⨁⨁◯◯ Low[b]	RD 0.00 (-0.12 to 0.12)	0 per 1,000	**0 fewer per 1,000** (120 fewer to 120 more) [c]	Sample size used to determine precision: 75-150 = serious imprecision, <75 = very serious imprecision.

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

b. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

c. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

1.1.6.1.12 Combination therapy: Onabotulinum toxin A (BOTOX) and functional electrical stimulation compared to onabotulinum toxin A (BOTOX) only

Table 41: Clinical evidence summary: onabotulinum toxin A (BOTOX) and functional electrical stimulation compared to onabotulinum toxin A (BOTOX) only

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Onabotulinum toxin A (BOTOX) only	Risk difference with Focal spasticity - Onabotulinum toxin A (BOTOX) + Functional Electrical Stimulation	
Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, final value) at ≤6 months	80 (1 RCT) follow-up: 12 weeks	⨁◯◯◯ Very low[a,b]	-	The mean spasticity outcome measures at ≤6 months was 2.88	MD **0.62 lower** (0.88 lower to 0.36 lower)	MID = 0.27 (0.5 x median baseline SD)
Physical function - lower limb (Fugl-meyer assessment, 0-34, higher values are better, final value) at ≤6 months	80 (1 RCT) follow-up: 12 weeks	⨁⨁◯◯ Low[a]	-	The mean physical function - lower limb at ≤6 months was 16.88	MD **8.28 higher** (7.96 higher to 8.6 higher)	MID = 3.4 (Fugl-Meyer lower extremity = Difference by 10% of the total scale)
Activities of daily living (Barthel index, 0-100, higher values are better, final value) at ≤6 months	80 (1 RCT) follow-up: 12 weeks	⨁⨁◯◯ Low[a]	-	The mean activities of daily living at ≤6 months was 61.87	MD **20.3 higher** (16.21 higher to 24.39 higher)	MID = Barthel Index 1.85 (established MID)

a. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias due to deviations from the intended interventions and bias due to missing outcome data)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1.1.6.2 Generalised spasticity

1.1.6.2.1 Tizanidine compared to oral baclofen

Table 42: Clinical evidence summary: tizanidine compared to oral baclofen

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Baclofen (oral)	Risk difference with Generalised spasticity - Tizanidine	
Withdrawal due to adverse events at >6 months	30 (1 RCT) follow-up: 12 months	⨁◯◯◯ Very low[a,b]	RR 0.25 (0.03 to 1.98)	267 per 1,000	**200 fewer per 1,000** (259 fewer to 261 more)	MID (precision) = RR 0.8-1.25.

[a.] Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias due to deviations from the intended interventions)

[b.] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1.1.6.2.2 Intrathecal baclofen compared to usual care

Table 43: Clinical evidence summary: intrathecal baclofen compared to usual care

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with usual care	Risk difference with Generalised spasticity - Intrathecal baclofen	
Person/participant generic health-related quality of life (EQ-5D-3L, -0.11-1, higher values are better, change score) at ≤6 months	51 (1 RCT) follow-up: 6 months	⨁◯◯◯ Very low[a,b]	-	The mean person/participant generic health-related quality of life at ≤6 months was 0.01	MD **0.08 higher** (0.04 lower to 0.2 higher)	MID = EQ-5D 0.03 (established MID)
Spasticity outcome measures (Modified Ashworth Scale, 0-4, lower values are better,	51 (1 RCT) follow-up: 6 months	⨁⨁⨁◯ Moderate[b]	-	The mean spasticity outcome measures at ≤6 months was -0.3	MD **0.53 lower** (0.92 lower to 0.14 lower)	MID = 0.36 (0.5 x median control group SD)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with usual care	Risk difference with Generalised spasticity - Intrathecal baclofen	
change score) at ≤6 months						
Pain (NRS, 0-10, lower values are better, change score) at ≤6 months	51 (1 RCT) follow-up: 6 months	⊕⊕◯◯ Low[a,b]	-	The mean pain at ≤6 months was 2.66	MD **1.17 higher** (0.6 lower to 2.94 higher)	MID = 1.56 (0.5 x median baseline SD)
Activities of daily living (Functional Independence Measure total score, 18-126, high values are better, change score) at ≤6 months	51 (1 RCT) follow-up: 6 months	⊕⊕⊕◯ Moderate[a]	-	The mean activities of daily living at ≤6 months was 19.45	MD **5.26 higher** (0.59 lower to 11.11 higher)	MID = Functional Independence Measure 22 (established MID)
Stroke-specific Patient-Reported Outcome Measures (SS-QOL, 1-5, higher values are better, change score) at ≤6 months	51 (1 RCT) follow-up: 6 months	⊕⊕◯◯ Low[a,b]	-	The mean stroke-specific Patient-Reported Outcome Measures at ≤6 months was 0.64	MD **0.21 higher** (0.11 lower to 0.53 higher)	MID = 0.34 (0.5 x median baseline SD)
Withdrawal due to adverse events at ≤6 months	60 (1 RCT) follow-up: 6 months	⊕⊕◯◯ Low[b]	Peto OR 6.93 (0.14 to 349.88)	0 per 1,000	**30 more per 1,000** (50 fewer to 120 more) [c]	MID (precision) = Peto OR 0.8-1.25.

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias in measurement of the outcome)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

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1.1.6.2.3 Acupuncture compared to placebo and usual care

Table 44: Clinical evidence summary: acupuncture compared to placebo

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with Generalised spasticity - Acupuncture	
Person/participant generic health-related quality of life (Nottingham health profile part 1, 0-100, higher values are better, change score) at ≤6 months	19 (1 RCT) follow-up: 3 months	⊕◯◯◯ Very low[a,b]	-	-	MD **1.27 lower** (7.5 lower to 4.96 higher)	MID = 3.42 (0.5 x mean difference SD)
Spasticity outcome measures (Modified Ashworth scale, unclear scale range, lower values are better, change score) at ≤6 months	238 (1 RCT) follow-up: 12 weeks	⊕⊕⊕◯ Moderate[b]	-	The mean spasticity outcome measures at ≤6 months was -12.91	MD **5.4 lower** (7.81 lower to 2.99 lower)	MID = 3.4 (0.5 x median baseline SD)
Spasticity outcome measures (Modified Ashworth scale wrist, 0-4, lower values are better, change score) at ≤6 months	19 (1 RCT) follow-up: 3 months	⊕⊕◯◯ Low[b,c]	-	-	MD **0.57 lower** (1.5 lower to 0.36 higher)	MID = 0.51 (0.5 x mean difference SD)
Spasticity outcome measures (Modified Ashworth scale elbow, 0-4, lower values are better, change score) at ≤6 months	19 (1 RCT) follow-up: 3 months	⊕◯◯◯ Very low[b,c]	-	-	MD **0.2 lower** (1.4 lower to 1 higher)	MID = 0.66 (0.5 x mean difference SD)
Physical function - general (FMA, 0-100, higher values are better, change score) at ≤6 months	238 (1 RCT) follow-up: 12 weeks	⊕⊕⊕◯ Moderate[b]	-	The mean physical function - general at ≤6 months was 24.9	MD **12.86 higher** (7.5 higher to 18.22 higher)	MID = 10.0 (Fugl-Meyer overall = Difference by 10% of the total scale)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with Generalised spasticity - Acupuncture	
Physical function - upper limb (FMA-UE, 0-66, higher values are better, change score) at ≤6 months	19 (1 RCT) follow-up: 3 months	⊕⊕⊕◯ Moderate [c]	-	-	MD **0.05 higher** (4.2 lower to 4.3 higher)	MID = 6.6 (Fugl-Meyer upper extremity = Difference by 10% of the total scale)
Pain (visual analogue scale, 0-10, lower values are better, change score) at ≤6 months	48 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b]	-	The mean pain at ≤6 months was 0.27	MD **1.38 lower** (2.7 lower to 0.06 lower)	MID = 1.3 (0.5 x median baseline SD)
Activities of daily living (Barthel index, 0-100, higher values are better, change score) at ≤6 months	305 (3 RCTs) follow-up: mean 11 weeks	⊕◯◯◯ Very low[b,d,e]	-	-	MD **5.2 higher** (4.96 lower to 15.36 higher)	MID = Barthel Index 1.85 (established MID)
Stroke-specific Patient-Reported Outcome Measures (stroke specialisation QOL scale, 49-245, higher values are better, change score) at ≤6 months	238 (1 RCT) follow-up: 12 weeks	⊕⊕⊕⊕ High	-	The mean stroke-specific Patient-Reported Outcome Measures at ≤6 months was 40.63	MD **26.59 higher** (17.3 higher to 35.88 higher)	MID = 16.7 (0.5 x median baseline SD)
Withdrawal due to adverse events at ≤6 months	48 (1 RCT) follow-up: mean 10 weeks	⊕◯◯◯ Very low[b,e]	RR 0.36 (0.03 to 3.67)	100 per 1,000	**64 fewer per 1,000** (97 fewer to 267 more)	MID (precision) = RR 0.8-1.25.

a. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a mixture of bias due to missing outcome data and bias in selection of the reported result)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias due to missing outcome data)

d. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

e. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias due to deviations from the intended interventions and bias due to missing outcome data)

1

2 **Table 45: Clinical evidence summary: acupuncture compared to usual care**

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with usual care	Risk difference with Generalised spasticity - Acupuncture	
Physical function - general (FMA total score, 0-226, higher values are better, change score) at ≤6 months	29 (1 RCT) follow-up: 2 weeks	⊕⊕⊕◯ Moderate[a]	-	The mean physical function - general at ≤6 months was 7.7	MD **2.2 lower** (11.74 lower to 7.34 higher)	MID = 26.6 (Fugl-Meyer total score = Difference by 10% of the total scale)
Physical function - general (FMA total motor score, 0-100, higher values are better, final values) at ≤6 months	215 (2 RCTs) follow-up: mean 4 weeks	⊕◯◯◯ Very low[b,c,d]	-	The mean physical function - general at ≤6 months was 37.0	MD **25.15 higher** (1.15 higher to 49.14 higher)	MID = 10.0 (Fugl-Meyer total score = Difference by 10% of the total scale)
Activities of daily living (Barthel Index, 0-100, higher values are better, final values) at ≤6 months	215 (2 RCTs) follow-up: mean 4 weeks	⊕◯◯◯ Very low[b,c]	-	The mean activities of daily living at ≤6 months was 46.29	MD **22.17 higher** (1.98 higher to 42.35 higher)	MID = Barthel Index 1.85 (established MID)
Activities of daily living (FIM, 18-126, higher values are better, change score) at ≤6 months	29 (1 RCT) follow-up: 2 weeks	⊕⊕⊕◯ Moderate[a]	-	The mean activities of daily living at ≤6 months was 8.5	MD **2.7 higher** (0.34 lower to 5.74 higher)	MID = Functional Independence Measure 22 (established MID)
Withdrawal due to adverse events at ≤6 months	157 (2 RCTs) follow-up: mean 3 weeks	⊕◯◯◯ Very low[a,d]	RR 1.33 (0.32 to 5.53)	34 per 1,000	**10 more per 1,000** (60 fewer to 90 more) [e]	MID (precision) = RR 0.8-1.25.

[a.] Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias arising from the randomisation process)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with usual care	Risk difference with Generalised spasticity - Acupuncture	

b. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias arising from the randomisation process and bias due to deviations from the intended intervention)

c. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

e. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

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2 ***1.1.6.2.4 Electroacupuncture compared to acupuncture and usual care***

3 **Table 46: Clinical evidence summary: electroacupuncture compared to acupuncture**

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Acupuncture	Risk difference with Generalised spasticity - Electroacupuncture	
Spasticity outcome measures (Modified Ashworth scale, 0-5, lower values are better, final value) at ≤6 months	25 (1 RCT) follow-up: 15 days	⊕⊕◯◯ Low[a]	-	The mean spasticity outcome measures at ≤6 months was 3.2	MD **1.1 lower** (1.74 lower to 0.46 lower)	MID = 0.44 (0.5 x median baseline SD)

a. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias arising from the randomisation process, bias due to deviations from the intended interventions and bias in measurement of the outcome)

4

5 **Table 47: Clinical evidence summary: electroacupuncture compared to usual care**

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with usual care	Risk difference with Generalised spasticity - Electroacupuncture	
Spasticity outcome measures (Composit	240 (1 RCT) follow-up: 6 weeks	⊕⊕◯◯ Low[a]	-	The mean spasticity outcome	MD **0.31 higher** (0.04 lower to 0.66 higher)	MID = 1.28 (0.5 x median

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with usual care	Risk difference with Generalised spasticity - Electroacupuncture	
e spasticity scale, 0-16, lower values are better, final value) at ≤6 months				measures at ≤6 months was 7.31		baseline SD)
Physical function - lower limb (Fugl Meyer lower limb, 0-34, higher values are better, final value) at ≤6 months	240 (1 RCT) follow-up: 6 weeks	⨁⨁◯◯ Low[a]	-	The mean physical function - lower limb at ≤6 months was 16.13	MD **1.25 higher** (0.37 higher to 2.13 higher)	MID = 3.4 (Fugl-Meyer lower extremity = Difference by 10% of the total scale)
Withdrawal due to adverse events at ≤6 months	240 (1 RCT) follow-up: 6 weeks	⨁⨁⨁◯ Moderate [b]	RD 0.00 (-0.02 to 0.02)	0 per 1,000	**0 fewer per 1,000** (20 fewer to 20 more) [c]	Sample size used to determine precision: 75-150 = serious imprecision, <75 = very serious imprecision.

a. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias arising from the randomisation process and bias in measurement of the outcome)

b. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias arising from the randomisation process)

c. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

See Appendix F or full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

Five health economic studies relating to botulinum toxin A were included in this review.[24, 72, 111 18, 69] Four studies focused on upper limb spasticity (stratified as focal spasticity in the protocol), with each evaluating a different form of botulinum toxin A (abobotulinum toxin A [Dysport®][111], incobotulinum toxin A [Xeomin®][72] or onabotulinum toxin A [BOTOX®][24, 69]), respectively. One study included a comparison of abobotulinum toxin A [Dysport®] with onabotulinum toxin A [BOTOX®] and included separate analyses in upper limb spasticity and lower limb spasticity.[18]

One health economic study in a subacute population comparing 4-6 dry needling sessions plus physiotherapy to physiotherapy alone was included in this review.[32]

These are summarised in the health economic evidence profiles below (Table 48, Table 49, Table 50, Table 51 and Table 52) and the health economic evidence tables in Appendix H .

No health economic studies were included that related to oral medicine, intrathecal baclofen, functional electrical stimulation (FES), neuromuscular electrical stimulation (NMES), transcutaneous electrical nerve stimulation (TENS), acupuncture or electroacupuncture.

1.1.7.2 Excluded studies

Four economic studies relating to this review question were identified but were excluded due to a combination of limited applicability and methodological limitations.[31, 33, 63, 104] These are listed in Appendix J with reasons for exclusion given.

See also the health economic study selection flow chart in Appendix G.

1.1.8 Summary of included economic evidence for focal spasticity

Table 48: Health economic evidence profile: abobotulinum toxin type A plus therapy versus therapy alone

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Shackley 2012[111] (UK)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Within-trial analysis based on BoTULS RCT by Shaw, 2010[113]. • Cost-utility analysis (QALYs) • Population: adults with spasticity and reduced upper limb function due to stroke greater than one month. • Comparators: 1. 4-week upper limb therapy programme (one hour of therapy twice weekly provided by a study therapist). 2. Abobotulinum toxin A (Dysport®); (mean dose: 505 units) plus a 4-week upper limb therapy programme. Time horizon: 3 months	£374[(c)]	0.004 QALYs	£93,500 per QALY gained	Probability of botulinum toxin type A plus therapy being cost-effective (£20K threshold): 36%. The ICER remained well above £20,000 per QALY gained in sensitivity analyses.

Abbreviations: ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life years; RCT= randomised controlled trial.

(a) 2005-2008 resource use and 2007-unit costs may not reflect current NHS context.

(b) 3-month time horizon will not fully capture differences in costs and outcomes: people were allowed repeat botulinum toxin A injections and/or upper limb therapy at 3, 6 and 9 months in the RCT which will not be captured; mean difference in EQ-5D was greater at 12 month follow-up than at 3 months and so differences appear to also continue beyond 3 months (although there was also much greater loss of participant responses in the RCT [85.2% at 3 months and 52.4% at 12 months] which was the rationale for not using this longer term data in the economic evaluation). Within-trial analysis and so by definition only reflects one of a number of studies identified in the clinical review relating to abobotulinum toxin A. Assumptions had to be made regarding the use of other health care and social services resources during the second month of the three-month analysis period as questionnaires were completed at 1 and 3 months but only asked about the previous month.

(c) 2007 UK pounds. Cost components incorporated: Drug cost of botulinum toxin type A, upper limb therapy sessions provided by chartered physiotherapists, other anti-spasticity medication, management of adverse events attributable to botulinum toxin type A (and/or upper limb therapy requiring a hospital contact) and other health care and social services resource use (e.g., GP, district nurse, physiotherapist, occupational therapist, clinical psychologist, and home care services). Abobotulinum toxin A unit costs similar to current UK costs (£156 vs £154 for 505 units).

1 **Table 49: Health economic evidence profile: onabotulinum toxin type A plus therapy versus therapy alone**

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Doan 2013[24] (Scotland)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Deterministic model assessed 3 costing scenarios using effectiveness evidence from Brashear 2002[7]: ○ Scenario 1: Onabotulinum toxin A use, specialist office visits and day-hospital visits. ○ Scenario 2: Onabotulinum toxin A use and specialist office visits only. ○ Scenario 3: Scenario one plus informal care costs. • Cost-utility analysis (QALYs) • Population: Adults with upper-limb post-stroke spasticity and moderate or severe disability (protocol strata: focal spasticity). • Comparators: 1. Usual care, defined as routine physical therapy and occupational therapy (but not drug therapy). 2. Onabotulinum toxin A (BOTOX®) (mean dose: 221.3 U/injection) plus usual care. • Time horizon: 5 years	2 vs 1[(c)]: Scenario 1: £1,099 Scenario 2: £2,903 Scenario 3: saves £1,899	Scenarios 1, 2 and 3: 0.107 QALYs	Scenario 1: £10,271 per QALY gained Scenario 2: £27,134 per QALY gained Scenario 3: Dominates intervention 1 (lower costs and higher QALYs).	Scenario 1: all ICERs <£20,000 in sensitivity analyses Scenario 2: all ICERs >£20,000 in sensitivity analysis. Scenario 3: NR
Lindsay 2022[69] (UK)	Partially applicable[(d)]	Potentially serious limitations[(e)]	• Secondary within-trial analysis based on RCT included in the clinical review (Lindsay 2021[70]) • Cost-effectiveness analysis (health outcomes: BI, ARAT)) • Population: Adults who developed upper limb spasticity within six weeks of a first stroke and no useful arm function (i.e., ARAT grasp-score of <2).	2 vs 1: Saves £1,081[(f)]	BI improvement ≤6 months (2 vs 1): 0.87[(g)] ARAT score (mean CFB) at ≤6 months:[70]	Saves £1,240 per unit of improvement on the BI. Saves £450 per unit of improvement for the ARAT.	Applying the upper 95% CI bounds of the results resulted in a cost per unit of improvement of £1,124 for the BI and £346 for the ARAT. This increased to £3,773 and £978

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			• Comparators: 1. Placebo/sham (n=48) 0.9% sodium chloride solution placebo. 2. Onabotulinum Toxin A (BOTOX®) (n=49). Intramuscular injections of onaBoNT-A were administered to all six muscles of the affected arm in predetermined doses. • Follow-up: 6 months		(2 vs 1): 2.9[g]	The cost savings and mean differences of the BI and ARAT score at 6 months were not statistically significant between study groups, however, the cost saving of £1,481 for the treatment of contractures was statistically significant for the onaBoNT-A group.	per point improvement when the lower 5% bounds were used for the BI and ARAT scores, respectively.

Abbreviations: ARAT= action research arm test (scale 0-57, higher values are better); BI= modified Barthel Index (scale 0-100, higher values are better); CFB= change from baseline; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health]; ICER= incremental cost-effectiveness ratio; NR= not reported; OnaBoNT-A= onabotulinumtoxinA ; QALY= quality-adjusted life years; RCT= randomised controlled trial. 95% CI= 95% confidence interva.

(a) Resource use and unit costs may not reflect current NHS context (2008-2010 UK unit costs and older published resource use). EQ-5D-3L USA tariff was but the NICE reference case specifies the UK tariff is preferred.

(b) It is unclear if the 5-year time horizon is sufficiently long to capture all costs and health outcomes of treatment; it appears that in the model people continue to receive botulinum toxin if obtaining benefit and it is not reported whether there are still people receiving it at 5 years. Transition probabilities between disability-based health states with usual care and onabotulinum toxin A are based on 12-week data from Brashear 2002 RCT (USA 1999 to 2000) included in clinical review (and for onabotulinum toxin A only also a 42-week follow-up study) and so only reflects this study and not the wider evidence base identified in the clinical review. Scenario 1 justified inclusion of reduction in day hospitalisation rate with onabotulinum toxin A based on it being the only significant difference in the BOTULS RCT analysis but this study also reported statistically significant differences in the proportion of participants reporting contacts for practice nurse and social worker; and overall its cost analysis also found an increase in other costs with botulinum toxin A. Probabilistic analysis was not undertaken to quantify parameter uncertainty. Study funded by Allergan (manufacture onabotulinum toxin A).

(c) 2008-2010 UK pounds. Cost components incorporated: Onabotulinum toxin A use, specialist office visits and day-hospital visits and informal care costs (inclusion of health care visits and informal care costs depended on the scenario). Onabotulinum toxin A unit costs same as current UK costs (£306 vs £306 for 221 units).

(d) QALYs not calculated as EQ-5D not reported. 2012-2013 resource use estimates may not reflect current UK context.
(e) Within-trial secondary analysis so costs and outcomes only reflect this trial with a small sample size and not the wider evidence base identified in the clinical review. 6-month follow-up may be insufficient to reflect differences in all costs and outcomes. Long-term costs for the management of contractures were taken from a 2001 US study (the method of currency conversion was also not reported).
(f) 2019 UK pounds. Total costs were not statistically significant between groups (p=0.655). Cost components included: drug costs at discharge from hospital and at 3 and 6 months; length of stay (initial hospitalisation and readmission), intervention costs and treatments to manage contractures.
(g) Change from baseline was not statistically significant between groups for both BI scores (p=0.47) and ARAT scores (0.51).

Table 50: Health economic evidence profile: incobotulinum toxin type A plus therapy versus therapy alone

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Makino 2019[72] (Australia)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Probabilistic decision analytic model based on RCT included in the clinical review (Kanovsky et al. 2009).[59] • Cost-utility analysis (QALYs) • Population: Adults who have had a stroke more than 2 months prior, experiencing moderate to severe upper limb spasticity. (protocol strata: focal spasticity). • Comparators: 1. Incobotulinum toxin A (Xeomin®) for a maximum of four cycles (everyone receives 2 cycles; responders get additional cycles up to 4). 2. Unlimited incobotulinum toxin-A (Xeomin®) treatment cycles (everyone receives treatment for 2 cycles, responders continue to get additional cycles with no upper limit) • Time horizon: 5 years	£2,153[(c)]	0.0758 QALYs	£28,457 per QALY gained	Probability Intervention 2 is cost effective (£20K/30K threshold): <10%/~55% (estimated from graph). Results were not sensitive to adjustments made to the model time horizon, response rate, utility and cost inputs, treatment discontinuation, disease natural resolution and discount rates.

Abbreviations: ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life years; RCT= randomised controlled trial.

(a) Australian 2010-2014 resource use and 2016 unit costs may not reflect current UK NHS context. Incobotulinum toxin A unit costs higher than current UK costs (£627 vs £457 for 352 units).EQ-5D-3L was calculated using Australian population valuation tariff was used but the NICE reference case specifies the UK tariff is preferred. Costs and health effects were discounted at a non-reference case rate (5% rather than 3.5%).

(b) Effectiveness based on data from Kanovsky 2009 RCT[59] included in clinical review (and open label extension) and so only reflects this study and not the wider evidence base identified in the clinical review. Response rates are based on botulinum toxin group in trial only and so do not account for response rate in those not receiving treatment in base-case analysis, however this is added in a sensitivity analysis. EQ-5D is based on data from the same RCT but difference by randomised group is not reported and this is not discussed. EQ-5D questionnaires collection times were not reported and analysis methods for estimation for responders and non-responders were unclear. Only costs directly associated with the provision of injections were included; if disability reduced then potentially other costs could be impacted. Funded by Merz Pharmaceuticals (manufacture incobotulinum toxin A).

(c) 2016 Australian dollars converted to UK pounds. Cost components included: Drug acquisition (drug costs and dispensing fees) and administration costs (a specialist consultation and other services associated with the administration procedure (e.g., injection, neuromuscular stimulation, ultrasound). Incobotulinum toxin A unit costs higher than current UK costs (£627 vs £457 for 352 units).

Table 51: Health economic evidence profile: onabotulinum toxin A versus abobotulinum toxin A

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Danchenko 2022[18] (UK)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Probabilistic (dynamic) decision analytic model with separate analyses conducted for adults with upper limb (AUL) and lower limb (ALL) spasticity. • Cost-utility analysis (health outcome: QALYs) • Population: Adults with post-stroke spasticity presenting for treatment with BoNT-A in routine clinical practice • Comparators: 1. OnabotulinumtoxinA (Botox®): AUL group received onaBoNT-A every 29 weeks (Mean (SD) dose: 256 units (136 U)). ALL group assumed to be given onaBoNT-A every 12 weeks (Mean (SD) dose: 400 units (NR)) 2. AbobotulinumtoxinA (Dysport®): AUL group received Dysport every 32 weeks (Mean (SD) dose: 843 units (353 U)). ALL grouped assumed to be	2 vs 1: Saves £304/£394 for AUL/ALL indications[(c)]	2 vs 1: 0.02/0.01 QALYs gained for AUL/ALL indications	AbobotulinumtoxinA (Dysport®) dominates OnabotulinumtoxinA (Botox®) (Less costs and higher QALYs)	Probability Intervention 2 cost effective (£20K/30K threshold): 100% for both AUL and ALL indications/NR Scenario analyses showed the results for both indications to be robust for all changes apart from scenario where ALL non-responders received one injection, which resulted in higher costs (incr. £215) and higher QALYs (incr. 0.01) for aboNT-A group (ICER of £21,234).

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			given aboBoNT-A every 12 weeks (Mean (SD) dose: 1,500 units (NR)) Time horizon: 1 year				

Abbreviations: AboNT-A= AbobotulinumtoxinA; ALL= Adults with lower limb [spasticity]; AUL= Adults with upper limb [spasticity]; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health]; ICER= incremental cost-effectiveness ratio; NR= not reported; OnaBoNT-A= onabotulinumtoxinA; QALYs= quality-adjusted life years.

(a) Control group was not incorporated into the analysis. Unclear whether AUL population is comprised of ≥80% stroke survivors. Utility values for ALL indication were calculated using EQ-5D-5L when NICE reference case prefers EQ-5D-3L.

(b) Utility values used, although taken from people with post-stroke spasticity, were not based on the same measure of response used in this analysis: MAS and GAS, but rather based on EQ-5D data for different walking speeds and DAS, respectively. Outcomes used for response rates have shortcomings as the MAS does not necessarily correlate directly with health-related quality of life (HRQoL) as a theoretical construct, while the subjective nature and variability in the assessment of GAS scores do not easily facilitate comparisons between patients or groups. Treatment response rates in the AUL indication was based on observational data. Resource use estimates were based on a survey of 12 UK physicians and not a systematic review of the literature. Resource use estimates and dosing assumptions for AUL were applied to the ALL indication as real-world data for ALL was not available. Assumption applied to frequency of treatment doses for ALL indication as no comparative data available. One year time horizon may not sufficiently capture all costs and outcomes associated with the interventions. Utility inputs for ALL were not based on a stroke-specific population. Study was funded by manufacturer (Ipsen) of AboNT-A (Dysport®).

(c) 2018-2020 UK pounds. Costs components include treatment acquisition and administration, healthcare appointments, and concomitant oral medications

Table 52: Dry needling plus physiotherapy versus physiotherapy

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Fernandez-Sanchis 2022[32] (Spain)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Within-trial analysis of an observational study (Zaldivar 2021[16] (n=80)) with no modelled extrapolation. • Cost-utility analysis (health outcome: QALYs) • Population: Adults (≥18 years old) diagnosed with stroke in the subacute phase (1–3 months) resulting in upper limb spasticity. • Comparators: 1. Control group (n=40) who received standard physiotherapy, 45-minute	2 vs 1[(c)]: • 4 weeks: £3,709 • 8 weeks: £7,229	2 vs 1: • 4 weeks: 0.02 QALYs • 8 weeks: 0.03 QALYs	2 vs 1: • 4 weeks: £161,283 per QALY gained (not cost-effective) 8 weeks: £216,527 per QALY gained (not cost-effective)	Probability Intervention 2 cost-effective (£26,645 (€25,000) threshold): • 4 weeks: 7.5% • 8 weeks: 8% Cost-effectiveness results using responder rates were positive in all cases for DNHS®. The results also indicated that 4 weeks of treatment

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			sessions were given five days per week for 8 weeks. 2. Intervention group (n=40) received standard physiotherapy plus dry needling with the DNHS® technique. DNHS® treatment was included in six of the standard treatment sessions. Follow-up: 4 and 8 weeks				could be more profitable than treatments lasting 8 weeks: the mean difference between cost per responder at 4 weeks was £39,593 cheaper than at 8 weeks.

Abbreviations: CI = 95% confidence interval; DNHS= dry needling for hypertonia and spasticity; EQ-5D= EuroQol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NA= not applicable; QALY= quality-adjusted life years; RCT= randomised controlled trial.

(a) Spanish healthcare system may not reflect current UK NHS practice. QALYs were estimated using EQ-5D-5L (Spanish tariff) when the NICE reference case currently prefers EQ5D-3L (UK tariff).

(b) Baseline outcomes and intervention effects were based on single non-randomised observational study excluded from clinical review. 8-week follow-up may not sufficiently assess the full costs and benefits. Only intervention related healthcare costs and resource use incorporated into the analysis, no downstream resource use included. References for unit costs (including cost year - with the exception of costs per patient stay) were not reported. One conflict of interest was declared as the DNHS® technique was registered by a study author.

(c) 2016 euros (€) converted to 2016 UK pounds purchasing power parities.[96] References for unit costs were not reported but were assumed to be 2016 as this was the same year used to assess the average cost per patient stay. Cost components incorporated: Dry needling materials, cost per physiotherapy session and average cost per day of neurological patients.

1.1.9 Economic modelThe key priority areas identified for further health economic modelling were BoNT-A and intrathecal baclofen (ITB), as they are high-cost interventions and sufficient clinical evidence has been identified to allow for modelling. ITB and BoNT-A are used at different lines of therapy – BoNT-A may be used first line in people with focal spasticity; ITB is only used when other treatments have not worked – as a result separate analyses have been undertaken (ITB costing and threshold analysis work reported in the unit cost section below).

Further rationale for prioritising BoNT-A for a de novo analysis was that the published cost effectiveness evidence was mixed with some studies finding it cost effective and others not (five cost utility analyses, reported above). Finally, although BoNT-A is used currently in people with stroke, the committee considered that a positive recommendation would result in increased use that could result in a significant resource impact.

Model methods

A cost-utility analysis was undertaken where quality-adjusted life years (QALYs) and costs over a 12 week, 1- and 2-year time horizon from a current UK NHS and personal social services perspective were considered. The rationale for not including a lifetime horizon was that there is no evidence to suggest spasticity treatments would impact mortality. Furthermore, based on assessment of need, the literature suggested that most people received up to 4 injection cycles, approximately every 12 weeks and the number of patients requiring additional cycles progressively decreases (Turner Stokes 2021, Shaw 2012). [113, 129] Therefore, a 1-year time horizon was deemed sufficient to capture the impact of repeat injections of BoNT-A. A sensitivity analysis was conducted exploring a longer 2-year horizon. Discounting at 3.5% for costs and health effects was applied for the 2-year scenario analysis. An incremental analysis was undertaken.

The population of the analysis was adults with post-stroke focal spasticity. Lower and upper limb focal spasticity were sub-grouped due to heterogeneity in the clinical review. The same approach was deemed appropriate in the health economic modelling, particularly as doses are different. Xeomin is not licensed for use in lower limb spasticity and so will not be a comparator in the lower limb model population. Of note, clinical evidence reporting outcomes that can inform the economic model is not available for all drugs for all indications (see summary of evidence below). As a result, the comparators included by type of focal spasticity were:

Lower limb spasticity:

1. Usual care
2. OnaBoNT-A (BOTOX®)

Upper limb spasticity:

1. Usual care
2. AboBoNT-A (Dysport®)
3. IncoBoNT-A (Xeomin®)

The dosing reported in the clinical trials informing the model was used to cost the different BoNT-A drugs.

QALYs were estimated using Modified Ashworth Scale (MAS) responder data from the clinical review. The studies defined a MAS responder as a ≥1 point reduction in MAS, as this is considered statistically meaningful. Three RCTs were identified in the systematic review of the literature reporting MAS responder data, one for each drug (Elovic 2016[28], Gracies 2015[37] and Wein 2018[137]). The MAS responder data was reported at multiple time points thus allowing for QALYs over the trial period to be estimated using an area under the curve

approach and applying 'responder' and 'non-responder' EQ-5D values, as done in one of the published cost utility analyses, Makino 2019.[72]

Several scenarios were explored whereby the time horizon was extend to 1 year and 2 years to account for repeat injections of BoNT-A. Repeat injections occur at a minimum of 12-week intervals. The total number of injections in a year was assumed to be 4 and the proportion receiving repeat injections progressively decreased. This was based on observational and UK RCT evidence. [113, 129]

For repeat injections, it is assumed the QALY gain after a repeat injection will be the same as the QALY gain after the first injection, as the responders will continue to respond, and non-responders will remain non-responders. The costs however will decrease if fewer people receive repeat injections over time.

The costs of administration and the drugs are included in this analysis. The impact of BoNT-A on downstream costs were considered uncertain and therefore a threshold analysis was conducted to estimate magnitude of savings needed for BoNT-A to be cost-effective.

Model inputs are described in full in the separate technical report, a summary of the model inputs is available in Table 53 below.

Table 53: Overview of parameters and parameter distributions used in the model

Input	Data	Source	Probability distribution
Comparators	Upper limb • Xeomin 400U • Dysport 500U • Dysport 1000U • Usual care (using placebo data) Lower limb • BOTOX 300U • Usual care (using placebo data)	Elovic 2016,[28] Gracies 2015[37] and Wein 2018[137]	n/a
Population	Adults with post stroke upper limb spasticity Adults with post stroke lower limb spasticity	Elovic 2016,[28] Gracies 2015[37] and Wein 2018[137]	n/a
Perspective	UK NHS & PSS	NICE reference case[88]	n/a
Time horizon	12 weeks, 1 year and 2 years.	12 week: Elovic 2016,[28] Gracies 2015[37] and Wein 2018[137] 1/2 years: Shaw 2010,[113] extrapolation and assumptions.	n/a
Discount rate	For 2-year analysis only: Costs: 3.5% Outcomes: 3.5%	NICE reference case[88]	n/a
Baseline probabilities			
Proportion of MAS responders in	0 weeks: 0% 4 weeks: 37.5%	Elovic 2016[28]	Beta distribution alpha=33; beta=55

Input	Data	Source	Probability distribution
placebo arm – Xeomin study	8 weeks: 38.6% 12 weeks: 28%		alpha=34; beta=54 alpha=22; beta=66
Proportion of MAS responders in placebo arm – Dysport study	0 weeks: 0% 4 weeks: 23% 12 weeks: 14% 16 weeks: 4% 20 weeks: 0%	Gracies 2015[37]	Beta distribution alpha=18; beta=61 alpha=11; beta=68 alpha=3; beta=76
Proportion of MAS responders in placebo arm – BOTOX study	0 weeks: 0% 2 weeks: 32% 4 weeks: 39% 6 weeks: 39% 8 weeks: 40% 12 weeks: 23%	Wein 2018[137]	Beta distribution alpha=76; beta=159 alpha=91; beta=144 alpha=92; beta=143 alpha=93; beta=142 alpha=54; beta=181
Relative treatment effects			
Mean difference in proportion of MAS responders: Xeomin versus placebo (SE)	0 weeks: 0% 4 weeks: 32% (5%) 8 weeks: 22% (6%) 12 weeks: 15% (5%)	Elovic 2016[28]	Normal distribution
Mean difference in proportion of MAS responders: Dysport 500U versus placebo (SE)	0 weeks: 0% 4 weeks: 51% (6%) 12 weeks: 29% (6%) 16 weeks: 15% (4%) 20 weeks: 10% (3%)	Gracies 2015[37]	Normal distribution
Mean difference in proportion of MAS responders: Dysport 1000U versus placebo (SE)	0 weeks: 0% 4 weeks: 56% (6%) 12 weeks: 34% (6%) 16 weeks: 23% (5%) 20 weeks: 10% (3%)	Gracies 2015[37]	Normal distribution
Mean difference in proportion of MAS responders: BOTOX versus placebo (SE)	0 weeks: 0% 2 weeks: 13% (4%) 4 weeks: 13% (4%) 6 weeks: 14% (4%) 8 weeks: 9% (4%) 12 weeks: 9%	Wein 2018[137]	Normal distribution
Repeat injections			
Time between repeat injections	12 weeks	Shaw 2010[113]	n/a
Proportion receiving repeat injections 1st year	2nd injection: 67.7% 3rd injection: 61% 4th injection: 51.4%	Shaw 2010[113]	Beta distribution alpha=70; beta=33 alpha=63; beta=7 alpha=53; beta=10
Scenario analyses: Repeat injections			
Proportion receiving repeat injections 2nd year (extrapolation)	5th injection: 46.5% 6th injection: 42.7% 7th injection: 39.7% 8th injection: 37.3%	Extrapolation of Shaw 2010, [113] using a power trendline.	Beta distribution alpha=48; beta=5 alpha=44; beta=4 alpha=41; beta=3 alpha=38; beta=2

Input	Data	Source	Probability distribution
Proportion receiving repeat injections 2nd year (assumption = 4th injection)	5th injection: 51.4% 6th injection: 51.4% 7th injection: 51.4% 8th injection: 51.4%	Assumption based on Shaw 2010[113]	Beta distribution alpha=53; beta=10
All receiving repeat injections 1st and 2nd year	Each injection (2nd to 8th): 100%	Assumption	fixed
Health-related quality of life (utilities)			
Responder utility (SE)	0.51 (0.02)	Makino 2019[72]	Beta distribution alpha=305; beta=294
Non-responder utility (SE)	0.39 (0.02)	Makino 2019[72]	Beta distribution alpha=222; beta=348
Costs			
Xeomin 400U	£519.60	BNF online, accessed November 2022[51]	n/a
Dysport 500U / 1000U	£154.00 / £308.00	BNF online, accessed November 2022[51]	n/a
BOTOX 300U	£414.60	BNF online, accessed November 2022[51]	n/a
First appointment for administration of BoNT-A	£244	Neurology, Consultant-led Multiprofessional Non-Admitted Face-to-Face Attendance, First. NHS reference costs 2019/2020[94]	n/a
Subsequent appointment for repeat injection BoNT-A	£187	Neurology, Consultant-led Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up. NHS reference costs 2019/2020[94]	n/a

Abbreviations: BoNT-A = botulinum toxin A; MAS = Modified Ashworth Scale; n/a = not applicable; SE = standard error, U = units.

The model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for most model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run 3,000 times for each analysis and results were summarised. In addition, various scenario sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed, and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change.

Results

All results are available in the separate technical report, below is a summary of the main findings.

When only the trial period (up to 12 weeks) data was utilised and therefore only a single BoNT-A injection cycle was administered, none of the BoNT-A drugs were cost effective compared to usual care at a threshold of £20,000 per QALY (probability cost effective of 0%).

When a one-year time horizon was explored, where all those in the BoNT-A comparator received repeat injections (total 4 in one year) irrespective of an assessment of need or assessment of response, none of the BoNT-A drugs were cost effective compared to usual care at a threshold of £20,000 per QALY. This was the case when the usual care arm did not or did receive twice annual follow up neurology consultant-led multidisciplinary attendances (SA2 & SA3).

When a one-year time horizon was explored, where the proportion receiving repeat injections was taken from BoTULS (Shaw 2012), up to a total of 4 injection cycles in one year, only Dysport (500U) was cost-effective compared to usual care (ICER: £19,361 per QALY, probability cost effective 53%) in the analysis where the usual care arm and those who did not have repeats received twice annual follow up neurology consultant-led multidisciplinary attendances (SA5). All other BoNT-A were not cost effective compared to usual care at £20,000 per QALY.

When a two-year time horizon was explored, where all those in the BoNT-A comparator received repeat injections (total 8 over two years) irrespective of an assessment of need or assessment of response, none of the BoNT-A drugs were cost effective compared to usual care at a threshold of £20,000 per QALY. This was the case when the usual care arm did not or did receive twice annual follow up neurology consultant-led multidisciplinary attendances (SA6 & SA7).

When a two-year time horizon was explored, where the proportion receiving repeat injections was taken from BoTULS (Shaw 2012) for the first year and extrapolated for the second year using a trendline, up to a total of 8 injection cycles over two years, only Dysport (500U) was cost-effective compared to usual care (ICER: £15,078 per QALY, probability cost effective 82%) in the analysis where the usual care arm and those who did not have repeats received twice annual follow up neurology consultant-led multidisciplinary attendances (SA9). All other BoNT-A were not cost effective compared to usual care at £20,000 per QALY.

When a two-year time horizon was explored, where the proportion receiving repeat injections was taken from BoTULS (Shaw 2012) for the first year and in the second year it was assumed the proportion receiving injections 5 to 8 was the same as the proportion receiving injection 4, only Dysport (500U) was cost-effective compared to usual care (ICER: £16,191 per QALY, probability cost effective 76%) in the analysis where the usual care arm and those who did not have repeats received twice annual follow up neurology consultant-led multidisciplinary attendances (SA11). All other BoNT-A were not cost effective compared to usual care at £20,000 per QALY.

In all scenarios, the ICER was lowest for Dysport 500U compared to usual care and highest for BOTOX versus usual care. The results are driven by higher proportion of responders in Dysport trial and the lower cost of Dysport.

The threshold analyses indicated the magnitude of downstream savings over each time horizon required for BoNT-A to be cost effective at £20,000 per QALY, this was lowest for Dysport (500U) (or Dysport 1000U if 500U was cost effective) and highest for Xeomin. In most scenarios substantial downstream savings are required for Xeomin, Botox or Dysport 1000U to be cost effective.

Limitations and generalisability of results

A number of limitations were identified, including the lack of clarity as to what current practice is in terms of follow up attendances for people with spasticity but not receiving BoNT-A. If they have no regular follow up attendances then BoNT-A is unlikely to be cost effective. In addition, this analysis is based on single RCTs (no meta-analysis possible) and not all indications reported here (upper and lower limb for each drug). Many other BoNT-A RCTS were identified in the clinical review, however only these three RCTs reported the same

outcome used in the economic model (MAS). It is not clear if they are representative of the full body of clinical evidence.

The RCTs included in this analysis do not include use BoNT-A treatment in the sub-acute stroke stage and therefore, benefits on contractures are not incorporated.

This analysis has not accounted for the longer time between injections reported in an observation trial (ULIS-III).[129] Increasing the duration between injections could result in either less injections for the same QALY gain or same number of injections but a longer QALY benefit. Therefore, the current model may underestimate the cost effectiveness of BoNT-A compared to an approach which allows longer intervals between injections (lowering costs and/or raising QALYs).

Uncertainty remains as to whether benefits in downstream costs could be realised in practice, more research required to quantify this potential saving.

Some concerns were noted with using the EQ-5D data from the Makino 2019[72] health economic model. Firstly, the EQ-5D data is provided by responder status not by randomised group and it is unclear if any adjustments were made to account for potential confounders. EQ-5D questionnaire collection times were not reported, and therefore it is not clear if these were done when the effects of treatment are expected to peak (approximately 4 weeks) or if they were done once the effects had started to diminish over time. According to Makino 2019, [72] Australian preference weights were applied. Finally, Kanovsky 2009[59] was an RCT in upper limb spasticity and using 400U Xeomin, therefore the EQ-5D data may be less applicable to lower limb spasticity benefits or to other BoNT-A types or doses.

Finally, the committee discussed the potentially higher costs of administration of BoNT-A in people with higher dependency due to the need for at home treatment or alternatively the need for transportation and longer outpatient appointments to account for any assistance required. It was also noted that the QoL benefit may be different in these people too. Therefore, the results of this analysis may not be generalisable to people with higher dependency.

Conclusions

BoNT-A may be cost-effective in very specific circumstances, outlined below:

- 500U Dysport used for upper limb spasticity.
- Proportion receiving repeat injections decreases over 1 or 2-year period (repeats given based on an assessment of need)
- Standard spasticity care includes twice yearly neurology attendances (therefore lowering administration costs for BoNT-A.

1.1.10 Unit costs and further analyses

This section includes unit costs relevant to the interventions being considered in this review as well as a threshold analysis for intrathecal baclofen.

Botulinum toxin A

Table 54 presents the unit costs of the different types of botulinum toxin and some illustrative drug costs per treatment for comparison based on the average doses applied in the economic analyses discussed above and based on the maximum recommended doses from the summaries of product characteristics. Separate costs are presented for upper and lower limb spasticity as dosing is different. Note that the included economic studies were all in people with upper limb spasticity. Treatment can be repeated, not less than 12 weeks apart. Botulinum toxin has to be delivered by someone with specialist training and so may also require additional appointments. Further detail on the cost of administration is provided n the full technical report for the health economic analysis of BoNT-A.

Table 54: Unit costs of botulinum toxin A

Botulinum toxin A type	Cost per vial[(a)]	Cost per treatment; mean dose reported in HE studies (upper limb)	Cost per treatment; maximum recommended dosage (upper limb)	Cost per treatment; maximum recommended dosage (lower limb)
Abobotulinum toxin A (Dysport®)	• 300 units: £93 • 500 units: £154	£156 (505 units)[(b)]	£308 (1000 units)[(e)]	£462 (1500 units)[(e)]
Incobotulinum toxin A (Xeomin®)	• 50 units: £72 • 100 units: £130 • 200 units: £260	£457 (352 units)[(c)]	£650 (500 units)[(f)]	Not indicated
Onabotulinum toxin A (BOTOX®)	• 50 units: £78 • 100 units: £138 • 200 units: £276	£306 (221 units)[(d)]	£354 (240 units)[(g)]	£553 (400 units)[(g)]

(a) Costs are based on the NHS indicative price from the BNF,[51] accessed 01/02/22
(b) Shackley 2012;[111] RCT reported an average of 1.01 vials (500 units per vial) per person (Shaw 2010)[113]
(c) Makino 2019;[72] mean dose per treatment was 352 units, thus requiring 3.52 100-unit vials per treatment
(d) Doan 2013;[24] mean dose of 221.3U was reported in the clinical trial for the first injection and was applied for all subsequent injections
(e) Maximum recommended dose for upper limb spasticity is 1000 units and for lower limb spasticity is 1500 (EMC 2022[29]), accessed 01/02/22
(f) Maximum recommended dose for upper limb spasticity is 500 units (EMC 2022[29]), accessed 01/02/22
(g) Maximum recommended dose for upper limb spasticity is 200-240 units and for lower limb spasticity is 400 units (EMC 2022[29]), accessed 01/02/22. Upper limb cost reflects 250 units to account for vial wastage.

Oral medications

Table 55 presents the costs of oral anti-spasticity medications included in the review. Costs are presented for the minimum and maximum dosage reported in the BNF[51] and for typical doses where identified.

Table 55: Unit costs of oral anti-spasticity medication

Drug	Units/pack	Cost/pack[a]	Cost/mg	Mg/day[b]	Cost/day	Cost/month	Cost/year
Baclofen 5mg/5ml oral solution	300	£2.07	£0.001	5[c]	£0.01	£0.21	£3
Baclofen 10mg tablets	84	£2.53	£0.003	10[c]	£0.03	£0.92	£11
				60[c]	£0.18	£5.50	£66
				100[c]	£0.30	£9.16	£110
Tizanidine 2mg tablets	120	£13.54	£0.056	2[d]	£0.11	£3.43	£41
				36[d]	£2.03	£61.78	£741
Tizanidine 4mg tablets	120	£40.05	£0.083	20[d]	£1.67	£50.76	£609
Dantrolene sodium 25 mg capsules	100	£16.87	£0.007	25[e]	£0.17	£5.13	£62
Dantrolene sodium 100 mg capsules	100	£43.07	£0.004	225[e]	£0.97	£29.48	£354
				400[e]	£1.72	£52.40	£629
Gabapentin 300mg capsules	100	£3.11	£0.000	900[f]	£0.09	£2.84	£34
				3600[f]	£0.37	£11.35	£136
Pregabalin 50mg tablets	84	£4.92	£0.001	50[g]	£0.06	£1.78	£21
				300[g]	£0.09	£2.81	£34
Clonidine 25mcg tablets	112	£6.83	£2.439	0.05[h]	£0.12	£3.71	£45
				0.075[h]	£0.18	£5.56	£67
Diazepam tablets 2mg tablets	28	£0.93	£0.017	2[i]	£0.03	£1.01	£12
Diazepam tablets 10mg tablets	28	£1.12	£0.004	60[i]	£0.24	£7.30	£88
Clonazepam 500mcg tablets	100	£31.82	£0.636	0.5[j]	£0.32	£9.68	£116
Clonazepam 2mg tablets	100	£34.50	£0.173	8[j]	£1.38	£41.98	£504

(a) Costs are based on the NHS Drug Tariff price from the BNF,[51] accessed 01/02/22
(b) Doses are from the BNF[51] unless otherwise specified, accessed 01/02/22. See individual footnotes for details.

(c) Dose range: 5mg-100mg, maximum dose: 100mg per day. EMC 2022[29] reported that satisfactory control of symptoms is usually obtained with doses of up to 60 mg daily.
(d) Dose range: 2mg-36mg, maximum dose per day: 36mg per day. One study in the clinical review (Medici 1989[52]) reported that patients received a maximum of 5 capsules per day (20mg tizanidine) administered in three daily doses.
(e) Dose range: 25mg-225mg, maximum dose per day: 100mg four times a day
(f) Gabapentin is indicated as an adjunct treatment, dose range: 900mg-3.6g
(g) Pregabalin is indicated as an adjunct treatment, dose range: 50-300mg per day
(h) Not indicated for spasticity. For prevention of recurrent migraine, dosage is initially 50 micrograms twice daily for 2 weeks, then increased if necessary to 75 micrograms twice daily.
(i) Dose range: 2mg-60mg, maximum dose per day: 60mg
(j) Dose range: 0.5mg-8mg

Intrathecal baclofen unit cost and threshold analysis

Intrathecal baclofen therapy consists of delivering baclofen in a liquid form into the spinal fluid. An infusion pump is implanted to deliver the infusion. Table 56 presents the drug costs related with provision of intrathecal baclofen therapy. The SPC notes a wide dose range but based on mean dosage intrathecal baclofen may typically cost between £500-£700 per year. In addition, there will be costs associated with the initial procedure to fit the infusion pump, initial dose titration and to refill the drug reservoir (typically every 3 months).

Table 56: Unit costs of intrathecal anti-spasticity medication[(a)]

	Daily dosage (micrograms) [(a)]	Cost per day [(a)]	Cost per year [(a)]
Baclofen (10mg tablets)	60-100mg [(b)]	£0.13 to £0.22	£47 to £79
Baclofen (intrathecal infusion), test dose	25–50 mg [(c)]	£2.50	Not applicable
Baclofen (intrathecal infusion, 500 micrograms/1ml – 20ml ampoules), maintenance	22mg to 1.4mg [(c)]	£0.11 to £7	£40.14 to £2,555
	276mg [(c)]	£1.38	£504
	307mg [(c)]	£1.54	£560
	297.6mg [(d)]	£1.49	£543
Baclofen (intrathecal infusion, 2mg/1ml – 20ml ampoules), maintenance	22mg to 1.4mg [(c)]	£0.14 to £8.75	£50 to £3,194
	276mg [(c)]	£1.73	£630
	307mg [(c)]	£1.92	£700
	297.6mg [(d)]	£1.86	£679

(a) Dosing and cost source: Drug tariff or NHS indicative price (if less than drug tariff or drug tariff not available), BNF,[51] Accessed 08/02/22
(b) 60mg daily maintenance dose, 100mg maximum dose
(c) Test dose 25–50 micrograms, to be given over at least 1 minute via catheter or lumbar puncture, then increased in steps of 25 micrograms (max. per dose 100 micrograms), not given more often than every 24 hours to determine appropriate dose, then dose-titration phase, most often using infusion pump (implanted into chest wall or abdominal wall tissues) to establish maintenance dose (ranging from 12 micrograms to 2 mg daily for spasticity of spinal origin or 22 micrograms to 1.4 mg daily for spasticity of cerebral origin, with a mean daily dosage of 276 micrograms per day at 12 months and 307 micrograms per day at 24 months) retaining some spasticity to avoid sensation of paralysis.[29]
(d) Mean dose at 6 months of intrathecal baclofen reported in SISTERS RCT[13, 14]

In the absence of economic evidence, a threshold analysis was conducted to estimate what the incremental cost of intrathecal baclofen (ITB) is compared to conventional medical management in order to be considered cost-effective against the NICE threshold of £20,000 per quality-adjusted life year (QALY) (See Table 57). This was done by extrapolating EQ-5D data reported in the SISTERS RCT by Creamer 2018,[13, 14] included in the clinical review. This trial observed significant quality of life treatment effects in favour of ITB over conventional medical management for changes from baseline to six months in a stroke population with spasticity. As the long term effects of ITB therapy are unknown, it was assumed that the quality of life benefit at six months is maintained and used this to estimate QALYs at 5-year and 7-year time horizons (shown in Figure 1), based on the battery pump life described in the Creamer study and clinical opinion from the committee, respectively. In accordance with NICE reference case, 3.5% discount rate was applied to the estimated

QALY gains, which were then used to calculate the maximum incremental cost that would allow ITB treatment to be cost-effective. Incremental costs would include the total cost associated with providing a certain intervention: direct intervention costs (such as staff time, drugs and equipment), downstream costs associated with the treatment (if the treatment is provided over a longer period), and potential cost savings from a reduction in healthcare resource use as a result of improvement in spasticity symptoms.

Figure 1: Extrapolation of EQ-5D data from SISTERS RCT[13, 14] for threshold analysis

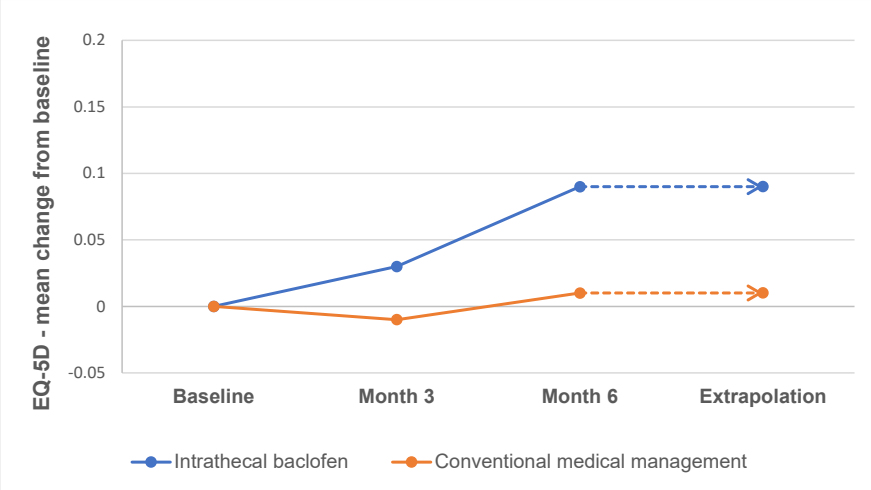

Table 57: Threshold analysis based on SISTERS RCT by Creamer 2018[13, 14]

Time horizon	QALYS (discounted)	Cost threshold
6 months (trial)	0.020	£400
5 years (extrapolated)	0.35	£7,077
7 years (extrapolated)	0.49	£9,726

The results of the threshold analysis found that the incremental cost of ITB would need to be no greater than £7,077 and £9,726, over a 5- and 7-year time horizon respectively, to be cost-effective at a threshold of £20,000 per QALY. These incremental costs were compared to the cost of ITB over 5 and 7 years (also discounted at 3.5% in accordance to the NICE reference case), estimated using two different approaches. Table 58 presents the first approach, which uplifted 1999 UK intervention costs described in a previously published cost-benefit analysis by Sampson 2002[107] to 2020/2021 prices using the NHS Cost Inflation Index.[52] The Sampson study was excluded from this review as it was published prior to the 2008 cut-off date set and was not in a stroke specific spasticity population. The study was also non-randomised with no comparator and quality of life improvements were based on clinical assumption. However, this study was included as evidence for the Spasticity under 19s NICE guideline (CG145)[89] and was used as the basis for developing their health economic model. This approach is limited as directly uplifting 1999 reference costs will not fully reflect current NHS costs. For instance, Sampson's costing included a number of items which were itemised separately based on the older NHS reference costs but are now likely to be grouped into one healthcare resource group (HRG) code. In addition, although drugs can be expected to cost less over time once they have gone off-patent, the direction of cost changes over time is not known for all resources. For example, simply uplifting the cost of the pump has increased the cost to beyond the current list price for this item (£12,404 uplifted cost versus £8,316 in NHS supply chain catalogue). Finally, Sampson also did not include the cost of complications or account for the cost incurred by people who undergo pre-

screening assessment and receive a test dose, but who do not go onto receiving the pump (non-responders).

Table 58: Uplifted cost from Sampson 2002[107]

Cost element	1999 cost		2020/2021 uplifted cost	
	Low estimate	High estimate	Low estimate	High estimate
Pre-screening assessment costs				
30 minutes neurosurgeon time	£330	£556	£605	£1,019
Test dose				
A542 injection of a therapeutic substance (minor)	£163	£163	£299	£299
1x lumbar puncture	£189	£189	£346	£346
1x lumbar catheter	£20	£30	£37	£55
Ward care/accommodation (E39) - assuming 2-night in-patient stay	£490	£1,102	£898	£2,020
Cost of drug	£60	£70	£110	£128
Physio assessment 1/2 hour	£20	£20	£37	£37
Test dose Total	£942	£1,574	£1,727	£2,885
Cost of implantation procedure				
Cost of pump	£6,768	£6,768	£12,404	£12,404
Cost of catheter	£229	£2,291	£420	£4,199
1x procedure - implant pump (code) - major procedure A3300	£509	£509	£933	£933
Ward care/accommodation (E39) - assuming 5-night in-patient stay	£1,225	£2,755	£2,245	£5,049
Pump implantation total	£8,731	£10,261	£16,002	£18,807
Other costs				
Laptop	Free - on loan	Free - on loan	Free - on loan	Free - on loan
Transport costs	£50	£100	£92	£183
Education requirement	not known	not known	not known	not known
Tests, pathology, radiology, microbiology (all)	£500	£500	£916	£916
Other costs total	£550	£600	£1,008	£1,100
Aftercare (post-op)				
Refill kit	£22	£22	£40	£40

Cost element	1999 cost		2020/2021 uplifted cost	
Drug costs (2000mcg baclofen)	£59	£72	£108	£132
Follow-up out-patient appointment / PIU	£50	£50	£92	£92
Physio assistant 1/2 hour per day	£10	£10	£18	£18
Aftercare (post-op) total	£141	£154	£258	£282
Pump replacement procedure				
1x procedure	£509	£509	£933	£933
Ward care/accommodation (E39) - range of nights stay	£1,225	£2,755	£2,245	£5,049
Pump (latest cost from Medtronic)	£6,768	£6,768	£12,404	£12,404
Catheter	£229	£229	£420	£420
Drugs	£59	£72	£108	£132
Pump replacement procedure total	£8,790	£10,333	£16,111	£18,939
Total costs for CIBI implantation - pre-screening, test dose, pump implantation, other costs and tests	£10,553	£12,991	£19,342	£23,810
Mid-point estimate	£11,772	£11,772	£21,576	£21,576

For these reasons, an attempt to micro-cost all resources involved in providing ITB therapy was performed using current NHS costs, ITB dosing from Creamer 2018,[13, 14] and clinical input from committee members (Table 59). Clinical input from committee members noted that the average number of refills occurs 3-4 times per year. By incorporating the 2-milligram infusion ampoule reported in the unit costs section (Table 56) in the costs, this would provide 134 days of infusion which means patients will only require around 3 refills per year. The 4-monthly drug costs and associated costs with refills are described in the ongoing costs section. The annual cost of oral baclofen was removed from the total ongoing costs per year to reflect the discontinuation of oral anti-spasticity following ITB treatment. This is also based on Creamer 2018,[13, 14] where 79% of the conventional medical management (CMM) group received oral baclofen.

There are limitations associated with this micro-costing, such as assumptions being made regarding number of ampoules required for test dose of ITB, the appropriate HRG codes for particular procedures and proportion of people who are expected to be non-responders and proportion of people who experience complications.

Table 59: Micro-costing approach based on current NHS costs[51, 93, 95]

Item	Currency/ HRG code/ NPC	Unit cost or B1 price	Total cost	Source, *assumptions*
Pre-screening assessment costs				

Item	Currency/ HRG code/ NPC	Unit cost or B1 price	Total cost	Source, *assumptions*
Consultant led NHS trusts Outpatient first attendance (Neurosurgery)	WF01B	£224	£224	
Consultant led NHS trusts Outpatient follow up attendance (Neurosurgery)	WF01A	£175	£175	NHS reference costs 2019/20 *Assumes two assessments required (source: ITB Clinical commissioning policy 2013)*[92]
Test dose				
Diagnostic Spinal Puncture, 19 years and over	HC72A	£829	£829	NHS reference costs 2019/20, Elective inpatient HRG.
Test dose drug cost, cost per 50microgram/1ml ampoule		£50	£100	BNF Online, Accessed March 2022. *Assumes up to 2 ampoules required for test dosing.*
Total screening costs		£1,328	**£1,594**	Consultant outpatient appointments, 5-day inpatient stay (incl. daily physio assessment) + test dose drug cost. *Assumes additional 20% cost, to account for people who do not go onto receiving pump but who undergo pre-screening assessment (non-responders).*
Cost of implantation procedure				
Insertion of Intrathecal Drug Delivery Device for Treatment of Neurological Conditions*	AA61A	£8,012	£8,012	NHS reference costs 2019/20, Elective inpatient.
Synchromed ii programmable infusion pump	FMB043	£8,316	£8,316	
Catheter kit - long. 2 piece	FMB034	£644	£644	NHS Supply Chain Catalogue 2021 (excluding 20% VAT)
3-month follow up appt face to face with a consultant physician for dose adjustment (probably standard OPD cost)	WF01A	£187	£187	NHS reference costs 2019/20, follow up face to face consultant appointment neurology
Initial 4-month drug cost		£57	£226	Baclofen 40mg/20ml solution for infusion ampoules (Aguettant Ltd), NHS indicative price, BNF, Accessed 08/02/22
Total implantation costs			**£17,385**	
Total screening/implantation costs			£18,979	Comprised of total screening costs (120%, to account for additional 20% non-

Item	Currency/ HRG code/ NPC	Unit cost or B1 price	Total cost	Source, *assumptions*
				responders who did not proceed to implantation) and 100% of the implantation costs.
Ongoing costs				
SynchroMed refill kit	FMB045	£22	£22	NHS Supply Chain Catalogue 2021 (excluding 20% VAT)
Day patient attendance with a consultant	AA57A	£668	£668	NHS reference cost 2019/20, Minimal intracranial procedures, day case HRG. HRG maps to OPCS A54.4 (Attention to intrathecal drug delivery device adjacent to spinal cord)
Drug costs (monthly cost)		£57	£226	Baclofen 40mg/20ml solution for infusion ampoules (Aguettant Ltd), NHS indicative price, BNF, Accessed 08/02/22
Total 4-monthly cost per refill			£916	Currently includes refill kit, outpatient appointment, 30 min assistant staff time and drug cost.
Total annual cost for refills			£2,638	Total 4-monthly cost per refill, minus the cost per year (£110) for the maximum recommended dose of oral baclofen (100mg daily), based on Creamer 2018 where 79% of the CMM group received oral baclofen.
Catheter revision or other correction fix a problem with the pump (5%)	AA57A	£2,605	£130	NHS reference cost 2019/20, Minimal intracranial procedures, elective inpatient HRG. HRG maps to OPCS A54.4 (Attention to intrathecal drug delivery device adjacent to spinal cord) *Catheter or pump revision, assume 5% only.*

**Note:* Pathology costs were assumed to be included in the implantation procedure costs

Table 60 below, summarises the total costs using the Sampson uplifted costs (over a 5-year horizon) and the discounted costs over a 5- and 7-year horizon using the micro-costing. It is important to note that these incremental costs are based on the difference in intervention costs, but do not include difference in healthcare resource use as a result of improved health and reduction in spasticity. These are presented alongside the estimated QALYs from Table 57. An ICER is reported for illustrative purposes. Furthermore, the incremental cost from the threshold analysis (Table 57) is presented as well as a further threshold, which estimates what incremental QALY gain would need to be achieved for ITB to be considered cost effective at £20,000 per QALY with these higher reported incremental costs.

Table 60: Illustrative cost-effectiveness results based on threshold analysis and costing approaches

Time horizon	Total costs discounted	Total QALYs discounted	ICER	Incr. cost required at current incr. QALY gain to be CE at £20K threshold	Incr. QALY gain at current incr. cost to be CE at £20k threshold
5 years	£30,519	0.35	£86,248	£7,077	1.53
7 years	£34,885	0.49	£71,738	£9,726	1.74
5 years (Sampson uplift, midpoint estimate)	£21,576	0.35	£60,976	£7,077	1.08

Given that both costing approaches present considerably higher costs than the incremental costs presented in the threshold analysis, it is unlikely that ITB therapy will be cost-effective based on current evidence. The cost of the pump alone was well above the incremental cost identified in the threshold analysis (Table 57). The pump will also need replaced every 5-7 years over a patient's lifetime, which includes the cost of a new pump as well as procedural and post-operative costs. It is likely that there would need to be considerable downstream cost savings for intrathecal baclofen to be cost effective.

Electrotherapies (FES, NMES, TENS)

Table 61 presents staff costs related to people who may deliver electrotherapies. In the clinical review, the frequency and duration for delivering TENS, FES and NMES varied across studies evaluating each intervention respectively. NMES was the most frequently evaluated of out the non-pharmacological interventions and ranged from 20 9-minute daily sessions to 60-minute sessions conducted five days per week for four weeks. NMES was also combined with other interventions such as mirror therapy, stretching (Proprioceptive Neuromuscular Facilitation [PNF]) and infrared which would increase resource use. FES was typically administered for 30 minutes a day, 5 days per week, with interventions lasting between 3 week and 6 months. The included evidence for TENS reported sessions lasting 20-60 minutes, predominantly for five days per week for 3 weeks up to 3 months. TENS can be delivered at home then returned for use by other patients which could lower resource use, however, NG 2009[90] and Park 2014[97] assessed interventions using TENS as well as telephone contact with patients or educational and practice sessions which would increase costs compared to no such provision.

Table 62 shows some the equipment costs related to TENS. The cost of a TENS machine varies (approximately £18-£50) depending on the type as a few are recorded in the NHS supply chain catalogue.[95] Previous economic evaluations of electrotherapy (TENS, NMES, FES) have not included the costs of equipment used by physiotherapists in the analysis as the per-use costs were expected to be small (MacPherson 2017[121], Woods 2017[139]).

A 2010 NHS Purchasing and Supply Agency report on FES for drop foot of central neurological origin[122] included an initial assessment appointment costing £140 and on a clinic model in which the cost of the FES device is incorporated in the ongoing clinical charges. Each ongoing clinical appointment was estimated at £300. FES can also be delivered at home but staff are required to attend a training course before providing people with the device and availability varies across current practice.

Table 61: Unit costs of healthcare professional who may be involved in delivering interventions to reduce spasticity

Resource	Cost per working hour (hospital / community) [(a)]	Source
Band 6 PT/OT	£52 / £50	PSSRU 2020[4]
Band 7 PT/OT	£62 / £60	
Band 6 nurse	£53 / £52	
Band 7 nurse	£62 / £61	
Band 6 SLT	£51/£50	
Band 7 SLT	£62/£60	

(a) Note: Costs per working hour include salary, salary oncosts, overheads (management and other non-care staff costs including administration and estates staff), capital overheads and qualification costs
(b) Taken from previous Guideline (GC162)10, Costs were calculated using PSSRU data and approach but with the salary band stated

Table 62: Equipment costs transcutaneous electrical nerve stimulation (TENS)

Resource	Cost	Source
Direct TENS machine full kit including 4 electrodes /Dual channel TENS machine/ TENS machine TPN 200 Plus	£44.99/£31.10/£17.40	NHS Supply Chain Catalogue 2021[95]

Acupuncture and electroacupuncture

In the clinical review, the frequency and duration for delivering acupuncture and electroacupuncture varied across studies.

Acupuncture ranged from 20-60 minutes, occurring anywhere from twice weekly to everyday, with interventions lasting between 2-24 weeks. The cost of delivering acupuncture is primarily based on staff time (Table 61), as a previous economic model developed for the Chronic Pain NICE guideline (NG193)[86] reported that the cost of the needles is small in comparison to the staff costs (Table 63). A large acupuncture individual patient meta-analysis reported the number of needles across studies, and the most frequent range was between 10 and 14 needles (Vickers, 2018).[130]

An outpatient procedure for acupuncture for pain management is £141 (2019/2020 NHS reference costs[93]). Costs in the community setting may be lower.

Table 63: Equipment costs related to acupuncture

Resource	Cost	Source
Cost per needle	£0.06[(a)]	NICE Chronic pain Guideline 2021(NG193)[86]

(a) Average of needle classic and needle with guide tube products on NHS supply chain

Resource use was less clear with electroacupuncture interventions, with one study (Gong 2009)[35] reporting 30 minute sessions, five days per week while Moon 2003[82] provided electrotherapy every other day for 15 days. The first two examples of electroacupuncture costs shown in Table 64 were taken from the analysis conducted as part of the osteoarthritis guideline update[87]. These devices were the ES-160 (included as it was used in two of the four clinical studies in the osteoarthritis review of electroacupuncture) and AS-super 4, which is a popular alternative in clinical practice. The analysis assumed that both devices have a lifespan of 5 years. Other costs associated with electrotherapy include batteries, needles, disinfectant swabs and surgeons' gloves.

Table 64: Example equipment costs of electroacupuncture devices

Device details	Device cost[(a)]	Cost of crocodile clips	Cost of lead cables
ES-160	£395[42]	£43.24[48 (b)]	£59.50[41 (b)]
AS-super 4	£240[40]	£23[39(c)]	£0

(a) Taken from online sources, excluding VAT.
(b) Cost of 10 units based on the assumption that 10 needles are utilised per session.
(c) Clips and cables sold together

Economic considerations: trade-off between net clinical effects and costs

1.1.11 Evidence statements

Effectiveness/Qualitative

Economic

- One original cost–utility analysis found that a single botulinum toxin A injection not cost effective after 12 weeks when compared to usual care. ICERs were £41,110, £50,690, £134,404, and £225,203 per QALY for Dysport 500U (upper limb), Dysport 1000U (lower

limb), Xeomin (upper limb) and Botox (lower limb) respectively. Dysport 500U (upper limb) was cost effective compared to usual care when proportion receiving repeat injections decreases over 1 or 2-year period (repeats given based on an assessment of need) and standard spasticity care includes twice yearly neurology attendances (therefore lowering administration costs for BoNT-A). This analysis was assessed as directly applicable with potentially serious limitations.

- One cost-utility analysis found that in people with post-stroke upper-limb spasticity, abobotulinum toxin A (Dysport) plus a 4-week upper limb therapy programme was not cost-effective (ICER of £93,500 per QALY) when compared to the upper limb therapy programme alone. This study was assessed as partially applicable with potentially serious limitations.
- One cost-utility analysis compared onabotulinum toxin A (Botox) plus usual care (defined as routine physical and occupational therapy) to usual care alone for people with upper-limb spasticity under three costing scenarios, with the results varying depending on the scenario applied: Scenario 1 was cost-effective, with an ICER of £10,000 per QALY. This scenario included intervention costs, i.e., the cost of Botox, specialist office visits and day-hospital visits. Scenario 2 did not include hospital visits and was not cost-effective, with an ICER of £27,000 per QALY. Scenario 3 incorporated informal care costs and was therefore not compared to the £20,000 NICE threshold. This study was assessed as partially applicable with potentially serious limitations.
- One cost-effectiveness analysis found that early treatment (first 6-weeks post-stroke) of upper-limb spasticity with an onabotulinum toxin A (Botox) injection compared to usual care resulted in no statistically significant differences in total costs or either health outcome at 6-months follow-up. However, a cost-saving of £1,481 (p=0.04) for the treatment of contractures was reported. This study was assessed as partially applicable with potentially serious limitations.
- One cost-utility analysis found that unlimited Incobotulinum toxin A (Xeomin) treatment cycles (everyone received treatment for 2 cycles while responders continued to receive additional cycles with no upper limit) so was not cost effective, (ICER of £28,457 per QALY) compared to limited treatment cycles, where everyone received 2 cycles while responders could receive to up to 4 additional cycles. This study was assessed as partially applicable with potentially serious limitations.
- One cost-utility analysis found that abobotulinum toxin A (Dysport) dominated onabotulinum toxin A (Botox) (i.e., less costs and higher QALYs) for the treatment of both upper and lower limb spasticity, with cost savings of £304 (with a 0.02 QALY gain) and £394 (0.01 QALY gain) for upper and lower limb indications, respectively. This study was assessed as partially applicable with potentially serious limitations.
- One cost-utility analysis found that dry needling plus standard physiotherapy was not cost-effective when compared to standard physiotherapy alone for post-stroke adults in the subacute phase (1–3 months) experiencing upper limb spasticity (4-week and 8-week ICERs were £161,283 and £216,527 per QALY, respectively). This study was assessed as partially applicable with potentially serious limitations.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

The committee included the following outcomes: person/participant generic health-related quality of life, carer generic health-related quality of life, spasticity outcome measures, physical function – general, physical function – upper limb, physical function – lower limb, pain, activities of daily living, stroke-specific Patient-Reported Outcome Measures, additional healthcare contacts, hospitalisation, stroke outcome – modified Rankin scale and withdrawal due to adverse events. All outcomes were considered equally important for decision making

and therefore have all been rated as critical. The committee noted pain as a particularly important outcome as this is associated with spasticity and can limit the persons engagement in therapy, along with person/participant health-related quality of life outcomes, which are important as a holistic measure of the impact on the person's quality of living. Similarly, activities of daily living were considered important as these determine people's functional independence and will influence future care needs.

The committee chose to investigate these outcomes at less than and equal to 6 months and more than 6 months, as they considered that there could be a difference in the short term and long-term effects of the intervention.

All outcomes were reported in at least one study however many comparisons did not report all of the outcomes. The outcomes which were most widely reported included spasticity, physical function for either the upper or lower limb, activities of daily living and withdrawal due to adverse events. Other outcomes were less frequently reported. In particular additional healthcare contacts, hospitalisation and the modified Rankin scale which were only reported by one study. There was a greater amount of evidence available at less than and equal to 6 months with evidence at >6 months being very limited.

1.1.12.2 The quality of the evidence

Eighty-seven randomised controlled trials (from eighty-nine studies) were included in the review (some studies included more than one comparison). Evidence was available for the following comparisons:

1.1.12.2.1 Focal spasticity

- Oral baclofen compared to incobotulinum toxin A (Xeomin)
- Tizanidine compared to onabotulinum toxin A (BOTOX), abobotulinum toxin A (Dysport) and placebo/sham
- Onabotulinum toxin A (BOTOX) compared to tizanidine, combination therapy, functional electrical stimulation (FES), placebo/sham and usual care or no treatment
- Abobotulinum toxin A (Dysport) compared to tizanidine, neuromuscular electrical stimulation (NMES), combination therapy, placebo/sham and usual care or no treatment
- Incobotulinum Toxin A (Xeomin) compared to oral baclofen, placebo/sham and usual care or no treatment
- Functional electrical stimulation (FES) compared to placebo/sham and usual care or no treatment
- Neuromuscular electrical stimulation (NMES) compared to abobotulinum toxin A (Dysport), transcutaneous electrical nerve stimulation (TENS), combination therapy, placebo/sham and usual care or no treatment
- Transcutaneous electrical nerve stimulation (TENS) compared to neuromuscular electrical stimulation (NMES), combination therapy, placebo/sham and usual care or no treatment
- Acupuncture compared to placebo/sham and usual care or no treatment
- Combination therapy: abobotulinum toxin A (Dysport) and transcutaneous electrical nerve stimulation (TENS) compared to transcutaneous electrical nerve stimulation (TENS) (and placebo injection)
- Combination therapy: abobotulinum toxin A (Dysport) and neuromuscular electrical stimulation (NMES) compared to abobotulinum toxin A (Dysport) only and neuromuscular electrical stimulation (NMES) only
- Combination therapy: onabotulinum toxin A (BOTOX) and functional electrical stimulation (FES) compared to onabotulinum toxin A (BOTOX) only

1.1.12.2.2 Generalised spasticity

- Oral baclofen compared to tizanidine
- Tizanidine compared to oral baclofen
- Intrathecal baclofen compared to usual care or no treatment
- Acupuncture compared to electroacupuncture, placebo/sham and usual care or no treatment
- Electroacupuncture compared to acupuncture and usual care or no treatment

No relevant clinical studies were identified for the following oral interventions:

- Dantrolene
- Gabapentin
- Pregabalin
- Clonidine
- Benzodiazepines (including diazepam and clonazepam)

The evidence varied from high to very low quality, with most of the outcomes rated low quality. Outcomes were commonly downgraded for risk of bias, heterogeneity, and imprecision due to uncertainty around the effect estimate. In the cases where inconsistency was present this was not resolved by sensitivity analyses or explained by subgroup analysis. More detail about the quality of evidence for each of the comparisons are listed below:

1.1.12.2.3 Focal spasticity – tizanidine

Evidence for tizanidine was available for 3 comparisons comparing tizanidine to placebo/sham, onabotulinum toxin A (BOTOX) and abobotulinum toxin A (Dysport).

- When tizanidine was compared to placebo/sham, two outcomes were reported both of which were very low quality. Outcomes were downgraded for risk of bias (due to bias arising from missing outcome data and bias in the selection of the reported results) and imprecision due to crossing one minimally important difference or due to zero events and a small sample size. In addition, both outcomes were downgraded due to indirectness as 10-20% of the population had a traumatic brain injury rather than a stroke.
- When onabotulinum toxin A (BOTOX) was compared to tizanidine, two outcomes were reported both of which were of very low quality. Outcomes were downgraded for risk of bias (due to missing outcome data and bias in the selection of the reported results), imprecision due to crossing one or both minimally important differences and indirectness as 10-20% of the population had a traumatic brain injury rather than a stroke.
- When abobotulinum toxin A (Dysport) was compared to tizanidine three outcomes were reported and all were rated low quality. Downgrading occurred due to risk of bias where all outcomes were downgraded (due to bias arising from the randomisation process, bias due to deviations from the intended interventions and bias due to missing outcome data).

1.1.12.2.4 Focal spasticity – oral baclofen

Evidence for oral baclofen was available comparing oral baclofen to incobotulinum toxin A (Xeomin).

- One small study compared incobotulinum toxin A (Xeomin) to oral baclofen and reported a benefit for activities of daily living, however, the other outcomes all reported no clinically important difference including; person/participant reported health related quality of life, spasticity outcome and physical function – upper limb.

1.1.12.2.5 Focal spasticity – onabotulinum toxin A (BOTOX)

Evidence was available for onabotulinum toxin A (BOTOX) compared to tizanidine, placebo/sham and usual care or no treatment.

- When onabotulinum toxin A (BOTOX) was compared to tizanidine, two outcomes were reported both of which were of very low quality. Outcomes were downgraded for risk of bias (due to missing outcome data and bias in the selection of the reported results), imprecision due to crossing one or both minimally important differences and indirectness as 10-20% of the population had a traumatic brain injury rather than a stroke.
- When onabotulinum toxin A (BOTOX) was compared to placebo/sham, the quality of the outcomes ranged from high to very low. However, the majority were rated moderate or low quality. Where downgrading occurred, this was most often for imprecision due to crossing one or both minimally important differences or due to zero events and small sample size. Several outcomes were downgraded for risk of bias (due to a mixture of bias arising from the randomisation process, bias due to missing outcome data and bias in selection of reported result) and others were downgraded for heterogeneity unexplained by subgroup analysis or due to conflicting number of events for dichotomous outcomes (where some had zero events while others did not) in different studies.
- When onabotulinum toxin A (BOTOX) was compared to usual care or no treatment, all outcomes were rated very low quality. Outcomes were most commonly downgraded for risk of bias (due to a mixture of bias arising from the randomisation process, bias due to deviation from intended intervention, bias due to missing outcome data and bias in measurement of the outcome) and indirectness. Indirectness was due population indirectness where a mixed population of focal 70% and multifocal spasticity 30% were included. Two outcomes were downgraded by for imprecision due to crossing one or both minimally important differences and one outcome for heterogeneity unexplained by subgroup analysis.

1.1.12.2.6 Focal spasticity – abobotulinum toxin A (Dysport)

Evidence was available for abobotulinum toxin A (Dysport) compared to tizanidine, neuromuscular electrical stimulation placebo/sham and usual care or no treatment.

- When abobotulinum toxin A (Dysport) was compared to tizanidine three outcomes were reported and all were rated low quality. Downgrading occurred due to risk of bias where all outcomes were downgraded (due to bias arising from the randomisation process, bias due to deviations from the intended interventions and bias due to missing outcome data).
- When abobotulinum toxin A (Dysport) was compared to neuromuscular electrical stimulation two outcomes were reported and all were rated very low quality. Both outcomes were downgraded for risk of bias (due to bias arising from the randomisation process) and for imprecision due to the confidence intervals crossing both minimally important differences.
- When abobotulinum toxin A (Dysport) was compared to placebo/sham the majority of evidence was low or very low quality however one outcome was rated high quality and another moderate quality. Outcomes were most commonly downgraded due to imprecision where confidence intervals crossed one or both minimally important differences and risk of bias (due to a mixture of bias arising from the randomisation process and bias in selection of the reported result). One outcome was downgraded for heterogeneity due to conflicting number of events for dichotomous outcomes (where some had zero events while others did not) in different studies.
- When abobotulinum toxin A (Dysport) was compared to usual care or no treatment the evidence ranged from moderate to very low quality with the vast majority of outcomes rated low quality. The majority of outcomes were downgraded for risk of bias (due to bias due to deviations from the intended intervention and bias in measurement of the outcome). Several outcomes were downgraded for imprecision as the confidence interval crossed one minimally important difference.

1.1.12.2.7 Focal spasticity – incobotulinum toxin A (Xeomin)

Evidence was available for incobotulinum toxin A (Xeomin) compared to oral baclofen, placebo/sham and usual care or no treatment.

- When incobotulinum toxin A (Xeomin) was compared to oral baclofen four outcomes were reported and all were rated very low quality. All outcomes were downgraded for risk of bias (due to a mixture of bias arising from the randomisation process, bias due to deviations from the intended interventions, bias due to missing outcome data and bias in measurement of the outcome), and for imprecision where confidence intervals crossed one or both minimally important differences.
- When incobotulinum toxin A (Xeomin) was compared to placebo/sham two outcomes were reported and both were rated low quality with downgrading occurring due to imprecision where the confidence interval crossed one or both minimally important differences or due to zero events and a small sample size. One outcome was downgraded for heterogeneity due to conflicting number of events for dichotomous outcomes (where some had zero events while others did not) in different studies.
- When incobotulinum toxin A (Xeomin) was compared to usual care or no treatment four outcomes were reported in this comparison and all were rated very low quality. All outcomes were downgraded for risk of bias (due to a mixture of bias due to deviations from the intended interventions, bias due to missing outcome data and bias in measurement of the outcome). Two outcomes were also downgraded for imprecision due to confidence intervals crossing one or both minimally important differences or due to zero events and a small sample size

1.1.12.2.8 Focal spasticity – functional electrical stimulation (FES)

Evidence was available for functional electrical stimulation compared to placebo/sham and usual care or no treatment.

- When functional electrical stimulation was compared to placebo/sham five outcomes were reported and all were rated very low quality. All outcomes were downgraded for risk of bias (due to a mixture of bias arising from the randomisation process and bias from missing outcome data) and once for imprecision due to confidence intervals crossing one minimally important difference or due to zero events and a small sample size.
- When functional electrical stimulation was compared to usual care or no treatment the majority of outcomes were rated very low quality. Outcomes were most commonly downgraded for risk of bias (due to a mixture of bias arising from the randomisation process, bias due to missing outcome data, deviations from the intended intervention and bias in measurement of the outcome). Many outcomes were also downgraded for imprecision where confidence intervals crossed one or both minimally important differences or due to zero events and small sample size. Two outcomes were downgraded for heterogeneity which was unexplained by subgroup analysis or due to a conflicting number of events for dichotomous outcomes (where some had zero events while others did not) in different studies.

1.1.12.2.9 Focal Spasticity – neuromuscular electrical stimulation (NMES)

Evidence was available for neuromuscular electrical stimulation compared to transcutaneous electrical stimulation, Abobotulinum toxin A (Dysport), placebo/sham and usual care or no treatment.

- When neuromuscular electrical stimulation was compared to transcutaneous electrical stimulation outcomes were rated low or very low quality. All outcomes were downgraded for risk of bias (due to bias due to missing outcome data and bias in measurement of the outcome) and for imprecision where the confidence interval crossed one or both minimally important difference.

- When abobotulinum toxin A (Dysport) was compared to neuromuscular electrical stimulation two outcomes were reported and all were rated very low quality. Both outcomes were downgraded for risk of bias (due to bias arising from the randomisation process) and for imprecision due to the confidence intervals crossing both minimally important differences.
- When neuromuscular electrical stimulation was compared to placebo/sham the majority of evidence was rated very low quality. Several outcomes were rated low quality and one of moderate quality. All outcomes were downgraded for risk of bias (due to a mixture of bias arising from the randomisation process and bias due to deviations from the intended interventions, bias in selection of the reported result and bias due to missing outcome data) and for imprecision either due to the confidence intervals crossing one or both minimally important differences or due to zero events and small sample size. One outcome was downgraded for heterogeneity due to conflicting number of events for dichotomous outcomes (where some had zero events while others did not) in different studies.
- When neuromuscular electrical stimulation was compared to usual care or no treatment outcomes were generally of low to very low quality, however, one outcome was of high quality and one of moderate quality. Outcomes were most commonly downgraded for risk of bias (due to a mixture of bias arising from the randomisation process, bias due to deviation from the intended interventions, bias due to missing outcome data and bias in measurement of the outcome) and imprecision where the confidence interval crossed one or both minimally important differences, or due to zero events and small sample size. Three outcomes were downgraded for heterogeneity which was unexplained by subgroup analysis or due to conflicting number of events for dichotomous outcomes (where some had zero events while others did not) in different studies.

1.1.12.2.10 Focal Spasticity – transcutaneous electrical nerve stimulation

Evidence was available for transcutaneous electrical nerve stimulation compared to placebo/sham and usual care or no treatment.

- When transcutaneous electrical nerve stimulation was compared to placebo/sham the majority of evidence was rated low or very low quality. All outcomes were downgraded for risk of bias (due to a mixture of bias arising from the randomisation process, bias due to deviation from the intended intervention and bias due to missing outcome data) and imprecision where the confidence interval crossed one or both minimally important differences, or due to zero events and small sample size. Two outcomes were downgraded for heterogeneity which was unexplained by subgroup analysis or due to conflicting number of events for dichotomous outcomes (where some had zero events while others did not) in different studies.
- When transcutaneous electrical nerve stimulation was compared to usual care or no treatment the evidence ranged from low to very low quality with the majority rated very low quality. Two outcomes high risk of bias (due to a mixture of bias arising from the randomisation process, bias due to missing outcome data and bias in measurement of the outcome) The majority of evidence was also downgraded for imprecision where the confidence interval crossed one or both minimally important differences. Two outcomes were downgraded for heterogeneity which was unexplained by subgroup analysis or due to conflicting number of events for dichotomous outcomes (where some had zero events while others did not) in different studies.

1.1.12.2.11 Focal spasticity – acupuncture

Evidence was available for acupuncture compared to placebo/sham and usual care or no treatment.

- When acupuncture was compared to placebo/sham the majority of evidence was rated low quality with one outcome of moderate quality and one of very low quality. Outcomes

were most commonly downgraded due to imprecision where the confidence interval crossed one or both minimally important differences, or due to zero events and small sample size, and risk of bias(due to bias due to deviations from the intended interventions).

- When acupuncture was compared to usual care or no treatment the evidence was mixed between moderate and low quality. Outcomes were downgraded by one or two increments for imprecision if the confidence interval crossed one or both minimally important differences, or due to zero events and a small sample size.

1.1.12.2.12 Focal spasticity – combination therapies

Evidence was available for the following combination therapies: abobotulinum toxin A (Dysport) and transcutaneous electrical nerve stimulation compared to placebo/sham and transcutaneous electrical nerve stimulation; abobotulinum toxin A (Dysport) and neuromuscular electrical stimulation (NMES) compared to abobotulinum toxin A (Dysport) alone; abobotulinum toxin A (Dysport) and neuromuscular electrical stimulation (NMES) compared to neuromuscular electrical stimulation (NMES) alone and onabotulinum toxin A (BOTOX) and functional electrical stimulation compared to onabotulinum toxin A (BOTOX) only.

- When abobotulinum toxin A (Dysport) and transcutaneous electrical nerve stimulation were compared to placebo/sham and transcutaneous electrical nerve stimulation three outcomes were reported and two were of low quality and one moderate quality. All outcomes were downgraded by one or two increments due to imprecision if the confidence interval crossed one or both minimally important differences, or due to zero events and a small sample size.
- When abobotulinum toxin A (Dysport) and neuromuscular electrical stimulation were (NMES) compared to abobotulinum toxin A (Dysport) alone, two outcomes were reported. One was rated low quality and the other very low quality. Both outcomes were downgraded for risk of bias (due to bias arising from the randomisation process) and by either one increment for imprecision where the confidence interval crossed one minimally important differences, or two increments due to zero events and a small sample size.
- When abobotulinum toxin A (Dysport) and neuromuscular electrical stimulation (NMES) were compared to neuromuscular electrical stimulation (NMES) alone two outcomes were reported. One was rated low quality and the other very low quality. Both outcomes were downgraded for risk of bias (due to bias arising from the randomisation process) and by either one increment for imprecision where the confidence interval crossed one minimally important difference, or two increments due to zero events and a small sample size.
- When onabotulinum toxin A (BOTOX) and functional electrical stimulation were compared to onabotulinum toxin A (BOTOX) alone three outcomes were reported. Two were of low quality and one very low. All outcomes were downgraded by two increments due to very high risk of bias (due to bias due to deviations from the intended interventions and bias due to missing outcome data). One outcome was downgraded for imprecision due to the confidence interval crossing both minimally important differences.

1.1.12.2.13 Generalised spasticity – tizanidine

Evidence was available for tizanidine compared to oral baclofen.

- When tizanidine was compared to oral baclofen one outcome of very low quality was reported. This was downgraded by one increment for risk of bias (due to bias due to deviations from the intended interventions) and by two increments for imprecision due to the confidence interval crossing both minimally important differences.

1.1.12.2.14 Generalised spasticity – oral baclofen

Evidence was available for tizanidine compared to oral baclofen.

- When tizanidine was compared to oral baclofen one outcome of very low quality was reported. This was downgraded by one increment for risk of bias (due to bias due to deviations from the intended interventions) and by two increments for imprecision due to the confidence interval crossing both minimally important differences.

1.1.12.2.15 Generalised spasticity – intrathecal baclofen

Evidence was available for intrathecal baclofen compared to usual care or no treatment.

- When intrathecal baclofen was compared to usual care or no treatment the evidence ranged from moderate to very low quality. The majority of evidence was of low quality and most commonly downgraded for imprecision due to the confidence interval crossing either one or two minimally important differences, or for risk of bias (due to bias in measurement of the outcome)

1.1.12.2.16 Generalised spasticity – acupuncture

Evidence was available for acupuncture compared to electroacupuncture, placebo/sham and usual care or no treatment.

- When electroacupuncture was compared to acupuncture the majority of the evidence was of low quality and one outcome was of very low quality. All of the outcomes were downgraded for risk of bias (due to a mixture of bias arising from the randomisation process, bias due to missing outcome data and bias in measurement of the outcome) and several of the outcomes were downgraded for imprecision due to the confidence interval crossing either one or two minimally important differences, or due to zero events and a small sample size.
- When acupuncture was compared to placebo/sham the evidence ranged from high to very low quality with the majority of evidence being rated low quality. The evidence was most commonly downgraded for imprecision due to the confidence interval crossing either one or two minimally important differences, or risk of bias (due to a mixture of bias due to deviations from the intended interventions, in the selection of the reported result and bias due to missing outcome data).one outcome was downgraded by two increments due to heterogeneity, unexplained by subgroup analysis.
- When acupuncture was compared to usual care or no treatment five outcomes were reported, with two rated moderate quality and three rated very low quality. All outcomes were downgraded for risk of bias (due to a mixture of bias arising from the randomisation process and bias due to deviations from the intended intervention). Two outcomes were also downgraded for heterogeneity which was unexplained by subgroup analysis and one outcome for imprecision due to the confidence interval crossing two minimally important differences.

1.1.12.2.17 Generalised spasticity – electroacupuncture

Evidence was available for electroacupuncture compared to acupuncture and usual care or no treatment.

- When electroacupuncture was compared to acupuncture the majority of the evidence was of low quality and one outcome was of very low quality. All of the outcomes were downgraded for risk of bias (due to a mixture of bias arising from the randomisation process, bias due to missing outcome data and bias in measurement of the outcome) and several of the outcomes were downgraded for imprecision due to the confidence interval crossing either one or two minimally important differences, or due to zero events and a small sample size.
- When electroacupuncture was compared to usual care the evidence was of moderate or low quality due to risk of bias (due to either bias arising from the randomisation process or that and bias in measurement of the outcome).

1.1.12.3 Benefits and harms

1.1.12.3.1 Key uncertainties

There was in general a lack of efficacy reported for botulinum toxin A which was against what the committee expected from what they had seen in clinical practice. The committee theorised that this could in part be due to the outcome measures used in the literature. They suggested that the Modified Ashworth scale (which was the most commonly used measure of spasticity in the evidence base) has many limitations and does not measure spasticity as effectively as other measures such as the Tardieu scale. They also noted that botulinum toxin A is often used as a palliative intervention, and this may explain the lack of efficacity in some of the functional related outcome measures or activities of daily living. Clinical outcomes such as pain or the presence of contractures were not widely reported or not included in our protocol. The committee agreed that these may have been useful in detecting the efficacy of botulinum toxin A injections in specific populations with more severe spasticity or limited active movement.

Evidence for oral medications was very limited. Few studies were available for oral baclofen and tizanidine and no relevant evidence was available for dantrolene, gabapentin, pregabalin, clonidine and benzodiazepines. The committee therefore used their expert opinion to make a consider recommendation for oral baclofen but were unable to give any further guideline on the use of other oral medications. They noted that oral medicines for spasticity were considered in other NICE guidelines (such as NG220 Multiple sclerosis in adults: management and NG119 Cerebral palsy in adults). The committee concluded that experts in spasticity management would be able to explore the options for spasticity management, and this would include whether oral medicines would be a part of this strategy. Therefore, they did not make recommendations discussing a range of oral medicines including tizanidine, where there was limited evidence, and the medicines where there was no evidence, referring to the judgement of experts in specialist services to make judgements about the use of these treatments.

The committee were unsure how widely used electrotherapy is in clinical practice as there appeared to a large variation in their use across different trusts. They therefore viewed the evidence base for all types of electrotherapy as one as there was limited evidence and consensus opinion to differentiate between the different types. Due to heterogenous nature of the evidence and included populations there was also uncertainty around specific patient groups who would particularly benefit and the optimum dose or duration of treatment. The committee therefore concluded that these decisions should be made by the treating clinician and stroke survivor.

1.1.12.4 Focal spasticity

1.1.12.4.1 Tizanidine

Evidence was available for tizanidine compared to placebo/sham. Only two outcomes were reported from one small study of very low quality. Results showed a clinically important harm of tizanidine for withdrawal due to adverse events and no clinically important difference for the spasticity outcome measure. Tizanidine was also compared to onabotulinum toxin A (BOTOX) in the same study and showed a clinically important benefit of onobotulinum toxin A (BOTOX) in the spasticity outcome measures and no clinically important difference in withdrawal due to adverse events at less than and equal to 6 months.

The committee acknowledged that that evidence was very limited and due to the lack of evidence available the committee discussed the efficacy of tizanidine and other oral medicines from their clinical experience. They noted that tizanidine is more commonly used for generalised spasticity due to the associated side effects of dizziness, drowsiness, widespread weakness and vomiting. They agreed that it is rarely used in current practice for

the treatment of focal spasticity and other treatment options should be discussed with the multidisciplinary team.

Due to the lack of evidence available the committee were reluctant to make a do not offer recommendation. Therefore, on consideration of the very limited evidence base and uncertainty in the reported outcomes the committee decided not to make a recommendation for tizanidine in a focal spasticity population.

1.1.12.4.2 Oral baclofen

One small study compared incobotulinum toxin A (Xeomin) to oral baclofen and reported a benefit for activities of daily living. However, the other outcomes all showed no clinically important difference including: person/participant reported health related quality of life, spasticity outcome measures and physical function – upper limb.

The committee acknowledged that that evidence was very limited and only based on one small study of 34 participants. Due to the lack of evidence available the committee discussed the efficacy of oral baclofen and drew from their clinical experience. They noted that oral baclofen is more commonly used for generalised spasticity although it is sometimes used in focal spasticity in certain circumstances. The committee's experience is that side effects including such as: drowsiness, dizziness, weakness, tiredness, headache, trouble sleeping, nausea are common and should be explained to the person before starting treatment and monitored closely.

Therefore, on consideration of the very limited evidence base and uncertainty in the reported outcomes the committee decided not to make a recommendation about oral baclofen for focal spasticity.

1.1.12.4.3 Onabotulinum toxin A (BOTOX)

Evidence was available for onabotulinum toxin A (BOTOX) compared to tizanidine, placebo/sham and usual care or no treatment. When onabotulinum toxin A (BOTOX) was compared to tizanidine only two outcomes were reported by one small study showing a benefit in the spasticity outcome and no clinically important difference in withdrawal due to adverse events at less than and equal to 6 months.

When onabotulinum toxin A (BOTOX) was compared to placebo/sham, clinically important benefits were identified in activities of daily living at less than and equal to 6 months and withdrawal due to adverse events at more than 6 months. An unclear effect where some outcomes showed a clinically important benefit while others showed no clinically important difference was seen in spasticity outcome measures at less than and equal to 6 months and stroke-specific Patient-Reported Outcome Measures at less than and equal to 6 months. No clinically important difference was seen in physical function – upper limb at less than and equal to 6 months, physical function – lower limb at less than and equal to 6 months, pain at less than and equal to 6 months and withdrawal due to adverse events at less than and equal to 6 months. A clinically important harm was seen in person/participant generic health-related quality of life at less than and equal to 6 months.

When onabotulinum toxin A (BOTOX) was compared to usual care or no treatment, clinically important benefits were identified in spasticity outcome measures and physical function – lower limb at less than and equal to 6 months. No clinically important difference was seen in physical function – lower limb and activities of daily living at less than and equal to 6 months.

There was one clinically important harm associated with onabotulinum toxin A (BOTOX) when compared to a placebo/sham for the person/participant health-related quality of life outcome measured using the EQ-5D. The committee acknowledged that this was based on the results from one small study, consisting of a chronic stroke population with mild spasticity and reporting a very specific aim to improve grasp-release function. The committee theorised that any benefits may have not been enough to impact a global measure quality of life such

as EQ-5D, and this in conjunction with the very small size of 28 patients and uncertainty around the effect estimate led the committee to interpret the result with caution.

On reviewing the evidence, the committee considered the balance of benefits and harms and were ultimately surprised that the results were not more convincing in favour of onabotulinum toxin A (BOTOX). Many committee members discussed the efficacy of botulinum toxin A injections when used in clinical practice and expected these benefits to be borne out in the clinical evidence. They noted that the benefit in the spasticity outcome measures were consistent across the studies which is in line with what they see in practice. However, they expected that these improvements would have translated to gains in other outcome measures such as activities of daily living and physical function, due to improvements in pain and mobility of the affected limb.

Several members of the committee suggested that the lack of convincing evidence in favour of onabotulinum toxin A (BOTOX) injections could be due to the populations reported in the studies which tended to be more chronic than those they would aim treat in clinical practice. The committee noted that botulinum toxin A injections are usually administered within the first three weeks post-stroke in people with focal spasticity. This was usually done in order to manage pain, improve activities of daily living, aid hygiene and to minimise the risk of future contractures. They explained that after this period mechanical changes can take place in the paretic limb leading to risks of contractures and pain which may explain the lack of efficacy reported in the studies. The committee also suggested that by not having these injections in a sub-acute setting could lead to increased admissions to secondary care later down the line. The committee noted that in the majority of studies only one dose of onabotulinum toxin A (BOTOX) was administered in the double-blind phase. However, in clinical practice several doses are often provided approximately twelve weeks apart which could be another possible explanation for the lack of benefits seen in the clinical evidence.

On weighing up the benefits and the potential harms, along with the limitations of the evidence, the committee noted that onabotulinum toxin A (BOTOX) could be a clinically effective treatment for spasticity. However, on taking into account the cost-effectiveness evidence, they did not make a recommendation for the treatment. They agreed a research recommendation for further research into the use of the treatment, including additional outcomes of interest and a cost-effectiveness analysis.

1.1.12.4.4 Abobotulinum toxin A (Dysport)

Evidence was available for abobotulinum toxin A (Dysport) compared to tizanidine, neuromuscular electrical stimulation, placebo/sham and usual care or no treatment. When abobotulinum toxin A (Dysport) was compared to tizanidine, two outcomes reported a clinically important benefit in favour of the injection including, spasticity outcome measures and withdrawal due to adverse events, with one no clinically important difference for physical function – upper limb. When compared to neuromuscular electrical stimulation, no clinically important difference was seen in spasticity outcome measures and withdrawal due to adverse events at less than and equal to 6 months.

When abobotulinum toxin A (Dysport) was compared to placebo/sham, clinically important benefits were seen in spasticity outcome measures at less than and equal to 6 months and more than 6 months, pain at less than and equal to 6 months and stroke outcome – modified Rankin scale at less than and equal to 6 months. No clinically important difference was seen in person/participant generic health-related quality of life, physical function – upper limb, physical function – lower limb, activities of daily living and withdrawal due to adverse events at less than and equal to 6 months.

When abobotulinum toxin A (Dysport) was compared to usual care or no treatment, clinically important benefits were seen in person/participant generic health-related quality of life at less than and equal to 6 months and more than 6 months. No clinically important difference was seen in spasticity outcome measures, physical function – upper limb, pain, activities of daily

living and stroke-specific Patient-Reported Outcome Measures at less than and equal to 6 months.

On reviewing the evidence, the committee were surprised by the limited number of outcomes reporting a clear benefit for abobotulinum toxin A (Dysport). The committee explained that in an NHS setting abobotulinum toxin A (Dysport) would be used as commonly as onabotulinum toxin A (BOTOX) and therefore, they would have expected the results to be more conclusive in favour of onabotulinum toxin A due to the aforementioned benefits with onabotulinum toxin A injections for spasticity that are widely seen in clinical practice.

The committee also acknowledged that despite the large number of outcomes reporting no clinically important difference, the general trend for these outcomes were in a positive direction which just fell short of the threshold for clinical significance. The committee also noted the benefits for person/participant health-related quality of life reported at both the less than and equal to 6 and more than 6 months follow up, pain and the improvement noted on modified Rankin scale as these were highlighted as outcomes that matter most and all were reported by studies with reasonable sample sizes despite being of very low quality.

Therefore, on the balance of the benefits identified in the evidence coupled with the lack of any clinical harms the committee concluded that there was sufficient evidence of clinical benefit of abobotulinum toxin A (Dysport). On examining the evidence of cost effectiveness, the committee recommended that abobotulinum toxin A could be considered for focal spasticity of the upper limb at a specific dosage delivered every 3 months, but only if people responded to treatment (if assessed to be ineffective after correct delivery alongside optimised treatment of other concomitant treatments at 3 months then the treatment should be discontinued).

1.1.12.4.5 Incobotulinum toxin A (Xeomin)

Evidence was available for incobotulinum toxin A (Xeomin) compared to oral baclofen, placebo/sham and usual care or no treatment. Evidence for these comparisons were limited with fewer studies reporting this type of botulinum toxin A than the previous two formulations. One small study compared incobotulinum toxin A (Xeomin) to oral baclofen and reported a benefit for activities of daily living, however, the other outcomes all showed no clinically important difference including: person/participant reported health-related quality of life, spasticity outcome measures and physical function – upper limb.

When incobotulinum toxin A (Xeomin) was compared to placebo/sham, a clinically important benefit was seen in spasticity outcome measures at less than and equal to 6 months. No clinically important difference was seen in physical function – lower limb and pain at less than and equal to 6 months and withdrawal due to adverse events at less than and equal to 6 months and more than 6 months. When incobotulinum toxin A (Xeomin) was compared to usual care, clinically important benefits were seen in spasticity outcome measures and activities of daily living at less than and equal to 6 months. No clinically important difference was seen in physical function – upper limb and withdrawal due to adverse events at less than and equal to 6 months.

The committee acknowledged that the evidence was very limited for these comparisons and sample sizes were small for many outcomes. They also noted that this injection is not so commonly used in clinical practice, so they were less confident in its efficacy from an anecdotal perspective.

On weighing up the benefits and the potential harms, along with the limitations of the evidence, the committee noted that incobotulinum toxin A (Xeomin) could be a clinically effective treatment for spasticity. However, on taking into account the cost-effectiveness evidence, they did not make a recommendation for the treatment. They agreed a research recommendation for further research into the use of the treatment, including additional outcomes of interest and a cost-effectiveness analysis.

1.1.12.4.6 Functional electrical stimulation (FES)

Evidence was available for functional electrical stimulation compared to placebo/sham and usual care or no treatment. When compared to placebo/sham, no clinically important benefits were reported and all outcomes including; spasticity outcome measures, physical function - lower limb, activities of daily living and withdrawal due to adverse events showed no clinically important difference.

However, when functional electrical stimulation was compared to usual care or no treatment, clinically important benefits were seen in spasticity outcome measures, physical function – upper limb and activities of daily living at less than and equal to 6 months. An unclear effect where some outcomes showed a clinically important benefit and others showed no clinically important difference was seen in physical function – lower limb at less than and equal to 6 months. No clinically important difference was seen in stroke-specific Patient-Reported Outcome Measures and withdrawal due to adverse events at less than and equal to 6 months.

On reviewing the evidence, the committee highlighted the benefits reported for the spasticity outcome measures, physical function outcomes and activities of daily living. These outcomes were considered important as they are directly related to the aims of the intervention, which is to regain the function of affected limb (through stimulation of the motor neurons during voluntary movement, in order to induce neuroplastic changes) and ultimately to improve engagement with activities of daily living. The fact that these benefits were not present in the placebo/sham comparison led to some uncertainly around the effect of the placebo. However, there were fewer studies available for this comparison and all of the evidence was of very low quality with uncertainty around the effect estimate.

The committee were unable to provide a clear consensus on how widely functional electrical stimulation is currently used in an NHS setting. They explained that it is currently influenced by clinician choice along with availability of the equipment and trained staff which appear to be postcode dependent. They also agreed that in general this would be used as an adjunct to other therapies and would not be offered as a stand-alone treatment. The committee therefore weighed up the benefits with the absence of any reported harms and agreed that functional electrical stimulation could be considered for people with focal spasticity. The committee also made a research recommendation to investigate further whether the treatment could be effective at managing spasticity given the uncertainty in the evidence.

1.1.12.4.7 Neuromuscular electrical stimulation (NMES)

Evidence was available for neuromuscular electrical stimulation compared to transcutaneous electrical stimulation, placebo/sham and usual care or no treatment. One small study compared neuromuscular electrical stimulation to transcutaneous electrical nerve stimulation and reported clinically important benefits in reducing pain and activities of daily living for the neuromuscular electrical stimulation arm. No differences were reported for the spasticity outcome measures, physical function – upper limb and stroke-specific Patient-Reported Outcome Measures. A clinically important harm was seen in withdrawal due to adverse events.

When neuromuscular electrical stimulation was compared to placebo/sham, clinically important benefits were seen in activities of daily living and withdrawal due to adverse events at less than and equal to 6 months. No clinically important difference was seen in spasticity outcome measures, physical function – upper limb, stroke-specific Patient-Reported Outcome Measures and hospitalisation at less than and equal to 6 months. Clinically important harms were seen in pain and additional healthcare contacts at less than and equal to 6 months.

When neuromuscular electrical stimulation was compared to usual care or no treatment, clinically important benefits were seen in reducing pain at less than and equal to 6 months.

An unclear effect where some outcomes showed a clinically important benefit while others showed no clinically important difference was seen in spasticity outcome measures, physical function – upper limb and activities of daily living at less than and equal to 6 months. No clinically important difference was seen in physical function – lower limb, stroke-specific Patient-Reported Outcome Measures and withdrawal due to adverse events at less than and equal to 6 months.

On reviewing the efficacy of neuromuscular electrical stimulation compared to placebo/sham the committee discussed the clinically important harm present for pain (which had led to an increase of almost 2 points on a visual analogue scale, scale range = 0-10). However, they noted that this was reported in a very small study of only 7 participants in each arm so should be interpreted with caution. This was also balanced against a clinically important benefit for pain in the usual care or no treatment comparison, which was reported by a larger study with 41 participants. The committee also considered the clinical harm in the outcome reporting additional health contacts. These healthcare contacts were specifically people accessing prescriptions for pain or spasticity medication and were deemed to be a clinical harm. However, the committee debated that these could equally be viewed as a clinical benefit if people are perhaps becoming more comfortable in approaching healthcare professionals and possibly taking ownership of or better managing their condition. Once again, this outcome was reported by a small study with only 48 participants.

The committee were unable to give a clear indication on how commonly neuromuscular electrical stimulation is used in an NHS setting. It appeared to be influenced by clinician choice along with availability of the equipment and trained staff which may vary between trusts. They agreed that in general this would be used as an adjunct to other therapies and would not be offered as a stand-alone treatment. Therefore, on the balance of the number of benefits reported in the usual care comparison against the several harms the committee decided to recommend that NMES could be considered for people with focal spasticity.

1.1.12.4.8 Transcutaneous electrical stimulation (TENS)

Evidence was available for transcutaneous electrical nerve stimulation compared to placebo/sham and usual care or no treatment. When compared to placebo/sham, a clinically important benefit was seen in activities of daily living at less than and equal to 6 months. An unclear effect where some outcomes showed a clinically important benefit while others showed no clinically important difference was seen in spasticity outcome measures and physical function – lower limb at less than and equal to 6 months. No clinically important difference was seen in withdrawal due to adverse events at less than and equal to 6 months.

When compared to usual care or no treatment, a clinically important difference was seen in spasticity outcome measures, activities of daily living and withdrawal due to adverse events at more than 6 months. An unclear effect where some outcomes showed a clinically important benefit while others showed no clinically important difference was seen in physical function – lower limb at less than and equal to 6 months. No clinically important difference was seen in spasticity outcome measures at less than and equal to 6 months, physical function – upper limb at less than and equal to 6 months and more than 6 months, pain, activities of daily living, stroke-specific Patient-Reported Outcome Measures and withdrawal due to adverse events at less than and equal to 6 months.

The committee noted that despite most of the outcomes reporting no clinically important difference that the majority of these showed a positive trend in favour of transcutaneous electrical nerve stimulation.

The committee also considered the fact that transcutaneous electrical nerve stimulation is readily available in an NHS setting, and devices are portable and simple for patients to self-administer. However, there was no consensus amongst the committee on how these are currently being used in clinical practice and again it appeared to be influenced by clinician choice along with availability of the equipment and trained staff which appear to be postcode

dependent. They agreed that in general this would be used as an adjunct to other therapies and would not be offered as a stand-alone treatment. One committee member advised that is often given to people with focal spasticity in the sub-acute phase post stroke before other more invasive treatments such as botulinum toxin A injections. On weighing up the benefits and harms, the committee concluded that TENS could be considered for people with focal spasticity.

1.1.12.4.9 Acupuncture

Evidence was available for acupuncture compared to placebo/sham and usual care or no treatment. When compared to placebo/sham, clinically important benefits were seen in person/participant generic health-related quality of life, spasticity outcome measures and activities of daily living at less than and equal to 6 months. No clinically important difference was seen in physical function – upper limb, physical function – lower limb and withdrawal due to adverse events at less than and equal to 6 months. When compared to usual care or no treatment, clinically important benefits were seen in physical function – lower limb and activities of daily living at less than and equal to 6 months. No clinically important difference was seen in spasticity outcome measures and withdrawal due to adverse events at less than and equal to 6 months.

The committee considered the limited evidence available for these comparisons in the treatment of focal spasticity. They also acknowledged that there was some ambiguity around the categorisation of the type of spasticity as this was often not reported in the studies. The type of spasticity (for example: generalised or focal) was therefore determined through consideration of the type of acupuncture applied and the outcomes reported. Due to the lack of evidence available for this comparison the committee therefore decided to view this evidence in conjunction with the evidence reported for generalised spasticity.

The committee weighed up the benefits with the absence of any reported harms and considered the very small sample sizes, low quality rating of the available evidence and fact that no studies were based in a UK setting. The committee also considered the fact that acupuncture is not widely available in an NHS setting meaning they have limited clinical experience on its efficacy. This led the committee to conclude that further high quality research particularly in a UK setting is required. A research recommendation to examine the effectiveness and cost effectiveness of acupuncture and electro-acupuncture to treat focal spasticity has been drafted.

1.1.12.4.10 Combination therapies

Evidence was available for the following combination therapies: abobotulinum toxin A (Dysport) and transcutaneous electrical nerve stimulation compared to placebo/sham and transcutaneous electrical nerve stimulation; abobotulinum toxin A (Dysport) and neuromuscular electrical stimulation (NMES) compared to abobotulinum toxin A (Dysport) alone; abobotulinum toxin A (Dysport) and neuromuscular electrical stimulation (NMES) compared to neuromuscular electrical stimulation (NMES) alone and onabotulinum toxin A (BOTOX) and functional electrical stimulation compared to onabotulinum toxin A (BOTOX) only.

All of the comparisons were only reported by 1 study with small sample sizes. Many of the comparisons reported inconclusive results with a mix of benefits and harms. One comparison, onabotulinum toxin A (BOTOX) and functional electrical stimulation (FES) compared to onabotulinum toxin A (BOTOX) alone showed benefits for all three outcomes reported including spasticity outcome measures, physical function – lower limb and activities of daily living. Due to the very limited evidence available for these combinations the committee did not make any recommendations for the combination therapies but noted that there were no significant concerns raised regarding the use of any therapies in combinations based on this evidence.

1.1.12.5 Generalised spasticity

1.1.12.5.1 Oral medicines: baclofen and tizanidine

Evidence was available for tizanidine compared to oral baclofen. Evidence for oral medications in general was very limited. Only one small study of 30 participants reported this comparison and only one outcome was included which showed a clinically important benefit of tizanidine over oral baclofen for withdrawal due to adverse events.

The committee noted that significant limitations in the evidence and that this had very little influence on their decision making. Instead, they discussed the efficacy of oral medications and agreed that oral baclofen is widely used in current practice to treat generalised spasticity. The benefits of this drug has been established for many years in clinical practice and the committee theorised that the evidence base remains very limited for these drugs in part due to their long established effectiveness.

The committee explained that baclofen is often given as the first line treatment for people with generalised spasticity in the acute and subacute phases post stroke and is generally effective, despite the associated side effects. The committee agreed that tizanidine is less commonly used in current practice. They also discussed the earlier harm reported for withdrawal due to adverse events when tizanidine was compared to placebo/sham in a focal spasticity population. However, this was based on one very small study and due to the lack of evidence available overall the committee were reluctant to make a do not offer recommendation for tizanidine as they could not be sure of its efficacy and there could be specific populations may benefit from this medication.

The committee therefore used their consensus opinion to recommend that the use of oral baclofen for people with generalised spasticity is considered as a first line treatment. The clinician should also explain the associated side effects of oral baclofen such as; drowsiness, dizziness, weakness, tiredness, headache, trouble sleeping, nausea to the person before starting treatment and monitor them closely. They agreed to not make a recommendation regarding the use of tizanidine.

1.1.12.5.2 Intrathecal baclofen

Evidence was available for intrathecal baclofen compared to usual care or no treatment. One study reported this comparison which was an international multi-centre randomised controlled trial based in eleven European centres and 7 US centres. Benefits were reported for person/participant health related quality of life and spasticity outcome measures. No clinically important differences were seen in pain, activities of daily living, stroke-specific Patient-Reported Outcome Measures and withdrawal due to adverse events. No clinically important harms were identified for any outcomes and all outcomes were reported at less than and equal to 6 months.

The committee highlighted the benefit reported for person/participant health-related quality of life on EQ-5D as particularly important, as this improvement could have huge implications on the person's lifestyle and care needs and could potentially be the difference in being discharged home as opposed to a nursing home. Despite no clinically important harms being reported overall, there was one incidence of mortality in the treatment group after the pump had been fitted. However, there was no information to suggest that this was directly related to the treatment. Therefore, the committee decided this was unlikely to be relevant to the decision as to whether to make a recommendation in this area.

The committee highlighted that intrathecal baclofen is currently one of the only treatment options available for a specific population of stroke survivors who have had a severe stroke and present with widespread spasticity, limited mobility and in which first line drug treatments have failed. As this intervention is very invasive and requires expensive equipment and specialist clinicians, the evidence base is limited in this area.

On weighing up the evidence of benefit, against the limited amount of evidence and the cost-effectiveness analysis, the committee agreed that they could not make an explicit recommendation for intrathecal baclofen. However, they agreed that people who have ongoing spasticity which has not responded to previous treatment, or who have complex needs in relation to spasticity management, should be referred to a specialist spasticity service for consideration of intrathecal baclofen. Specialist spasticity services will have the scope to assess the relevance of providing specialist services, and this should include intrathecal baclofen as an option where appropriate.

1.1.12.5.3 Acupuncture

Evidence was available for acupuncture compared to placebo/sham and usual care or no treatment. When compared to placebo/sham, clinically important benefits were seen in physical function – general, pain, activities of daily living, stroke-specific Patient-Reported Outcome Measures and withdrawal due to adverse events at less than and equal to 6 months. An unclear effect, where some outcomes showed a clinically important benefit and others showed no clinically important difference was seen in spasticity outcome measures at less than and equal to 6 months. No clinically important difference was seen in person/participant generic health-related quality of life and physical function – upper limb at less than and equal to 6 months. When compared to usual care or no treatment, a clinically important benefit was seen in activities of daily living at less than and equal to 6 months. An unclear effect, where some outcomes showed a clinically important benefit and others showed no clinically important difference was seen in physical function – general and activities of daily living at less than and equal to 6 months. No clinically important difference was seen in withdrawal due to adverse events at less than and equal to 6 months.

On reviewing this evidence, the committee concluded that the results overall indicated a benefit of acupuncture for treating generalised spasticity particularly when compared to the placebo/sham arm. They also noted that the majority of outcomes showing no clinically important difference were in the direction of a benefit for acupuncture.

However, while the majority of evidence was positive, the committee acknowledged the limitations in the quality of the evidence, with outcomes ranging between high and very low quality, and most of the outcomes rated very low quality. Sample sizes were relatively small and no studies took place in the UK in an NHS setting.

The committee weighed up the benefits of acupuncture reported in the evidence along with their clinical expertise. They admitted that their experience of acupuncture in clinical practice is fairly limited as it is not widely available on the NHS, so not commonly used in their clinical settings. However, they suggested that it would be a good alternative to oral medications in people with generalised spasticity to avoid the associated side effects.

Therefore, due to the limitations of the evidence and heterogeneity between the studies in the description of the acupuncture applied the committee were unable to make a recommendation for acupuncture and they agreed that further high-quality research is required. The committee made a research recommendation for further clinical trials looking at the clinical and cost effectiveness of acupuncture and electroacupuncture for spasticity in a UK based setting.

1.1.12.5.4 Electroacupuncture

Evidence was available for electroacupuncture compared to acupuncture and usual care or no treatment. Compared to acupuncture, electroacupuncture showed a clinically important benefit in spasticity outcome measures at less than and equal to 6 months. Compared to usual care there was no clinically important difference in spasticity outcome measures, physical function – lower limb and withdrawal due to adverse events at less than and equal to 6 months.

The committee acknowledged that the evidence base was very limited. They also admitted that their experience of electroacupuncture in clinical practice was limited as it is not commonly used in an NHS setting. Due to the limitations of the evidence and inconclusive findings the committee were unable to make a recommendation for this intervention but made a research recommendation for further clinical trials looking at the effectiveness and cost effectiveness of acupuncture and electroacupuncture for spasticity in a UK based setting.

1.1.13 Cost effectiveness and resource use

The economic evidence review identified six relevant published economic evaluations – five of which assessed different brands of botulinum toxin type A (BoNT-A), while one assessed dry needling. Four further studies were excluded due to limited applicability and methodological limitations. No health economic studies were included that related to oral medicine, intrathecal baclofen, functional electrical stimulation (FES), neuromuscular electrical stimulation (NMES), transcutaneous electrical nerve stimulation (TENS), acupuncture or electroacupuncture.

1.1.13.1 Botulinum toxin type A (BoNT-A)

The first study (Shackley 2012[111]), compared a mean dose of 505 units of abobotulinum toxin A (Dysport®) plus a 4-week upper limb therapy programme to the therapy programme alone for people with post-stroke upper limb spasticity. This was a within-trial analysis of the BoTULS RCT (N=283)[113] which was conducted as part of the Health Technology Assessment (HTA) programme and was included in the clinical review. The study concluded that Dysport was not cost-effective, as the QALY gain associated with the intervention was small (0.004) relative to the incremental cost (£374), resulting in an incremental cost-effectiveness ratio (ICER) of £93,500 per QALY gained. This was significantly above the £20,000 willingness-to-pay (WTP) threshold set by NICE, and the probability of it being cost-effective at this threshold was 36%. These results were robust to a number of sensitivity analyses.

This study was assessed as partially applicable for this review as it used 2005–2008-unit costs and resource use estimates which may not reflect the current NHS context. Dysport was only used to treat upper limb spasticity, limiting the applicability of the study conclusions for people experiencing lower limb spasticity. The recommended dosing for lower limb is higher and so is likely to have higher drug costs compared to the cost presented in this analysis (£154). Potentially serious limitations were identified, in part due to the within-trial analysis which only captures evidence from the BoTULS trial and therefore doesn't reflect the wider evidence base. Assumptions had to be made regarding the use of other health care and social services resources during the second month of the three-month analysis period, as questionnaires were completed at 1 and 3 months but only asked about the previous month. Committee members also highlighted concern towards the 3-month time horizon, as this may not fully capture costs and outcomes when people are allowed repeat injections every 12 weeks in both the study and in current practice. EQ-5D was collected for 12 months but was not used in this analysis as only 52.4% of participants responded at this time point, which was considerably lower than the corresponding figures for baseline (100%), 1 month (83.7%) and 3 months (85.2%). However, they did not conduct a sensitivity analysis to investigate this further.

The second study (Doan 2013[24]) compared a mean dose of 221 units of onabotulinum toxin A (BOTOX®) plus usual care (defined as routine physical and occupational therapy) to usual care alone for people with upper-limb spasticity. Three costing scenarios were considered, with the results varying depending on the scenario applied: Scenario 1 was cost-effective, with an ICER of £10,000. This scenario included intervention costs, i.e., the cost of Botox, specialist office visits and day-hospital visits. Scenario 2 did not include hospital visits and was not cost-effective as a result, with an ICER of £27,000. Scenario 3 incorporated informal

care costs (which is not an NHS or PSS cost) and is therefore not a reference case analysis. As such, it was not appropriate to compare it to the threshold. Results for Scenarios 1 and 2 were robust to sensitivity analyses.

Doan 2013 was partially applicable as the study population was treated for upper-limb spasticity alone and EQ-5D scores were estimated using the USA population tariff when the NICE reference case specifies a preference for the UK tariff. The use of 2008-2010 UK unit costs and older published resource use estimates may also not reflect current NHS context; however, the committee were informed that the cost of Botox in the study is the same as current UK costs (£306 for 221 units). Potentially serious limitations were noted, including how transition probabilities between disability-based health states with usual care and Botox are based on 12-week data from a single study included in clinical review (and for Botox only also a 42-week follow-up study). In addition, Scenario 1 justified inclusion of reduction in day hospitalisation rate with Botox based on it being the only significant difference in the BOTULS RCT economic analysis, however, the BoTULS study also reported statistically significant differences in the proportion of participants reporting contacts for practice nurse and social worker; overall its cost analysis also found an increase in other costs with botulinum toxin A. Furthermore, probabilistic analyses were not undertaken to quantify parameter uncertainty. The study was also funded by the manufacturer of Botox (Allergan).

Lindsay, 2022[69] was a UK within-trial cost-effectiveness analysis based on an RCT (n=93) included in the clinical review,[70] which assessed outcomes associated with early treatment (first 6 weeks post-stroke) of upper-limb spasticity with an onabotulinum toxin A (BOTOX®) injection (mean dose: 160 units) and the subsequent impact on resource utilisation compared to usual care at baseline and 6 months. The results showed no statistically significant differences in total costs or health outcomes at 6-months follow-up, however a cost-saving of £1,481 (p=0.04) for the treatment of contractures was reported. This study was deemed partially applicable as QALYs (and therefore cost per QALYs) were not reported and the use of 2012-2013 resource use estimates may not reflect the UK NHS context. Potentially serious limitations were identified as follows: within-trial secondary analysis meant that costs and outcomes only reflect this trial and not the wider evidence base; 6-month follow-up may be insufficient to reflect differences in all costs and outcomes; long-term costs for the management of contractures were taken from a 2001 US study (and the method of currency conversion was also not reported) and no probabilistic sensitivity analyses were conducted.

The fourth study (Makino 2010[72]) was an Australian cost-utility analysis that modelled a mean dose of 352 units of incobotulinum toxin A (Xeomin®) for people with upper limb spasticity. The study design differed from the other included economic analyses as a Markov model compared limited Xeomin treatment cycles (where everyone received 2 cycles while responders could receive to up to 4 additional cycles) to unlimited Xeomin treatment cycles (everyone received treatment for 2 cycles while responders continued to receive additional cycles with no upper limit). The results found that continuing Xeomin in responders beyond 4 treatments compared to not doing so was not cost effective, with an ICER of £28,457. Study conclusions on cost-effectiveness were not sensitive to adjustments made to model inputs.

This study was assessed as partially applicable, on account of incorporating 2010-2016 Australian unit costs and resource use estimates, which may not reflect the current UK NHS context and for only assessing the effects of Xeomin® on upper limb spasticity (although it is not indicated for lower limb spasticity). EQ-5D scores were also estimated using the Australian population tariff when the NICE reference case specifies the UK tariff is preferred, and costs and health effects were discounted at a non-reference case rate (5% rather than 3.5%). Potentially serious limitations were identified as clinical data was based on a single RCT (and open label extension) and so only reflects this study and not the wider evidence base identified in the clinical review. In addition, the potential cost impact of reducing disability was not included as the analysis only incorporated costs directly associated with the provision of injections. When assessing quality of life inputs, it was noted that EQ-5D scores are based on data from the same RCT but difference by randomised group is not

reported and this is not discussed. EQ-5D questionnaire collection times were also not reported, which was noted as important by the committee as it takes 4 weeks for the full effects of BoNT-A to be realised. The study was also funded by the manufacturer of Xeomin® (Merz Pharmaceuticals).

The last study that evaluated BoNT-A was a UK cost-utility analysis (Danchenko, 2022,[18]) which compared onabotulinum toxin A (BOTOX®) to abobotulinum toxin A (Dysport®) for adults with upper and lower limb post-stroke spasticity, respectively. The base case assumption was that all patients in the model continued to receive botulinum toxin type A (BoNT-A) treatments at regular intervals regardless of treatment response status. The results suggested that Dysport dominates Botox (i.e., less costs and higher QALYs), with cost savings of £304 (with a 0.02 QALY gain) and £394 (0.01 QALY gain) for upper and lower limb indications, respectively. The probability that Dysport is cost effective at a £20K threshold was reported to be 100% for both upper limb and lower limb indications. Scenario analyses showed the results for both indications to be robust across all parameters tested, apart from a scenario where lower-limb non-responders received one injection, which resulted in higher costs (£215) and higher QALYs (0.01) for Dysport group (ICER of £21,234).

This study was partially applicable as a control group was not incorporated into the analysis. In addition, there was uncertainty concerning the applicability of the upper limb analysis, as it was unclear whether the lower limb population consisted of ≥80% stroke survivors. EQ-5D-5L was also used to estimate utility values for the lower limb indication, when NICE reference case prefers EQ-5D-3L. Potentially serious limitations that were noted such as the utility values used were not based on MAS and GAS response rates but rather on EQ-5D data for different walking speeds and Disability Assessment Scale (DAS), respectively. Further limitations included: the use of observational data for treatment response rates in the upper limb indication; using a survey of 12 UK physicians for the upper limb group's resource use estimates (which were then applied to the lower limb group); incorporating non-stroke specific utility inputs for the lower limb group; and that the analysis was funded by the manufacturer (Ipsen) of Dysport.

The health economic evidence for BoNT-A is mixed, with most analyses suggesting it is not cost-effective and others suggesting it may be cost effective under certain assumptions. Some of the health economic evidence does not compare to a control group and therefore does not provide information as to whether it is cost effective compared to usual care. A number of aforementioned issues identified with each study created uncertainty towards the study conclusions. For these reasons it was decided that original economic modelling should be performed for this review question. A de novo cost utility analysis was conducted making use of RCT evidence identified in the clinical review. QALYs were estimated using Modified Ashworth Scale (MAS) responder data from the clinical review (MAS responder defined as a ≥1 point reduction in MAS). Three RCTs were identified in the systematic review of the literature reporting MAS responder data, one for each drug: Botox (lower limb),[137] Dysport (upper limb)[37] and Xeomin (upper limb).[28] The MAS responder data was reported at multiple time points thus allowing for QALYs over the trial period to be estimated using an area under the curve approach and applying 'responder' and 'non-responder' EQ-5D values, as done in one of the published cost utility analyses, Makino 2019. The same concerns noted for Makino 2019[72] with regards to the EQ5D data apply here. However, modelling using MAS was the best and only approach available to explore uncertainty in cost effectiveness of as it makes use of additional clinical evidence not used in current CUA.

Several scenarios were explored whereby the time horizon was extend to 1 year and 2 years to account for repeat injections of BoNT-A. Repeat injections were modelled as occurring at 12-week intervals. The total number of injections in a year was assumed to be four and the proportion receiving repeat injections progressively decreased. This was based on observational and UK RCT evidence (Turner Stokes 2021, Shaw 2012).[113, 129] For repeat injections, it is assumed the QALY gain after a repeat injection will be the same as the QALY

gain after the first injection, as the responders will continue to respond, and non-responders will remain non-responders. The costs however will decrease if fewer people receive repeat injections over time. A sensitivity analysis was conducted where all those in the intervention group received repeats irrespective of need, and therefore the costs continue to be incurred. The costs of administration and the drugs were included in all analyses. There was uncertainty with regards to what constituted standard spasticity care, in the base case analysis it was assumed all administration appointments for BoNT-A were over and above standard care. A sensitivity analysis was conducted however where those in the usual care arm would have 2 follow up appointments a year and those receiving BoNT-A injections would have one appointment for each injection (up to 4 over a year). The impact of BoNT-A on downstream costs were considered uncertain and therefore a threshold analysis was conducted to estimate magnitude of savings needed for BoNT-A to be cost-effective. This de novo analysis found that a single BoNT-A injection not cost effective (12-week horizon), ICERs were £41,110, £50,690, £134,404, and £225,203 per QALY for Dysport 500U, Dysport 1000U, Xeomin and Botox respectively versus usual care. Repeat injections are not cost effective if given to all people, irrespective of response/assessment of need (ICERs between £26,086 and £210,942 per QALY, depending on BoNT-A and time horizon). Finally, the analysis found that repeat BoNT-A injection may be cost effective only when all the following conditions are met: the person is receiving 500U Dysport for upper limb spasticity, the proportion receiving repeat injections decreases over a 1 or 2 year period (thus assuming that repeats are given based on an assessment of need) and that standard spasticity care includes twice yearly neurology attendances (therefore reducing the incremental costs of BoNT-A versus usual care). When all these conditions were met the ICER was £19, 361 per QALY at a 1-year time horizon and between £15,078 and £16,191 per QALY depending on extrapolation assumptions for the proportion receiving repeat injections. The threshold analyses suggest that substantial downstream savings are required for Xeomin, Botox or Dysport 1000U to be cost effective in most scenarios. The results are driven by higher proportion of responders in Dysport trial and the lower cost of Dysport.

Several outcomes were not incorporated in the analysis, and these were discussed qualitatively with the committee. For example, this analysis was not based on RCT evidence in a sub-acute stroke population and therefore did not account for the potential benefits of early treatment with BoNT-A on contracture reduction. In addition, observational data suggests that the duration between injections could be increased particularly for Dysport. This could result in either less injections (lower cost) for the same QALY gain or same number of injections but a longer QALY benefit. It was also considered that the administration costs used in this analysis (based on a face-to-face outpatient attendance with neurology MDT) may not be reflective of the cost of administration for a person with a higher level of dependency. These individuals may need ambulatory care or treatment at home, which are both more costly. Furthermore, the benefits in such a group may also be different to the ones observed.

Based on this de novo analysis and the clinical evidence, the committee made a consider recommendation for BoNT-A, clearly qualifying the drug, indication and dose as well as conditions in which such a treatment would be considered likely to be cost effective.

1.1.13.2 Acupuncture/Dry needling

The last study included in the economic evidence review (Fernandez-Sanchis, 2022[32]) was a Spanish within-trial cost-utility analysis based on an observational study (Zaldivar 2021[16] (n=80)) that compared standard physiotherapy (45-minute sessions, five days per week for 8 weeks) to 6 sessions of dry needling plus standard physiotherapy for post-stroke adults in the subacute phase (1–3 months) experiencing upper limb spasticity. The results indicated that dry needling was not cost-effective, as the 4-week and 8-week ICERs were £161,283 and £216,527, respectively. The probability that dry-needling was cost effective at a £26,645

(€25,000) threshold was 7.5% at 4 weeks and 8% at 8 weeks. This study was assessed as partially applicable for this review as Spanish healthcare system may not reflect current UK NHS practice. Furthermore, QALYs were estimated using EQ-5D-5L (Spanish tariff) when the NICE reference case currently prefers EQ5D-3L (UK tariff). Potentially serious limitations included the use of baseline outcomes, intervention effects and resource use estimates from a single non-randomised observational study excluded from clinical review. The 8-week follow-up may also not sufficiently assess the full costs and benefits. Only intervention-related healthcare costs and resource use were incorporated into the analysis; no downstream resource use included. References for unit costs (including cost year - with the exception of costs per patient stay) were not reported. One conflict of interest was declared as the dry-needling technique used was registered by a study author.

The committee were also presented with unit costs associated with dry needling and acupuncture, taken from UK national databases. Varied resource use was also reported in the clinical review, as the frequency of acupuncture sessions ranged from 20-60 minutes, occurring anywhere from twice weekly to everyday, with interventions lasting between 2-24 weeks. The cost of delivering acupuncture is primarily based on staff time. A previous economic model developed for the Chronic Pain NICE guideline (NG193)[86] reported that the cost of the needles is small (£0.06 per needle, with 10-14 needles used per session) in comparison to the staff costs. An outpatient procedure for acupuncture for pain management is £141,[93] although costs in the community setting may be lower. Aside from the staff time required to deliver electroacupuncture, example costs of electroacupuncture devices were presented to the committee, which ranged from £240-£395. Other costs associated with electrotherapy include clips, lead cables, batteries, needles, disinfectant swabs and surgeons' gloves. The committee regarded acupuncture and electroacupuncture to one of the less frequently provided treatments for spasticity following stroke, meaning that staff training may be required to deliver these interventions.

The limited clinical evidence for acupuncture included a clinically important benefit for pain at <6 months for acupuncture when compared to both placebo/sham and usual care or no treatment. Clinical evidence for electroacupuncture was based on a single study that indicated a clinically important benefit for pain at <6 months when compared to placebo/sham. The lack of clinical evidence for acupuncture may have been due to several studies that were not assessed because they were not published in English. Considering the lack of clinical data available for acupuncture to be incorporated into an economic analysis and limitations of the dry needling economic evidence, the committee decided that there was insufficient evidence to consider recommending all forms of acupuncture and dry needling interventions. A research recommendation was made. Committee members emphasised that although there is insufficient evidence to recommend acupuncture or dry needling, patients and carers should be made aware of such options to allow them to explore alternative way of managing symptoms outside of NHS funding.

1.1.13.3 Electrotherapies (TENS/NMES/FES)

The cost of electrotherapies relates primarily to the staff time to administer it and will depend on frequency and duration of therapy sessions, as well as the duration of treatment. There are also equipment costs, however, previous economic evaluations of electrotherapy (TENS, NMES, FES) have not included the costs of equipment used by physiotherapists in the analysis as the per-use costs were expected to be small.[71, 139]

1.1.13.4 Transcutaneous electrical nerve stimulation (TENS)

The committee stated that transcutaneous electrical nerve stimulation is currently used in clinical practice but agreed that it is generally used in addition to other standard therapies, with its usage varying across NHS settings due to clinician preferences and availability of equipment and trained staff. The cost of a TENS machine varies (approximately £18-£50) and can be used at home which could lower resource use if staff time is only required for an

initial appointment rather than for delivering each intervention session. The clinical evidence described in section **Error! Reference source not found.** indicated a positive trend in favour of transcutaneous electrical nerve stimulation, despite most of the outcomes reporting no clinically important difference. Due to the limited evidence of clinical benefit and lack of economic evidence, the committee made a 'consider' recommendation to provide a trial of either TENS or NMES or FES for the treatment of post-stroke focal spasticity.

1.1.13.5 Functional electrical stimulation (FES)

Previous NHS reports on FES[122] included an economic model which incorporated an initial assessment appointment costing £140, while the costs of the FES device were incorporated into ongoing clinical charges. Each ongoing clinical appointment was estimated at £300. While experiences of committee members noted that FES can also be delivered at home, additional resource use could be required as it was noted that the availability of FES devices varies across current practice and a recommendation would result in more staff-training. It was also acknowledged that FES is generally used in combination with other therapies. Section **Error! Reference source not found.** describes the clinical evidence for FES, which benefits for the reported for the spasticity outcome measures, physical function outcomes and activities of daily living when compared to usual care. However, these benefits were not present in the placebo/sham comparison which led to some uncertainly around the effect of the placebo. Given the heterogenous nature of the clinical evidence and lack of cost-effective evidence, the committee agreed that a trial of either FES, TENS or NMES should be considered for post-stroke focal spasticity.

1.1.13.6 Neuromuscular electrical nerve stimulation (NMES)

NMES was the most frequently evaluated of out the electrotherapy interventions was compared to transcutaneous electrical nerve stimulation (TENS), placebo/sham and usual care, or no treatment. Resource use was challenging to assess as the study interventions varied in terms of the frequency and duration, with sessions ranging from 20 9-minute daily sessions to 60-minute sessions conducted five days per week for four weeks. NMES was also combined with other interventions such as mirror therapy, stretching (Proprioceptive Neuromuscular Facilitation [PNF]) and infrared which would increase resource use. Similar to TENS and FES, the committee noted that in current practice NMES is generally used as an adjunct to other therapies but that its usage varies across NHS services, attributable to clinician preferences along with availability of the equipment and trained staff which appear to be postcode dependent. As described in section **Error! Reference source not found.**, clinical benefits and harms were seen when NMES was compared to placebo/sham, however, when compared to usual care or no treatment there were benefits for spasticity outcome measures, physical function - upper limb, pain and activities of daily living with no clinically important harms present. Despite committee acknowledgement of the inconsistency seen between the comparisons to placebo/sham and to usual care or no treatment, it was agreed that there was more evidence of benefit than harm. For this reason, and the lack of published health economic evidence, the committee agreed that a trial of NMES or TENS of FES should be considered for the treatment of post-stroke focal spasticity.

1.1.13.7 Oral Medication

The committee were presented with costs for oral anti-spasticity medications included in the review. Unit costs were presented for the minimum and maximum dosage reported in the BNF.[51] Limited clinical evidence was reported for oral baclofen and tizanidine, while no relevant studies were identified for the remaining oral medications (Dantrolene, Gabapentin, Pregabalin, Clonidine and Benzodiazepines (including diazepam and clonazepam)). For oral baclofen, the electronic medicines compendium (EMC)[29] reported that satisfactory control of symptoms is usually obtained with doses of up to 60 mg daily, which would cost £66 per year. One study in the clinical review (Medici 1989[79] reported that patients received a maximum of 5 capsules (20mg) per day of tizanidine, which would cost £609 per year.

Although no economic evidence was identified, the low cost these medications alongside committee acknowledgement of their use in current practice, no resource impact is expected.

Due to the limited clinical evidence for oral medication use to manage post stroke spasticity, the committee felt they could not use the results of the clinical studies to meaningfully aid their decision making and instead discussed their own experiences in clinical practice. They suggested that the benefits of oral baclofen and tizanidine have been established for many years in clinical practice and have been recommended in previous guidance which would account for why they are so commonly used. They noted that oral baclofen is more commonly used for generalised spasticity and emphasised the need for patients to be made aware of the associated side effects. For this reason, the committee made a 'consider' recommendation for oral baclofen for people with general spasticity following a stroke, with the stipulation that people are informed of the potential side effects and are monitored closely.

1.1.13.8 Intrathecal baclofen

The annual unit cost of intrathecal baclofen (ITB) for the drug alone was between £543 and £679, depending on which ampoule is used. This cost does not include the costs associated with administering the drug, which are substantial. The SISTERS RCT [13, 14] was a trial included in the clinical review comparing ITB to conventional medical management in stroke patients who are experiencing spasticity which reported EQ5D up to 6 months. A threshold analysis was undertaken to estimate the incremental cost of ITB for it to be cost effective at £20,000 per QALY. The threshold analysis was undertaken at a 5- and 7- year time horizon to account the for the lifetime of the pump. The quality-of-life benefit at six months was assumed to be maintained over this time horizon. This incremental cost was then compared to the results of two costing approaches on the full resource use required for ITB. The threshold analysis suggested that the incremental cost of ITB should be no more than £7,077 and £9,726 over 5 and 7 years respectively. This is significantly less than the estimated intervention costs of £21,576 at 5 years from the uplifted Sampson 2002 costs and the difference even greater when compared to the micro-costed approach, which estimated costs of £30,519 at 5 years and £34,885 at 7 years. These analyses suggest that ITB is unlikely to be cost effective based on current evidence. Of note, as the long-term effects of ITB beyond 6 months are unknown and the benefits observed could potentially increase or decrease over time rather than be maintained, therefore it is possible that the quality-of-life extrapolation could lead to an under or overestimation of the true cost effectiveness of ITB.

The intervention cost estimates found that ITB treatment was much more expensive than conventional medical treatment. The committee were also made aware of the number of uncertainties surrounding the clinical and cost components of ITB therapy. Firstly, long-term improvements to quality of life resulting from ITB therapy are not certain. Creamer 2018 only reported EQ-5D data up to six months, at which time utility gains were still increasing. It is unknown whether such gains would continue to increase (and for how long) or stabilise over the duration of the ITB pump's battery life.

There is also uncertainty for the long-term costs associated with ITB therapy. For instance, potential downstream cost-savings may occur from reducing nursing home or care assistant costs if a stroke survivor, as a result of reduced spasticity, is able to be more mobile and undertake daily activities independently. Furthermore, they may become able to undertake physical therapy or other non-pharmacological interventions to improve their mobility that were otherwise not possible due to severe spasticity. While this would evidently improve their quality of life, it is unknown whether such improvements would offset the therapy and equipment costs required to maintain or improve their mobility. Committee members highlighted that the prevention or relieving of pressure sores as a result of reduced spasticity and greater mobility was another long-term saving of ITB that was not captured in this analysis. A 2012 study[20] estimated that the cost of treating pressure ulcers was between £1,214 (for category 1: 28 days to heal) to £14,108 (for category IV: 155 days), and results

from Jaul 2014[49] suggested that those with severe spasticity constituted the largest group to suffer from the most difficult to cure wounds. Significant cost savings therefore could be realised and are not currently accounted for in the costing analyses. Unfortunately, the magnitude of pressure sore relief caused by ITB therapy is unknown, as well as the extent to which such clinical benefits are currently captured in the QALY gains.

Due to the high intervention costs, the limitations of both costing approaches and the lack of evidence for long-term clinical benefits, the committee decided there was too much uncertainty to make a specific recommendation for ITB treatment but highlighted that patients should still be referred to specialists when deemed appropriate.

1.1.12.5 Other factors the committee took into account

There was limited evidence available for a range of interventions. Stroke survivors and their families may seek treatment from a range of sources and may include treatments outside of those recommended in the guideline that require further research (such as acupuncture). The committee agreed that further research is required in this area.

Because spasticity is disabling and hard to manage, patients and carers often ask for information about it. The committee felt that it was important to provide information about the nature of spasticity and potential treatments.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.15.1 to 1.15.8 and the research recommendations on spasticity – acupuncture, spasticity – botulinum toxin and spasticity – electrotherapy in Appendix K.

1.1.14 References

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Appendices

Appendix A – Review protocols

Review protocol for the clinical and cost-effectiveness of interventions for spasticity after stroke

ID	Field	Content
0.	PROSPERO registration number	CRD42021254952
1.	Review title	In people after stroke, what is the clinical and cost effectiveness of interventions (for example: oral baclofen, intrathecal baclofen, botulinum toxin, acupuncture and TENS [transcutaneous electrical nerve stimulation]), in reducing spasticity?
2.	Review question	4.10 In people after stroke, what is the clinical and cost effectiveness of interventions (for example: oral baclofen, intrathecal baclofen, acupuncture and TENS [transcutaneous electrical nerve stimulation]), in reducing spasticity?
3.	Objective	To determine the clinical and cost-effectiveness of interventions (for example baclofen, botulinum toxin, acupuncture and transcutaneous electrical nerve stimulation) aiming to reduce spasticity after stroke
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikas • AMED Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews

		The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Adults and young people (16 or older) after a stroke

6.	Population	Inclusion:
		• Adults (age ≥16 years) who have had a stroke who have spasticity
		  ○ Stratification by site of spasticity:
		  – Focal spasticity (affecting one specific part of the body – for example: left arm)
		  – Multifocal spasticity (affecting multiple, but specific parts of the body – for example: left arm and right leg)
		  – Segmental spasticity (affecting a segment [for example: just the lower half of the body])
		  – Generalised spasticity (affecting multiple, widespread muscle groups)
		  – Mixed spasticity (both focal and generalised spasticity)
		
		Where studies include a mixture of the above categories studies will be included if at least 80% satisfy the criteria for one category. If <10% of participants are in a different category (for example: 9% focal, 91% receive multifocal), this study will be included in the majority category without downgrading for indirectness. If 10-20% are in a different category, this study will be included in the majority category and downgraded for population indirectness.
		
		Exclusion:
		• Children (age <16 years)
		• People with other conditions that cause spasticity
		• People who had a transient ischaemic attack

7.	Intervention	• Oral medicine ○ Baclofen (dose: 5mg is lowest dose, maximum dose: 100mg per day)

		○ Tinzanidine (dose: 2mg-36mg, maximum dose per day: 36mg per day) ○ Dantrolene (dose: 25mg-225mg, maximum dose per day: 100mg four times a day) ○ Gabapentin (as an adjunct treatment, dose: 900mg-3.6 grams) ○ Pregabalin (as an adjunct treatment, dose: 50-300mg per day) ○ Clonidine ○ Benzodiazepines – Diazepam (dose: 2mg-60mg, maximum dose per day: 60mg) – Clonazepam (dose: 0.5mg-8mg) • Intramuscular medicine ○ Botulinum toxin type A – Onabotulinum toxin A (BOTOX®) (maximum recommended dose is 200-240 units in the arm, 300 units in the leg for a single injection) – Abobotulinum toxin A (Dysport®) (maximum recommended dose is 1500 units in the arm or leg in a single adult injection session)) – Incobotulinum toxin A (Xeomin®) (maximum recommended dose is 500 units in the arm and no more than 250 units in the shoulder muscles in a single adult injection session) • Intrathecal medicine ○ Baclofen (dose range = 22 micrograms/day-1.4mg/day) • Functional Electrical Stimulation • Neuromuscular electrical stimulation (NMES)Transcutaneous electrical nerve stimulation (TENS) • Acupuncture/dry needling • Electroacupuncture • Combinations of the above Where studies include a mixture of the above categories studies will be included if at least 80% satisfy the criteria for one category. If <10% of participants are in a different category (for example: 9% oral baclofen, 91% receive botulinum toxin), this study will be included in the majority category without downgrading for indirectness. If 10-20% are in a different category, this study will be included in the majority category and downgraded for intervention indirectness.

8.	Comparator/Confounding factors	• Each other • Placebo/sham • Usual care or no treatment Confounding factors (for non-randomised studies only): • Presence of comorbidities • Severity of spasticity • Age
9.	Types of study to be included	• Systematic reviews of RCTs • Parallel RCTs • Non-randomised studies (if insufficient RCT evidence is available) ○ Prospective cohort studies Retrospective cohort studiesPublished NMAs and IPDs will be considered for inclusion. Non-randomised studies will only be included if all of the key confounders have been accounted for in a multivariate analysis. In the absence of multivariate analysis, studies that account for key confounders with univariate analysis or matched groups will be considered.
10.	Other exclusion criteria	• Non-English language studies • Crossover RCTs • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	People with spasticity after a stroke. This may include people in an acute, subacute or chronic time horizon.

12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical:
		At time periods:
		• ≤6 months
		• >6 months
		
		If multiple outcomes are reported before or after these time period then the latest time period that is ≤6 months or >6 months will be extracted and used in the analysis.
		
		• Person/participant generic health-related quality of life (continuous outcomes will be prioritised)
		  ○ EQ-5D
		  ○ SF-6D
		  ○ SF-36

		○ SF-12 ○ Other utility measures (AQOL, HUI, 15D, QWB) • Carer generic health-related quality of life (continuous outcomes will be prioritised) ○ EQ-5D ○ SF-6D ○ SF-36 ○ SF-12 ○ Other utility measures (AQOL, HUI, 15D, QWB) • Spasticity outcome measures (continuous outcomes prioritised) ○ Modified Asworth Scale ○ Tardaieu Scale ○ Patient-reported Impact of Spasticity Measure ○ Modified Penn Spasm Frequency Scale? ○ Numeric Rating Scale for Spasticity • Physical function (continuous outcomes will be prioritised) ○ General – Fugl-Meyer assessment (unless reporting only subscales by limbs) – Functional Independence Measure – Motor Subscale ○ Physical function – upper limb – Action Research Arm Test – Chedoke Arm and Hand Activity Inventory – Nine-hole peg test – Motricity Index Scale – Muscle Power Assessment (MRC scale) – Wolf Motor Function Test – Motor Activity Log ○ Physical function – lower limb – Rivermead Motor Assessment – Rivermead Mobility Scale – Berg Balance Scale – 6 minute walk distance – 10 meter walk test – Timed up and go – Walking speed – Motricity Index Scale – Stairs test – Muscle Power Assessment – Stroke Rehabilitation Assessment of Movement – Timed Up and Go

		– Short Physical Performance Battery – Tinnetti Performance Oriented Mobility Assessment – Dynamic Gait Index – Physical Performance Test – 5-Time Sit-to-Stand • Pain (continuous outcomes will be prioritised) o Visual analogue scale/numeric rating scale • Activities of daily living (continuous outcomes will be prioritised) o Barthel Index o National Institutes of Health Stroke Scale o Orpington Prognostic Scale o Canadian Occupational Performance Measure o Extended activities of daily living • Stroke-specific Patient-Reported Outcome Measures (continuous outcomes will be prioritised) o Stroke-Specific Quality of Life (SS-QOL) o Stroke Impact Scale (SIS) o Stroke-specific Sickness Impact Profile (SA-SIP30) o Neuro-QOL o PROMIS-10 o Satisfaction with International Classification of Functioning, Disability and Health – Stroke (SATIS-Stroke) • Additional health care contacts (dichotomous outcome) • Hospitalisation (dichotomous outcome) • Stroke outcome – modified Rankin scale (continuous outcomes will be prioritised) • Withdrawal due to adverse events(dichotomous outcome) If not mentioned above, other validated scores will be considered and discussed with the committee to deliberate on their inclusion.
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated.

		10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I
16.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be

		conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. 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/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. • WinBUGS will be used for network meta-analysis, if possible given the data identified.
17.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS]): • Mild (or MAS 1) • Moderate (or MAS 2) • Severe (or MAS 3) • Very severe (or MAS 4) Time period after stroke when trial starts: • Hyperacute <72 hours • Acute 72 hours – 7 days • Subacute 7 days – 6 months • Chronic >6 months Acupuncture/dry needling • Acupuncture • Dry needling For focal and multifocal spasticity only, area affected: • Upper limb (including shoulder girdle) • Lower limb • Chest

		• Neck • Face • Tongue • Mixed	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	24/02/2021	
22.	Anticipated completion date	14/12/2022	
23.	Stage of review at time of this submission	Review stage	Started / Completed
		Preliminary searches	☐ / ☐
		Piloting of the study selection process	☐ / ☐
		Formal screening of search results against eligibility criteria	☐ / ☐
		Data extraction	☐ / ☐
		Risk of bias (quality) assessment	☐ / ☐
		Data analysis	☐ / ☐
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail StrokeRehabUpdate@nice.nhs.uk 5e Organisational affiliation of the review	

		National Institute for Health and Care Excellence (NICE) and National Guideline Centre
25.	Review team members	From the National Guideline Centre: Bernard Higgins (Guideline lead) George Wood (Senior systematic reviewer) Madelaine Zucker (Systematic reviewer) Kate Lovibond (Health economics lead) Claire Sloan (Health economist) Joseph Runicles (Information specialist) Nancy Pursey (Senior project manager)
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10175
29.	Other registration details	N/A
30.	Reference/URL for published protocol	N/A
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication

		• publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Acupuncture; Adults; Baclofen; Intervention; Intrathecal; Non-pharmacological; Oral; Pharmacological; Spasticity; Stroke; Transcutaneous electrical nerve stimulation	
33.	Details of existing review of same topic by same authors	N/A	
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☒	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	N/A	
36.	Details of final publication	www.nice.org.uk	

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1 Review protocol for health economic literature review

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. Databases searched: • Centre for Reviews and Dissemination NHS Economic Evaluations Database (NHS EED) – all years (closed to new records April 2015) • Centre for Reviews and Dissemination Health Technology Assessment database – all years (closed to new records March 2018) • International HTA database (INAHTA) – all years • Medline and Embase – from 2014 (due to NHS EED closure)
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2006 (including those included in the previous guideline), abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[88] Studies published in 2006 or later that were included in the previous guideline will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in

	discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2006 or later (including any such studies included in the previous guideline) but that depend on unit costs and resource data entirely or predominantly from before 2006 will be rated as 'Not applicable'. • Studies published before 2006 (including any such studies included in the previous guideline) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

1 Appendix B – Literature search strategies

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	Inception – 08 January 2023	Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	Inception – 08 January 2023	Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
The Cochrane Library (Wiley)	Cochrane Reviews to 2023 Issue 1 of 12 CENTRAL to 2023 Issue 1 of 12	Exclusions (clinical trials, conference abstracts)
AMED, Allied and Complementary Medicine (OVID)	Inception – 08 January 2023	Exclusions (animal studies, letters, comments, case reports) English language
Epistemonikos (The Epistemonikos Foundation)	Inception – 08 January 2023	Exclusions (Cochrane reviews) English language

Medline (Ovid) search terms

1.	exp Stroke/
2.	Stroke Rehabilitation/
3.	exp Cerebral Hemorrhage/
4.	(stroke or strokes or cva or poststroke* or apoplexy or "cerebrovascular accident").ti,ab.
5.	((cerebro* or brain or brainstem or cerebral*) adj3 (infarct* or accident*)).ti,ab.
6.	"brain attack*".ti,ab.
7.	or/1-6
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/

13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice or rodent*).ti.
25.	or/18-24
26.	7 not 25
27.	limit 26 to English language
28.	exp Paraparesis/
29.	parapares*.ti,ab.
30.	Muscle Spasticity/
31.	(spastic* or spasm*).ti,ab.
32.	exp Spasm/
33.	Mobility limitation/ or Movement/ or Locomotion/
34.	((limit* or difficult* or disorder* or impair*) adj2 (walk* or ambulat* or mobility or move or moving or movement or locomotion or muscle* or muscular)).ti,ab.
35.	((stiff* or heaviness or heavy or contract* or tone or weak* or tight* or tense or tensed or tension) adj2 (muscle* or muscular)).ti,ab.
36.	or/28-35
37.	electric stimulation/ or electric stimulation therapy/ or electroacupuncture/ or transcutaneous electric nerve stimulation/
38.	exp Acupuncture Therapy/ or dry needling/
39.	Trigger Points/
40.	(FES or TENS or ES or NMES).ti,ab.
41.	(acupunctur* or electroacupunctur* or electro acupunctur* or acupoint* or meridian* or needling).ti,ab.
42.	(trigger adj3 (area* or point*)).ti,ab.
43.	((electric* or electro or neuromuscular or neuro muscular) adj3 stimulat*).ti,ab.
44.	baclofen/
45.	(Baclofen* or baclophen* or ciba-34,647-ba or (chlorophenyl adj gaba) or lioresal).ti,ab.
46.	exp Botulinum Toxins/
47.	(botulin* or onabotulinum* or abobotulinum* or incobotulinum* or prabotulinum* or rimabotulinum*).ti,ab.
48.	(Azzalure or Bocouture or Botox or Dysport or Vistabel or Xeomin or Myobloc or Jeuveau).ti,ab.
49.	gabapentin/
50.	(gabapentin* or 1-aminomethylcyclohexaneacetic acid or convalis or Neurontin).ti,ab.
51.	pregabalin/
52.	(pregabalin* or 3 isobutyl gaba or 3-aminomethyl-5-methylhexanoic acid or lyrica).ti,ab.

53.	dantrolene/
54.	(Dantrolene or Dantrium).ti,ab.
55.	benzodiazepines/ or clonazepam/ or exp diazepam/
56.	(benzodiazepinone* or clonazaepam* or diazepam* or Nordazepam*).ti,ab.
57.	exp Imidazolines/
58.	(imidazoline* or clonidine* or catapres* or clo*elin* or dixarit or Tizanidine* or Zanaflex).ti,ab.
59.	or/37-58
60.	27 and 36
61.	59 and 60

1 **Embase (Ovid) search terms**

1.	exp Cerebrovascular accident/
2.	exp Brain infarction/
3.	Stroke Rehabilitation/
4.	(stroke or strokes or cva or poststroke* or apoplexy or "cerebrovascular accident").ti,ab.
5.	((cerebro* or brain or brainstem or cerebral*) adj3 (infarct* or accident*)).ti,ab.
6.	"brain attack*".ti,ab.
7.	Intracerebral hemorrhage/
8.	or/1-7
9.	letter.pt. or letter/
10.	note.pt.
11.	editorial.pt.
12.	case report/ or case study/
13.	(letter or comment*).ti.
14.	(conference abstract or conference paper).pt.
15.	or/9-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animal/ not human/
19.	nonhuman/
20.	exp Animal Experiment/
21.	exp Experimental Animal/
22.	animal model/
23.	exp Rodent/
24.	(rat or rats or mouse or mice or rodent*).ti.
25.	or/17-24
26.	8 not 25
27.	limit 26 to English language
28.	exp paraplegia/
29.	parapares*.ti,ab.
30.	spastic paraplegia/
31.	spastic paresis/
32.	spasticity/

33.	(spastic* or spasm*).ti,ab.
34.	exp muscle spasm/
35.	walking difficulty/
36.	body movement/ or limb movement/ or locomotion/ or voluntary movement/
37.	((limit* or difficult* or disorder* or impair*) adj2 (walk* or ambulat* or mobility or move or moving or movement or locomotion or muscle* or muscular)).ti,ab.
38.	((stiff* or heaviness or heavy or contract* or tone or weak* or tight* or tense or tensed or tension) adj2 (muscle* or muscular)).ti,ab.
39.	or/28-38
40.	27 and 39
41.	electrostimulation/ or electroacupuncture/ or electrotherapy/ or transcutaneous electrical nerve stimulation/
42.	acupuncture/ or dry needling/
43.	trigger point/
44.	(FES or TENS or ES or NMES).ti,ab.
45.	(acupunctur* or electroacupunctur* or electro acupunctur* or acupoint* or meridian* or needling).ti,ab.
46.	(trigger adj3 (area* or point*)).ti,ab.
47.	((electric* or electro or neuromuscular or neuro muscular) adj3 stimulat*).ti,ab.
48.	baclofen/
49.	(Baclofen* or baclophen* or ciba-34,647-ba or (chlorophenyl adj gaba) or lioresal).ti,ab.
50.	gabapentin/
51.	(gabapentin* or 1-aminomethylcyclohexaneacetic acid or convalis or Neurontin).ti,ab.
52.	pregabalin/
53.	(pregabalin* or 3 isobutyl gaba or 3-aminomethyl-5-methylhexanoic acid or lyrica).ti,ab.
54.	dantrolene/
55.	(Dantrolene or Dantrium).ti,ab.
56.	benzodiazepine/ or benzodiazepine derivative/
57.	clonazepam/
58.	diazepam/
59.	(benzodiazepinone* or clonazaepam* or diazepam* or Nordazepam*).ti,ab.
60.	imidazoline/ or imidazole derivative/
61.	(imidazoline* or clonidine* or catapres* or clo*elin* or dixarit or Tizanidine* or Zanaflex).ti,ab.
62.	botulinum toxin/
63.	(botulin* or onabotulinum* or abobotulinum* or incobotulinum* or prabotulinum* or rimabotulinum*).ti,ab.
64.	(Azzalure or Bocouture or Botox or Dysport or Vistabel or Xeomin or Myobloc or Jeuveau).ti,ab.
65.	or/41-64
66.	40 and 65

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Stroke] explode all trees
#2.	MeSH descriptor: [Stroke Rehabilitation] explode all trees
#3.	MeSH descriptor: [Cerebral Hemorrhage] explode all trees
#4.	(stroke or strokes or cva or poststroke* or apoplexy or "cerebrovascular accident"):ti,ab

#5.	((cerebro* or brain or brainstem or cerebral*) near/3 (infarct* or accident*)):ti,ab
#6.	brain attack*:ti,ab
#7.	(or #1-#6)
#8.	conference:pt or (clinicaltrials or trialsearch):so
#9.	#7 not #8
#10.	MeSH descriptor: [Paraparesis] explode all trees
#11.	parapares*:ti,ab
#12.	MeSH descriptor: [Muscle Spasticity] explode all trees
#13.	(spastic* or spasm*):ti,ab
#14.	MeSH descriptor: [Spasm] explode all trees
#15.	MeSH descriptor: [Mobility Limitation] this term only
#16.	MeSH descriptor: [Movement] this term only
#17.	MeSH descriptor: [Locomotion] this term only
#18.	((limit* or difficult* or disorder* or impair*) NEAR/2 (walk* or ambulat* or mobility or move or moving or movement or locomotion or muscle* or muscular)):ti,ab
#19.	((stiff* or heaviness or heavy or contract* or tone or weak* or tight* or tens*) NEAR/2 (muscle* or muscular)):ti,ab
#20.	(or #10-#19)
#21.	#9 and #20
#22.	MeSH descriptor: [Electric Stimulation] explode all trees
#23.	MeSH descriptor: [Electric Stimulation Therapy] explode all trees
#24.	MeSH descriptor: [Electroacupuncture] explode all trees
#25.	MeSH descriptor: [Transcutaneous Electric Nerve Stimulation] explode all trees
#26.	MeSH descriptor: [Trigger Points] explode all trees
#27.	(FES or TENS or ES or NMES):ti,ab
#28.	(acupunctur* or electroacupunctur* or electro acupunctur* or acupoint* or meridian* or needling):ti,ab
#29.	(trigger near/3 (area* or point*)):ti,ab
#30.	((electric* or electro or neuromuscular or neuro muscular) near/3 stimulat*):ti,ab
#31.	MeSH descriptor: [Baclofen] explode all trees
#32.	(Baclofen* or baclophen* or ciba 34,647 ba or (chlorophenyl near/1 gaba) or lioresal):ti,ab
#33.	MeSH descriptor: [Botulinum Toxins] explode all trees
#34.	(botulin* or onabotulinum* or abobotulinum* or incobotulinum* or prabotulinum* or rimabotulinum*):ti,ab
#35.	(Azzalure or Bocouture or Botox or Dysport or Vistabel or Xeomin or Myobloc or Jeuveau):ti,ab
#36.	MeSH descriptor: [Gabapentin] explode all trees
#37.	(gabapentin* or 1 aminomethylcyclohexaneacetic acid or convalis or Neurontin):ti,ab
#38.	MeSH descriptor: [Pregabalin] explode all trees
#39.	(pregabalin* or 3 isobutyl gaba or 3 aminomethyl 5 methylhexanoic acid or lyrica):ti,ab
#40.	MeSH descriptor: [Dantrolene] explode all trees
#41.	(Dantrolene or Dantrium):ti,ab
#42.	MeSH descriptor: [Benzodiazepines] explode all trees
#43.	MeSH descriptor: [Clonazepam] explode all trees
#44.	MeSH descriptor: [Diazepam] explode all trees

#45.	(benzodiazepinone* or clonazaepam* or diazepam* or Nordazepam*):ti,ab
#46.	MeSH descriptor: [Imidazolines] explode all trees
#47.	(imidazoline* or clonidine* or catapres* or clo*elin* or dixarit or Tizanidine* or Zanaflex):ti,ab
#48.	(or #22-#47)
#49.	#21 and #48

1 **Epistemonikos search terms**

1.	(title:(stroke OR strokes OR cerebral hemorrhage OR cva OR poststroke OR apoplexy OR cerebrovascular accident OR brain infarction OR brain accident OR cerebral infarction OR cerebral accident) OR abstract:(stroke OR strokes OR cerebral hemorrhage OR cva OR poststroke OR apoplexy OR cerebrovascular accident OR brain infarction OR brain accident OR cerebral infarction OR cerebral accident)) AND (title:(spasticity OR spasm OR paraparesis OR spastic OR mobility limitation OR mobility impairment OR mobility disorder OR mobility difficulty OR walking impairment OR walking difficulty OR walking disorder OR muscular impairment OR muscular disorder OR muscular difficulty) OR abstract:(spasticity OR spasm OR paraparesis OR spastic OR mobility limitation OR mobility impairment OR mobility disorder OR mobility difficulty OR walking impairment OR walking difficulty OR walking disorder OR muscular impairment OR muscular disorder OR muscular difficulty))

2 **AMED search terms**

1.	exp Stroke/
2.	exp Cerebral Hemorrhage/
3.	(stroke or strokes or cva or poststroke* or apoplexy or "cerebrovascular accident").ti,ab.
4.	((cerebro* or brain or brainstem or cerebral*) adj3 (infarct* or accident*)).ti,ab.
5.	"brain attack*".ti,ab.
6.	or/1-5
7.	case report/
8.	(letter or comment*).ti.
9.	or/7-8
10.	randomized controlled trials/ or random*.ti,ab.
11.	9 not 10
12.	animals/ not humans/
13.	(rat or rats or mouse or mice or rodent*).ti.
14.	or/11-13
15.	6 not 14
16.	Limit 15 to English language
17.	exp Paraparesis/
18.	parapares*.ti,ab.
19.	Muscle Spasticity/
20.	(spastic* or spasm*).ti,ab.
21.	exp Spasm/
22.	Mobility limitation/ or Movement/ or Locomotion/
23.	((limit* or difficult* or disorder* or impair*) adj2 (walk* or ambulat* or mobility or move or moving or movement or locomotion or muscle* or muscular)).ti,ab.
24.	((stiff* or heaviness or heavy or contract* or tone or weak* or tight* or tense or tensed or tension) adj2 (muscle* or muscular)).ti,ab.

25.	or/17-24
26.	electric stimulation/ or electric stimulation therapy/ or electroacupuncture/ or transcutaneous electric nerve stimulation/
27.	exp Acupuncture Therapy/ or dry needling/
28.	Trigger Points/
29.	(FES or TENS or ES or NMES).ti,ab.
30.	(acupunctur* or electroacupunctur* or electro acupunctur* or acupoint* or meridian* or needling).ti,ab.
31.	(trigger adj3 (area* or point*)).ti,ab.
32.	((electric* or electro or neuromuscular or neuro muscular) adj3 stimulat*).ti,ab.
33.	baclofen/
34.	(Baclofen* or baclophen* or ciba-34,647-ba or (chlorophenyl adj gaba) or lioresal).ti,ab.
35.	exp Botulinum Toxins/
36.	(botulin* or onabotulinum* or abobotulinum* or incobotulinum* or prabotulinum* or rimabotulinum*).ti,ab.
37.	(Azzalure or Bocouture or Botox or Dysport or Vistabel or Xeomin or Myobloc or Jeuveau).ti,ab.
38.	gabapentin/
39.	(gabapentin* or 1-aminomethylcyclohexaneacetic acid or convalis or Neurontin).ti,ab.
40.	pregabalin/
41.	(pregabalin* or 3 isobutyl gaba or 3-aminomethyl-5-methylhexanoic acid or lyrica).ti,ab.
42.	dantrolene/
43.	(Dantrolene or Dantrium).ti,ab.
44.	benzodiazepines/ or clonazepam/ or exp diazepam/
45.	(benzodiazepinone* or clonazaepam* or diazepam* or Nordazepam*).ti,ab.
46.	exp Imidazolines/
47.	(imidazoline* or clonidine* or catapres* or clo*elin* or dixarit or Tizanidine* or Zanaflex).ti,ab.
48.	Or/26-47
49.	16 and 25
50.	48 nd 49

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Stroke Rehabilitation population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies. Additional searches were run in CINAHL and PsycInfo looking for health economic evidence.

Table: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics	Health economics studies Quality of life studies

Database	Dates searched	Search filters and limits applied
	1 January 2014 – 08 January 2023 Quality of Life 1946 – 08 January 2023	Exclusions (animal studies, letters, comments, editorials, case studies/reports,) English language
Embase (OVID)	Health Economics 1 January 2014 – 08 January 2023 Quality of Life 1974 – 08 January 2023	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 08 January 2023	English language
PsycINFO (OVID)	1 January 2014 – 08 January 2023	Health economics studies Human, Exclusions (animal studies, letters, case reports) English language
Current Nursing and Allied Health Literature - CINAHL (EBSCO)	1 January 2014 – 08 January 2023	Health economics studies Exclusions (Medline records, animal studies, letters, editorials, comments, theses) Human English language

1 **Medline (Ovid) search terms**

1.	exp Stroke/
2.	exp Cerebral Hemorrhage/

3.	(stroke or strokes or cva or poststroke* or apoplexy or "cerebrovascular accident").ti,ab.
4.	((cerebro* or brain or brainstem or cerebral*) adj3 (infarct* or accident*)).ti,ab.
5.	"brain attack*".ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/17-23
25.	6 not 24
26.	Economics/
27.	Value of life/
28.	exp "Costs and Cost Analysis"/
29.	exp Economics, Hospital/
30.	exp Economics, Medical/
31.	Economics, Nursing/
32.	Economics, Pharmaceutical/
33.	exp "Fees and Charges"/
34.	exp Budgets/
35.	budget*.ti,ab.
36.	cost*.ti.
37.	(economic* or pharmaco?economic*).ti.
38.	(price* or pricing*).ti,ab.
39.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
40.	(financ* or fee or fees).ti,ab.

41.	(value adj2 (money or monetary)).ti,ab.
42.	or/26-41
43.	quality-adjusted life years/
44.	sickness impact profile/
45.	(quality adj2 (wellbeing or well being)).ti,ab.
46.	sickness impact profile.ti,ab.
47.	disability adjusted life.ti,ab.
48.	(qal* or qtime* or qwb* or daly*).ti,ab.
49.	(euroqol* or eq5d* or eq 5*).ti,ab.
50.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/43-61
63.	25 and 42
64.	25 and 62
65.	limit 63 to English language
66.	limit 64 to English language

1 **Embase (Ovid) search terms**

1.	exp Cerebrovascular accident/
2.	exp Brain infarction/
3.	(stroke or strokes or cva or poststroke* or apoplexy or "cerebrovascular accident").ti,ab.
4.	((cerebro* or brain or brainstem or cerebral*) adj3 (infarct* or accident*)).ti,ab.
5.	"brain attack*".ti,ab.
6.	Intracerebral hemorrhage/
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	case report/ or case study/
12.	(letter or comment*).ti.

13.	or/8-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animal/ not human/
17.	nonhuman/
18.	exp Animal Experiment/
19.	exp Experimental Animal/
20.	animal model/
21.	exp Rodent/
22.	(rat or rats or mouse or mice).ti.
23.	or/15-22
24.	7 not 23
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	quality adjusted life year/
40.	"quality of life index"/
41.	short form 12/ or short form 20/ or short form 36/ or short form 8/
42.	sickness impact profile/
43.	(quality adj2 (wellbeing or well being)).ti,ab.
44.	sickness impact profile.ti,ab.
45.	disability adjusted life.ti,ab.
46.	(qal* or qtime* or qwb* or daly*).ti,ab.
47.	(euroqol* or eq5d* or eq 5*).ti,ab.
48.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
49.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
50.	(hui or hui1 or hui2 or hui3).ti,ab.
51.	(health* year* equivalent* or hye or hyes).ti,ab.
52.	discrete choice*.ti,ab.
53.	rosser.ti,ab.

54.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
55.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
56.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
57.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
58.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
59.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
60.	or/39-59
61.	limit 24 to English language
62.	38 and 61
63.	60 and 61

1 **NHS EED and HTA (CRD) search terms**

#1.	MeSH DESCRIPTOR Stroke EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Cerebral Hemorrhage EXPLODE ALL TREES
#3.	(stroke* or cva or poststroke* or apoplexy or "cerebrovascular accident")
#4.	(((cerebro* or brain or brainstem or cerebral*) adj3 (infarct* or accident*)))
#5.	("brain attack*")
#6.	#1 OR #2 OR #3 OR #4 OR #5

2 **INAHTA search terms**

1.	(brain attack*) OR (((cerebro* or brain or brainstem or cerebral*) and (infarct* or accident*))) OR ((stroke or strokes or cva or poststroke* or apoplexy or "cerebrovascular accident")) OR ("Cerebral Hemorrhage"[mhe]) OR ("Stroke"[mhe])

3 **CINAHL search terms**

1.	MH "Economics+"
2.	MH "Financial Management+"
3.	MH "Financial Support+"
4.	MH "Financing, Organized+"
5.	MH "Business+"
6.	S2 OR S3 or S4 OR S5
7.	S1 not S6
8.	MH "Health Resource Allocation"
9.	MH "Health Resource Utilization"
10.	S8 OR S9
11.	S7 OR S10
12.	(cost or costs or economic* or pharmacoeconomic* or price* or pricing*) OR AB (cost or costs or economic* or pharmacoeconomic* or price* or pricing*)
13.	S11 OR S12
14.	PT editorial
15.	PT letter
16.	PT commentary
17.	S14 or S15 or S16
18.	S13 NOT S17
19.	MH "Animal Studies"

20.	(ZT "doctoral dissertation") or (ZT "masters thesis")
21.	S18 NOT (S19 OR S20)
22.	PY 2014-
23.	S21 AND S22
24.	MW Stroke or MH Cerebral Hemorrhage
25.	stroke* or cva or poststroke* or apoplexy or "cerebrovascular accident"
26.	(cerebro* OR brain OR brainstem OR cerebral*) AND (infarct* OR accident*)
27.	"brain attack*"
28.	S24 OR S25 OR S26 OR S27
29.	S23 AND S28

1 **PsycINFO search terms**

1.	exp Stroke/
2.	exp Cerebral hemorrhage/
3.	(stroke or strokes or cva or poststroke* or apoplexy or "cerebrovascular accident").ti,ab.
4.	((cerebro* or brain or brainstem or cerebral*) adj3 (infarct* or accident*)).ti,ab.
5.	"brain attack*".ti,ab.
6.	Cerebrovascular accidents/
7.	exp Brain damage/
8.	(brain adj2 injur*).ti.
9.	or/1-8
10.	Letter/
11.	Case report/
12.	exp Rodents/
13.	or/10-12
14.	9 not 13
15.	limit 14 to (human and english language)
16.	First posting.ps.
17.	15 and 16
18.	15 or 17
19	"costs and cost analysis"/
20.	"Cost Containment"/
21.	(economic adj2 evaluation$).ti,ab.
22.	(economic adj2 analy$).ti,ab.
23.	(economic adj2 (study or studies)).ti,ab.
24.	(cost adj2 evaluation$).ti,ab.
25.	(cost adj2 analy$).ti,ab.
26.	(cost adj2 (study or studies)).ti,ab.
27.	(cost adj2 effective$).ti,ab.
28.	(cost adj2 benefit$).ti,ab.
29.	(cost adj2 utili$).ti,ab.

30.	(cost adj2 minimi$).ti,ab.
31.	(cost adj2 consequence$).ti,ab.
32.	(cost adj2 comparison$).ti,ab.
33.	(cost adj2 identificat$).ti,ab.
34.	(pharmacoeconomic$ or pharmaco-economic$).ti,ab.
35.	or/19-34
36.	(0003-4819 or 0003-9926 or 0959-8146 or 0098-7484 or 0140-6736 or 0028-4793 or 1469-493X).is.
37.	35 not 36
38.	18 and 37

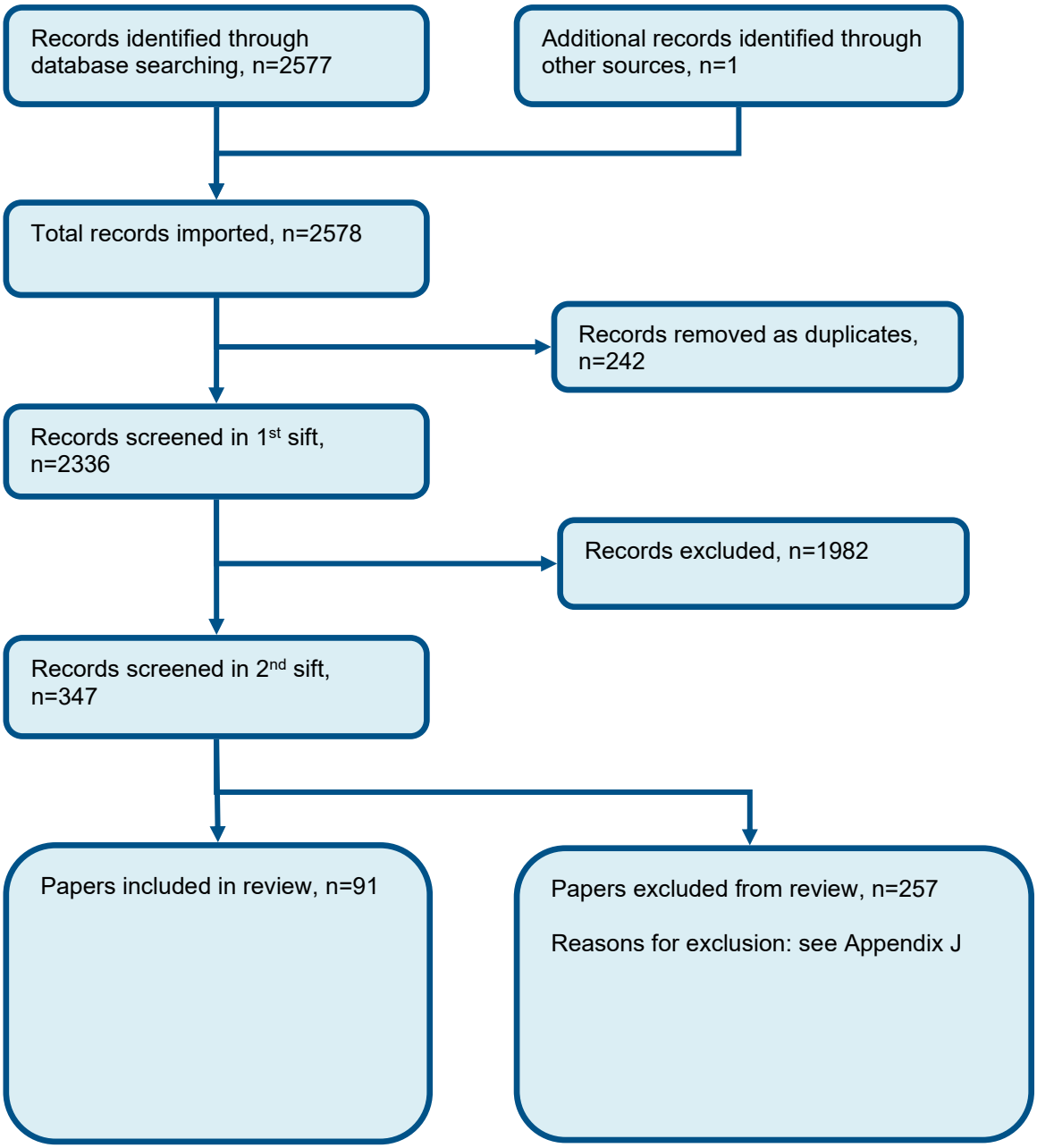
1

2

3

Appendix C– Effectiveness evidence study selection

Figure 2: Flow chart of clinical study selection for the review of interventions for spasticity after stroke



Appendix D – Effectiveness evidence

Alexander, 2004

Bibliographic Reference	Alexander, D. N.; Cen, S.; Sullivan, K. J.; Bhavnani, G.; Ma, X.; Azen, S. P.; group, Asap study; Effects of acupuncture treatment on poststroke motor recovery and physical function: a pilot study; Neurorehabilitation & Neural Repair; 2004; vol. 18 (no. 4); 259-67

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	United States of America
Study setting	Stroke inpatient rehabilitation unit
Study dates	Not stated/unclear

Sources of funding	Supported in part by The Lucy Gonda Foundation.
Inclusion criteria	Acute stroke resulting in hemiparesis, diagnosed by a neurologist and confirmed with CT or MRI scan.
Exclusion criteria	History of a previous stroke; inability to cooperate or follow directions for examination and tests; coma or subarachnoid haemorrhage; any other acute life-threatening illness or severe complications; significant systemic disease or disease that interferes with the assessment of stroke; patients who were not independent in activities of daily living prior to stroke onset.
Stratification - Type of spasticity	Generalised spasticity
Recruitment / selection of participants	People admitted to the inpatient stroke rehabilitation unit at Daniel Freeman Rehabilitation Center, Los Angeles, California. Study enrolment occurred within 60 days of stroke onset.
Intervention(s)	Acupuncture N=16 Conventional stroke rehabilitation care and 30 additional minutes of acupuncture therapy 7 days per week for 2 weeks (14 total acupuncture sessions) during the inpatient stay. A standardized approach was used that included manual needle insertion (not electroacupuncture) to the hemiparetic limb, in which the acupuncturist could select specific sites based on patient symptoms. The acupuncture points included were Du 20 (Bai Hui), Du 19 (Qian Ding), Du 21 (Hou Ding), UB 7 (Tong Tian), GB 20 (Feng Chi), Du14 (Da Zhui), Ren 6 (Qi Hai), Ren12 (Zhong Wan), and St 25 (Tian Shu). They also selected the supplementary points, including LI 15 (Jian Yu), LI 11 (Qu Chi), SJ 5 (Wai Guan), LI 4 (He Gu), and Lu 7 (Lie Que) for upper limbs; and GB 31 (Feng Shi), St 36 (Zuo San Li), GB 34 (Yang Ling Quan), Sp 6 (San Yin Jiao), St 40 (Feng Long), St 41 (Jie Xi), and Liv 3 (Tai Chong) for lower limbs. Within 2 weeks of the stroke episode, the following were added: Ba Feng, Ren 23 (Lian Quan) and Ht 5 (Tong Li) for aphasia, St 4 (Di Cang), SI 18 (Quan Liao) and St 6 (Jia Che) for facial paralysis, and UB 6 (Cheng Guang) and Gb 37 (Guang Ming) for vision problems. Concomitant therapy: Conventional stroke rehabilitation care included 3 hours of physical, occupational and/or speech therapy, 6 days per week for the duration of the inpatient stay.
Subgroup 1: Severity of spasticity (as stated by category or as measured by	Not stated/unclear

modified Ashworth scale [MAS])	
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	Acupuncture
Subgroup 4: For focal and multifocal spasticity only, area affected	not applicable
Population subgroups	No additional information
Comparator	Usual care N=16 Conventional stroke rehabilitation care only. Concomitant therapy: Conventional stroke rehabilitation care included 3 hours of physical, occupational and/or speech therapy, 6 days per week for the duration of the inpatient stay.
Number of participants	32
Duration of follow-up	2 weeks (end of intervention)
Indirectness	No additional information
Additional comments	Available case analysis

Study arms

Acupuncture (N = 16)
Conventional stroke rehabilitation care and 30 additional minutes of acupuncture therapy 7 days per week for 2 weeks (14 total acupuncture sessions) during the inpatient stay. A standardized approach was used that included manual needle insertion (not electroacupuncture) to the hemiparetic limb, in which the acupuncturist could select specific sites based on patient symptoms. The acupuncture points included were Du 20 (Bai Hui), Du 19 (Qian Ding), Du 21 (Hou Ding), UB 7 (Tong Tian), GB 20 (Feng Chi), Du14 (Da Zhui), Ren 6 (Qi Hai), Ren12 (Zhong Wan), and St 25 (Tian Shu). They also selected the supplementary points, including LI 15 (Jian Yu), LI 11 (Qu Chi), SJ 5 (Wai Guan), LI 4 (He Gu), and Lu 7 (Lie Que) for upper limbs; and GB 31 (Feng Shi), St 36 (Zuo San Li), GB 34 (Yang Ling Quan), Sp 6 (San Yin Jiao), St 40 (Feng Long), St 41 (Jie Xi), and Liv 3 (Tai Chong) for lower limbs. Within 2 weeks of the stroke episode, the following were added: Ba Feng, Ren 23 (Lian Quan) and Ht 5 (Tong Li) for aphasia, St 4 (Di Cang), SI 18 (Quan Liao) and St 6 (Jia Che) for facial paralysis, and UB 6 (Cheng Guang) and Gb 37 (Guang Ming) for vision problems. Concomitant therapy: Conventional stroke rehabilitation care included 3 hours of physical, occupational and/or speech therapy, 6 days per week for the duration of the inpatient stay.

Usual care (N = 16)
Conventional stroke rehabilitation care only. Concomitant therapy: Conventional stroke rehabilitation care included 3 hours of physical, occupational and/or speech therapy, 6 days per week for the duration of the inpatient stay.

Characteristics

Arm-level characteristics

Characteristic	Acupuncture (N = 16)	Usual care (N = 16)
% Female Sample size	n = 7 ; % = 43.8	n = 8 ; % = 50

Characteristic	Acupuncture (N = 16)	Usual care (N = 16)
Mean age (SD) (years) Mean (SD)	66.5 (8.8)	55.7 (12)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
African American Sample size	n = 7	n = 6 ; % = 37.5
Asian Sample size	n = 1 ; % = 6.2	n = 2 ; % = 12.5
Hispanic Sample size	n = 4 ; % = 25	n = 3 ; % = 18.8
Caucasian Sample size	n = 4 ; % = 25	n = 5 ; % = 31.2
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Severity of spasticity Mean (SD)	NR (NR)	NR (NR)
Time period after stroke (days) Mean (SD)	21.7 (5.1)	22.5 (5)

Characteristic	Acupuncture (N = 16)	Usual care (N = 16)
Type of spasticity Sample size	n = NR	n = NR ; % = NR

Outcomes

Study timepoints

- Baseline
- 2 week (<6 months)

Continuous outcomes

Outcome	Acupuncture, Baseline, N = 16	Acupuncture, 2 week, N = 14	Usual care, Baseline, N = 16	Usual care, 2 week, N = 15
Activities of daily living (total Functional Independence Measure) Scale range: 0-49. Change scores. Mean (SD)	15.9 (5.7)	11.2 (4.5)	19.9 (8.8)	8.5 (3.8)
Physical function - general (Fugl Meyer assessment total) Scale range: 0-226. Change scores. Mean (SD)	138.4 (31.8)	5.5 (13.8)	157.3 (35.6)	7.7 (12.3)

Activities of daily living (total Functional Independence Measure) - Polarity - Higher values are better
Physical function - general (Fugl Meyer assessment total) - Polarity - Higher values are better

Dichotomous outcome

Outcome	Acupuncture, Baseline, N = 16	Acupuncture, 2 week, N = 16	Usual care, Baseline, N = 16	Usual care, 2 week, N = 16
Withdrawal due to adverse events Acupuncture: 1 died. No of events	n = NA ; % = NA	n = 1 ; % = 6.3	n = NA ; % = NA	n = 0 ; % = 0

Withdrawal due to adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuousoutcomes-Activitiesofdailyliving(totalFunctionalIndependenceMeasure)-MeanSD-Acupuncture-Usual care-t2

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Physicalfunction-general(FuglMeyerassessmenttotal)-MeanSD-Acupuncture-Usual care-t2

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcome-Withdrawalduetoadverseevents-NoOfEvents-Acupuncture-Usual care-t2

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Bakheit, 2000

Bibliographic Reference	Bakheit, A. M.; Thilmann, A. F.; Ward, A. B.; Poewe, W.; Wissel, J.; Muller, J.; Benecke, R.; Collin, C.; Muller, F.; Ward, C. D.; Neumann, C.; A randomized, double-blind, placebo-controlled, dose-ranging study to compare the efficacy and safety of three doses of botulinum toxin type A (Dysport) with placebo in upper limb spasticity after stroke; Stroke; 2000; vol. 31 (no. 10); 2402-6

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)

Study location	International, multicenter trial. Conducted in the United Kingdom, Germany and Austria.
Study setting	Rehabilitation units in hospitals.
Study dates	No additional information
Sources of funding	The study was sponsored by Ipsen Limited, Maidenhead, Berkshire, UK, who also designed the study in consultation with the senior authors and was responsible for the recruitment of the researchers and monitoring of the data collection. The statistical analysis of the study data was performed by Hartington Statistics and Data Management Limited, London, UK. None of the authors were employees or paid consultants of Ipsen Ltd.
Inclusion criteria	People with hemiplegic stroke and severe or moderately severe muscle spasticity were recruited at least 3 months after the onset of the cerebrovascular event. They were included if they had a muscle tone score of at least 2 on the Modified Ashworth Scale in the wrist, elbow and finger flexors.
Exclusion criteria	People with muscle contractures of the upper limb joints (defined as severe restriction of the joint range of motion on passive stretch); previous treatment with botulinum toxin, phenol or alcohol nerve blocks, or motor point injections for upper limb spasticity; de novo treatment with antispasticity drugs.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	No additional information
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Severe (or MAS 3) Reported to be moderately severe or severe
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)

Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	Botulinum toxin type A (Dysport) N=63 Botulinum toxin type A (Dysport) delivered at three different doses: 500 U (n=22), 1000 U (n=22) and 1500 U (n=19). Dysport was presented in powder form and was reconstituted in 2mL of 0.9% sodium chloride solution to give the correct dosage. The following muscles were injected: the biceps brachii (doses ranging from 200-600 U), flexor digitorum profundus (doses ranging from 75-225 U), flexor digitorum superficialis (doses ranging from 75-225 U), flexor carpi ulnaris (doses ranging from 75-225 U) and flexor carpi radialis (doses ranging from 75-225 U). The injections were placed in the motor endplate zone with the use of anatomic landmarks, as in routine electromyography. Concomitant therapy: No additional information.
Comparator	Placebo N=19 2mL of 0.9% sodium chloride solution. The placebo was identical to the active drug. The same muscles were injected with the same placement of injections. Concomitant therapy: No additional information.
Number of participants	82
Duration of follow-up	2, 4, 8, 12 and 16 weeks after injection (the 16 week results will be included in this data extraction).

Indirectness	No additional information.
Additional comments	Intention-to-treat analysed by logistic regression analysis, with the study center and baseline of MAS included as terms in the model.

Study arms

Abobotulinum toxin type A (Dysport) (N = 63)

Botulinum toxin type A (Dysport) delivered at three different doses: 500 U (n=22), 1000 U (n=22) and 1500 U (n=19). Dysport was presented in powder form and was reconstituted in 2mL of 0.9% sodium chloride solution to give the correct dosage. The following muscles were injected: the biceps brachii (doses ranging from 200-600 U), flexor digitorum profundus (doses ranging from 75-225 U), flexor digitorum superficialis (doses ranging from 75-225 U), flexor carpi ulnaris (doses ranging from 75-225 U) and flexor carpi radialis (doses ranging from 75-225 U). The injections were placed in the motor endplate zone with the use of anatomic landmarks, as in routine electromyography. Concomitant therapy: No additional information.

Placebo (N = 19)

2mL of 0.9% sodium chloride solution. The placebo was identical to the active drug. The same muscles were injected with the same placement of injections. Concomitant therapy: No additional information.

Characteristics

Arm-level characteristics

Characteristic	Abobotulinum toxin type A (Dysport) (N = 63)	Placebo (N = 19)
% Female Sample size	n = 24 ; % = 38	n = 7 ; % = 37
Mean age (SD) (years)	62.2 (13.2)	63.6 (14.1)

Characteristic	Abobotulinum toxin type A (Dysport) (N = 63)	Placebo (N = 19)
Mean (SD)		
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Severity of spasticity Sample size	n = NR ; % = NR	n = NR ; % = NR
Time period after stroke Mean (SD)	NR (NR)	NR (NR)
Type of spasticity Sample size	n = NA ; % = NA	n = NA ; % = NA

Outcomes

Study timepoints

- Baseline
- 4 week (<6 months - for some outcomes where 16 week data is not reported)
- 16 week (<6 months)

Continuous outcomes

Outcome	Abobotulinum toxin type A (Dysport), Baseline, N = 63	Abobotulinum toxin type A (Dysport), 4 week, N = 63	Abobotulinum toxin type A (Dysport), 16 week, N = 63	Placebo, Baseline, N = 19	Placebo, 4 week, N = 19	Placebo, 16 week, N = 19
Spasticity outcome measures (modified Ashworth scale) Scale range unclear (modified Ashworth scale is normally a 0-4 scale, however, the values reported are much larger. Appears to be calculated by area under the curve to make the analysis. Range may be 0-100). Change scores. The three botulinum toxin arms were combined in the analysis. Values converted from mean SE to mean SD. Values for elbow, wrist and fingers combined in the analysis. Reported 500 U elbow/wrist/fingers = -16.2 (2.8)/-17.1 (3.3)/-11.8 (3.3). Reported 1000 U elbow/wrist/fingers: -15.0 (2.8)/-20.7 (3.3)/-16.3 (3.3). Reported 1500 U elbow/wrist/fingers: -14.2 (3.0)/-18.5 (3.5)/-13.4 (3.5). Reported placebo elbow/wrist/fingers: -3.2 (3.1)/-6.3 (3.6)/-6.3 (3.6). Mean (SD)	NR (NR)	NA (NA)	-15.9 (14.9)	NR (NR)	NA (NA)	-5.3 (15.1)
Activities of daily living (barthel index) Scale range: 0-100. Change scores. Reported 500 U = 0.1 (1.4). Reported 1000 U = 0.1 (2.5). Reported 1500 U = 0.8 (2.6). Mean (SD)	NR (NR)	0.3 (2.2)	NR (NR)	NR (NR)	0.7 (1.2)	NR (NR)
Physical function - Upper limb (Rivermead Motor Assessment arm section)	NR (NR)	0.2 (0.8)	NR (NR)	NR (NR)	0.2 (0.7)	NR (NR)

Outcome	Abobotulinum toxin type A (Dysport), Baseline, N = 63	Abobotulinum toxin type A (Dysport), 4 week, N = 63	Abobotulinum toxin type A (Dysport), 16 week, N = 63	Placebo, Baseline, N = 19	Placebo, 4 week, N = 19	Placebo, 16 week, N = 19
Scale range unclear. Change scores. Reported 500 U = 0.2 (1.0). Reported 1000 U = 0.3 (0.7). Reported 1500 U = 0.1 (0.5). Mean (SD)						

Spasticity outcome measures (modified Ashworth scale) - Polarity - Lower values are better
Activities of daily living (barthel index) - Polarity - Higher values are better
Physical function - Upper limb (Rivermead Motor Assessment arm section) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuousoutcomes-Spasticityoutcomemeasures(modifiedAshworthscale)-MeanSD-Botulinum toxin type A (Dysport)-Placebo-t16

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Activitiesofdailyliving(barthelindex)-MeanSD-Botulinum toxin type A (Dysport)-Placebo-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Physicalfunction-Upperlimb(RivermeadMotorAssessmentarmsection)-MeanSD-Botulinum toxin type A (Dysport)-Placebo-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Bakhtiary, 2008

Bibliographic Reference	Bakhtiary, A. H.; Fatemy, E.; Does electrical stimulation reduce spasticity after stroke? A randomized controlled study; Clinical Rehabilitation; 2008; vol. 22 (no. 5); 418-25

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with	No additional information

this study included in review	
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Iran
Study setting	The neurology clinic of the Semnan University of Medical Sciences.
Study dates	No additional information
Sources of funding	No additional information
Inclusion criteria	Stroke patients, ranging in age from 42 to 65 years with upper motor neuron lesion and ankle plantarflexor spasticity recruited voluntarily from the neurology clinic
Exclusion criteria	Sensory deficit; taking medicine for reducing muscle tonicity.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	No additional information
Intervention(s)	Neuromuscular electrical stimulation (NMES) N=20 Fifteen minutes of inhibitory Bobath techniques (including passive movement of the ankle joint dorsi-flexion, knee joint extension, abduction and external rotation of the hip joint, known as the reflex inhibitory pattern) in combination with 9 minutes of electrical stimulation on the dorsiflexor muscles for 20 sessions daily. Neuromuscular electrical stimulation included 9 minutes of supramaximal (25% over the intensity needed to produce maximum contraction of the muscle) muscle stimulation. The stimulation current included 100 Hz pulse stimulation (pulse duration = 0.1ms, pulse interval = 0.9 ms) which was applied in surge mode (surge duration = 4 seconds and rest between surge = 6 seconds). The cathode was placed on the tibialis anterior muscle and the anode over the fibular head.

	Concomitant therapy: In both groups, before starting treatment the subject's lower limbs were exposed to 10 minutes of infrared at a distance of 50 cm to warm up the limbs.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Severe (or MAS 3)
Subgroup 2: Time period after stroke when trial starts	Not stated/unclear
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb
Population subgroups	No additional information
Comparator	Usual care/no treatment N=20 Bobath technique exercises only. Concomitant therapy: In both groups, before starting treatment the subject's lower limbs were exposed to 10 minutes of infrared at a distance of 50 cm to warm up the limbs.

Number of participants	40
Duration of follow-up	4 weeks
Indirectness	No additional information
Additional comments	No additional information

Study arms

Neuromuscular electrical stimulation (NMES) (N = 20)
Fifteen minutes of inhibitory Bobath techniques (including passive movement of the ankle joint dorsi-flexion, knee joint extension, abduction and external rotation of the hip joint, known as the reflex inhibitory pattern) in combination with 9 minutes of electrical stimulation on the dorsiflexor muscles for 20 sessions daily. Neuromuscular electrical stimulation included 9 minutes of supramaximal (25% over the intensity needed to produce maximum contraction of the muscle) muscle stimulation. The stimulation current included 100 Hz pulse stimulation (pulse duration = 0.1ms, pulse interval = 0.9 ms) which was applied in surge mode (surge duration = 4 seconds and rest between surge = 6 seconds). The cathode was placed on the tibialis anterior muscle and the anode over the fibular head. Concomitant therapy: In both groups, before starting treatment the subject's lower limbs were exposed to 10 minutes of infrared at a distance of 50 cm to warm up the limbs.

Usual care/no treatment (N = 20)
Bobath technique exercises only. Concomitant therapy: In both groups, before starting treatment the subject's lower limbs were exposed to 10 minutes of infrared at a distance of 50 cm to warm up the limbs.

1 **Characteristics**

2 ***Arm-level characteristics***

Characteristic	Neuromuscular electrical stimulation (NMES) (N = 20)	Usual care/no treatment (N = 20)
% Female Sample size	n = NR ; % = NR	n = NR ; % = NR
Mean age (SD) Mean (SD)	NR (NR)	NR (*empty data*)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Severity of spasticity Mean (SD)	3.5 (0.76)	3 (1.08)
Time period after stroke Mean (SD)	NR (NR)	NR (NR)
Type of spasticity Sample size	n = NR ; % = NR	n = NR ; % = NR

3

Outcomes

Study timepoints

- Baseline
- 4 week (End of intervention. <6 months.)

Continuous outcomes

Outcome	Neuromuscular electrical stimulation (NMES), Baseline, N = 20	Neuromuscular electrical stimulation (NMES), 4 week, N = 20	Usual care/no treatment, Baseline, N = 20	Usual care/no treatment, 4 week, N = 20
Spasticity outcome measures (modified Ashworth scale) Scale range: 0-4. Change scores. Mean (SD)	3.5 (0.76)	-1.6 (0.5)	3 (1.08)	-1.1 (0.31)

Spasticity outcome measures (modified Ashworth scale) - Polarity - Lower values are better

Dichotomous outcomes

Outcome	Neuromuscular electrical stimulation (NMES), Baseline, N = 20	Neuromuscular electrical stimulation (NMES), 4 week, N = 20	Usual care/no treatment, Baseline, N = 20	Usual care/no treatment, 4 week, N = 20
Withdrawal due to adverse events NMES = 2 (not completed because of diseases and private reason). Usual care/no treatment = 3 (not completed because of diseases and private reason). No of events	n = NA	n = 3 ; % = 15	n = NA ; % = NA	n = 2 ; % = 10

Withdrawal due to adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuousoutcomes-Spasticityoutcomemeasures(modifiedAshworthscale)-MeanSD-Neuromuscular electrical stimulation (NMES)-Usual care/no treatment-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Withdrawalduetoadverseevents-NoOfEvents-Neuromuscular electrical stimulation (NMES)-Usual care/no treatment-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Bethoux, 2014

Bibliographic Reference	Bethoux, F.; Rogers, H. L.; Nolan, K. J.; Abrams, G. M.; Annaswamy, T. M.; Brandstater, M.; Browne, B.; Burnfield, J. M.; Feng, W.; Freed, M. J.; Geis, C.; Greenberg, J.; Gudesblatt, M.; Ikramuddin, F.; Jayaraman, A.; Kautz, S. A.; Lutsep, H. L.; Madhavan, S.; Meilahn, J.; Pease, W. S.; Rao, N.; Seetharama, S.; Sethi, P.; Turk, M. A.; Wallis, R. A.; Kufta, C.; The effects of peroneal nerve functional electrical stimulation versus ankle-foot orthosis in patients with chronic stroke: A randomized controlled trial; Neurorehabilitation and Neural Repair; 2014; vol. 28 (no. 7); 688-697

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT0187957
Study type	Randomised controlled trial (RCT)
Study location	United States of America
Study setting	30 rehabilitation centers across the USA.
Study dates	April 27, 2010 and April 26, 2012.
Sources of funding	This study was sponsored by Innovative Neurotronics.
Inclusion criteria	At least 6 months post stroke; inadequate dorsiflexion with inadequate limb clearance during the swing phase of gait; positive response to peroneal nerve stimulation testing; adequate cognitive function (MMSE score >17); not currently using FES for the treatment of foot drop; at least 30 days post inpatient or outpatient stroke, cardiac, pulmonary, or any other lower extremity physical rehabilitation; able to walk at least 10 meters with or without an assist device; initial gait speed of >0.0 m/s and <0.8 m/s; eligible for Medicare or Medicare Choice/Advantage benefits at time of consent; at least 90 days post myocardial infarction; at least 90 days post stenting procedure (i.e. peripheral, cardiac, carotid and/or renal); at least 90 days post major orthopedic surgery (i.e. hip, knee and/or ankle joint replacement); at least 6 months post coronary artery bypass graft or cardiac valve procedure; able and willing to give written consent and comply with study procedures, including follow-up visits.

Exclusion criteria	Ankle joint instability other than foot drop; needs AFO for stance control of the foot, ankle and/or knee; unable to safely clear toes in swing phase on the involved lower extremity, defined as >-5 degrees plantar flexion, with the WA device (determined at fitting); diagnosed with peripheral neuropathy and symptoms obstruct or limit ambulation or participation in study; diagnosed with significant peripheral vascular disease accompanied by lower extremity ulceration and/or disabling claudication; underlying condition(s) that would limit study participation; severe hypertonicity resulting in the need for more involved orthotic strategies; excessive dysesthetic pain secondary to neurological involvement; moderate to very severe COPD, as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD); New York Heart Association class III-IV; malignant skin lesions below the knee on the affected lower extremity; history of seizure disorder and is currently on seizure control medication for this disorder; aphasia, defined as inability to verbalize commands; Beck Depression Index score of >29 indicating severe depression; life expectancy less than 12 months; received Botulinum Toxin injections in the lower extremity within past 6-months; Baclofen pump with unstable dosing in the last 3 months; participating in another clinical trial that, according to the Principal Investigator, is likely to affect study outcome or confound results; Patient has existing electrical stimulation devices (ICD, Pacemaker, Spinal Stimulation, TENS).
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	No additional information.
Intervention(s)	Functional Electrical Stimulation (FES) N=242 Functional Electrical Stimulation with the WA (a battery-operated single channel electrical stimulator) for 6 months. The device consists of a cuff worn around the proximal part of the lower leg, which holds the control module and surface electrodes. The device uses a tilt sensor and accelerometer to trigger ankle dorsiflexion and control the timing and duration of peroneal nerve stimulation during the swing phase of gait. After initial fitting, programming and patient education performed by a trained clinician, people are able to use the device to facilitate walking in daily activities. Fitting was performed by a WA-certified orthotist or a licensed physical therapist. After completing a 2-week progressive wearing schedule, people were instructed to wear their device on a full time basis (for all walking activities throughout the day). Concomitant therapy: No additional information.

Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Not stated/unclear
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb
Population subgroups	No additional information.
Comparator	Usual care/no treatment N=253 Ankle-Foot Orthosis (AFO) for 6 months. Fitting for the AFO was performed by a licensed orthotist; subjects coming into the study with AFOs that met the standard of care were able to continue in their own orthosis. AFOs provided for subjects or AFOs fabricated as replacements were custom molded and either articulated or fixed at the ankle based on the professional opinion of the orthotist and clinical needs of the subject. Concomitant therapy: No additional information.
Number of participants	495

Duration of follow-up	6 months
Indirectness	No additional information
Additional comments	Intention to treat.

Study arms

Functional Electrical Stimulation (FES) (N = 242)
Functional Electrical Stimulation with the WA (a battery-operated single channel selectrical stimulator) for 6 months. The device consists of a cuff worn around the proximal part of the lower leg, which holds the control module and surface electrodes. The device uses a tilt sensor and accelerometer to trigger ankle dorsiflexion and control the timing and duration of peroneal nerve stimulation during the swing phase of gait. After initial fitting, programming and patient education performed by a trained clinician, people are able to use the device to facilitate walking in daily activities. Fitting was performed by a WA-certified orthotist or a licensed physical therapist. After completing a 2-week progressive wearing schedule, people were instructed to wear their device on a full time basis (for all walking activities throughout the day). Concomitant therapy: No additional information.

Usual care/no treatment (N = 253)
Ankle-Foot Orthosis (AFO) for 6 months. Fitting for the AFO was performed by a licensed orthotist; subjects coming into the study with AFOs that met the standard of care were able to continue in their own orthosis. AFOs provided for subjects or AFOs fabricated as replacements were custom molded and either articulated or fixed at the ankle based on the professional opinion of the orthotist and clinical needs of the subject. Concomitant therapy: No additional information.

1 **Characteristics**

2 ***Arm-level characteristics***

Characteristic	Functional Electrical Stimulation (FES) (N = 242)	Usual care/no treatment (N = 253)
% Female Sample size	n = 95 ; % = 39.26	n = 96 ; % = 37.94
Mean age (SD) (years) Mean (SD)	63.87 (11.33)	64.3 (12.01)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
American Indian/Alaskan Sample size	n = 0 ; % = 0	n = 2 ; % = 0.79
Asian Sample size	n = 2 ; % = 0.83	n = 3 ; % = 1.19
Black/African American Sample size	n = 55 ; % = 22.73	n = 55 ; % = 21.74
Hawaiian/Pacific Islander Sample size	n = 0 ; % = 0	n = 1 ; % = 0.4
Other Sample size	n = 8 ; % = 3.31	n = 5 ; % = 1.98

Characteristic	Functional Electrical Stimulation (FES) (N = 242)	Usual care/no treatment (N = 253)
White (Caucasian) Sample size	n = 177 ; % = 73.14	n = 187 ; % = 73.91
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Severity of spasticity Mean (SD)	NR (NR)	NR (NR)
Time period after stroke (years) Mean (SD)	6.9 (6.43)	6.86 (6.64)
Type of spasticity Sample size	n = NA ; % = NA	n = NA ; % = NA

Outcomes

Study timepoints

- Baseline
- 6 month (</=6 months)

Continuous outcomes

Outcome	Functional Electrical Stimulation (FES), Baseline, N = 242	Functional Electrical Stimulation (FES), 6 month, N = 242	Usual care/no treatment, Baseline, N = 253	Usual care/no treatment, 6 month, N = 253
Physical function - lower limb (Berg Balance Scale) Scale range: 0-56. Final values. Mean (SE)	42.3 (0.6)	44.9 (0.6)	43.4 (0.7)	44.7 (0.8)
Stroke-specific Patient-Reported Outcome Measures (Stroke-Specific Quality of Life) Scale range: 49-245. Final values. Mean (SE)	177.1 (2.5)	181.6 (2.6)	180.5 (2.3)	184 (2.5)

Physical function - lower limb (Berg Balance Scale) - Polarity - Higher values are better

Stroke-specific Patient-Reported Outcome Measures (Stroke-Specific Quality of Life) - Polarity - Higher values are better

Dichotomous outcomes

Outcome	Functional Electrical Stimulation (FES), Baseline, N = 242	Functional Electrical Stimulation (FES), 6 month, N = 242	Usual care/no treatment, Baseline, N = 253	Usual care/no treatment, 6 month, N = 253
Withdrawal due to adverse events FES = 2 deceased, 7 exited due to medical reasons. Usual care = 2 deceased, 4 exited due to medical reasons. No of events	n = NA ; % = NA	n = 9 ; % = 4	n = NA ; % = NA	n = 6 ; % = 2

Withdrawal due to adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuousoutcomes-Physicalfunction-lowerlimb(BergBalanceScale)-MeanSE-Functional Electrical Stimulation (FES)-Usual care/no treatment-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Stroke-specificPatient-ReportedOutcomeMeasures(Stroke-SpecificQualityofLife)-MeanSE-Functional Electrical Stimulation (FES)-Usual care/no treatment-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Withdrawalduetoadverseevents-NoOfEvents-Functional Electrical Stimulation (FES)-Usual care/no treatment-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Boyaci, 2013

Bibliographic Reference	Boyaci, A.; Topuz, O.; Alkan, H.; Ozgen, M.; Sarsan, A.; Yildiz, N.; Ardic, F.; Comparison of the effectiveness of active and passive neuromuscular electrical stimulation of hemiplegic upper extremities: a randomized, controlled trial; International Journal of Rehabilitation Research; 2013; vol. 36 (no. 4); 315-22

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	Turkey
Study setting	An inpatient rehabilitation program
Study dates	December 2005 and August 2006
Sources of funding	No additional information.
Inclusion criteria	Poststroke period at least 4 weeks; between 18 and 80 years of age; the ability to understand and communicate; no visual or auditory defect; adequately motivated and willing to participate; medically stable condition; the ability to voluntarily extend the wrist.

Exclusion criteria	Previous hemiparesis; flaccid hemiplegia; volitional wrist extension in synergy or in isolation with muscle grade at least 3/5; spasticity >stage 3 according to the modified Ashworth scale; deformity leading to a upper extremity dysfunction; neurological comorbidity leading to an impaired upper extremity; cardiac pacemaker; history of seizures within the previous 2 years; history of potentially fatal cardiac arrhythmia.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	People were recruited from the Department of Physical Medicine and Rehabilitation
Intervention(s)	Neuromuscular electrical stimulation (NMES) N=20 A combination of active NMES (n=10) and passive NMES (n=10). Each treatment regimen was applied five times per week for 45 minutes for 3 weeks. Active NMES consisted of people initiating wrist/finger extension until a target threshold level of EMG activity was achieved voluntarily, which triggered the NMES to assist the muscle to reach a full range of motion and provided visual and audio feedback. The sensitivity of the EMG biofeedback ranged from 0 to 100 microvolts. When people reached the threshold level, the therapist could manually increase it for the next session. If it were not met it could be decreased. The settings for electrical stimulation was a 2s rampup, 10s of symmetric biphasic stimulation at 50 Hz (mA 20-47, pulse width of 200 microseconds), and 2s rampdown. The current amplitude was adjusted to patient comfort. Passive stimulation was set to a duty cycle of 10s on and 15s off (with a symmetric biphasic stimulation at 50 Hz, 2s rampup and rampdown, 20-47 mA, pulse width 200 microseconds). Stimulation treatments were applied for 45 minutes, five times per week for 3 weeks. Concomitant therapy: All people performed the same neurophysiologic exercise program for 45 minutes five times per week for 3 weeks.
Subgroup 1: Severity of spasticity (as stated by category or as measured by	Mild (or MAS 1)

modified Ashworth scale [MAS])	
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	No additional information.
Comparator	Placebo/sham N=10 The electrodes were placed away from all motor points and people received cutaneous stimulation just above the sensory threshold without motor activation (monophasic constant current twin pulses at 50 Hz). Stimulation treatments were applied for 45 minutes, five times per week for 3 weeks. Concomitant therapy: All people performed the same neurophysiologic exercise program for 45 minutes five times per week for 3 weeks.
Number of participants	30
Duration of follow-up	3 weeks
Indirectness	No additional information

Additional comments	No additional information.

Study arms

Neuromuscular electrical stimulation (NMES) (N = 20)
A combination of active NMES (n=10) and passive NMES (n=10). Each treatment regimen was applied five times per week for 45 minutes for 3 weeks. Active NMES consisted of people initiating wrist/finger extension until a target threshold level of EMG activity was achieved voluntarily, which triggered the NMES to assist the muscle to reach a full range of motion and provided visual and audio feedback. The sensitivity of the EMG biofeedback ranged from 0 to 100 microvolts. When people reached the threshold level, the therapist could manually increase it for the next session. If it were not met it could be decreased. The settings for electrical stimulation was a 2s rampup, 10s of symmetric biphasic stimulation at 50 Hz (mA 20-47, pulse width of 200 microseconds), and 2s rampdown. The current amplitude was adjusted to patient comfort. Passive stimulation was set to a duty cycle of 10s on and 15s off (with a symmetric biphasic stimulation at 50 Hz, 2s rampup and rampdown, 20-47 mA, pulse width 200 microseconds). Stimulation treatments were applied for 45 minutes, five times per week for 3 weeks. Concomitant therapy: All people performed the same neurophysiologic exercise program for 45 minutes five times per week for 3 weeks.

Placebo/sham (N = 10)
The electrodes were placed away from all motor points and people received cutaneous stimulation just above the sensory threshold without motor activation (monophasic constant current twin pulses at 50 Hz). Stimulation treatments were applied for 45 minutes, five times per week for 3 weeks. Concomitant therapy: All people performed the same neurophysiologic exercise program for 45 minutes five times per week for 3 weeks.

1 **Characteristics**

2 ***Arm-level characteristics***

Characteristic	Neuromuscular electrical stimulation (NMES) (N = 20)	Placebo/sham (N = 10)
% Female Sample size	n = 7 ; % = 35	n = 6 ; % = 60
Mean age (SD) (years) Mean (SD)	60.3 (9.3)	57.6 (16.4)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 17 ; % = 85	n = 8 ; % = 80
Diabetes mellitus Sample size	n = 8 ; % = 40	n = 3 ; % = 30
Cardiac disease Sample size	n = 3 ; % = 15	n = 3 ; % = 30
Severity of spasticity Modified Ashworth scale Mean (SD)	1.29 (1.05)	0.6 (0.9)

Characteristic	Neuromuscular electrical stimulation (NMES) (N = 20)	Placebo/sham (N = 10)
Time period after stroke (Weeks) Mean (SD)	17.2 (17.4)	15.1 (17.1)
Type of spasticity Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- Baseline
- 3 week (</=6 months)

Continuous outcomes

Outcome	Neuromuscular electrical stimulation (NMES), Baseline, N = 20	Neuromuscular electrical stimulation (NMES), 3 week, N = 20	Placebo/sham, Baseline, N = 10	Placebo/sham, 3 week, N = 10
Stroke outcome measures (Modified Ashworth scales) Scale range: 1-5. Combination of the wrist flexor and finger flexor spasticity. Final values. Mean (SD)	1.29 (1.05)	1.24 (0.96)	0.6 (0.9)	1.05 (1.12)
Activities of daily living (Functional Independence	24.13 (10.26)	27.81 (10.02)	19.2 (5.97)	22 (8.17)

Outcome	Neuromuscular electrical stimulation (NMES), Baseline, N = 20	Neuromuscular electrical stimulation (NMES), 3 week, N = 20	Placebo/sham, Baseline, N = 10	Placebo/sham, 3 week, N = 10
Measure Self-Care subscale) Scale range unclear. Final values. Mean (SD)				
Physical function - upper limb (Fugl Meyer Assessment - Upper Extremity) Scale range: 0-66. Final values. Mean (SD)	32.04 (13.84)	38.54 (15.48)	33.7 (19.05)	34.7 (20.17)

Stroke outcome measures (Modified Ashworth scales) - Polarity - Lower values are better
Activities of daily living (Functional Independence Measure Self-Care subscale) - Polarity - Higher values are better
Physical function - upper limb (Fugl Meyer Assessment - Upper Extremity) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuousoutcomes-Strokeoutcomemeasures(ModifiedAshworthscales)-MeanSD-Neuromuscular electrical stimulation (NMES)-Placebo/sham-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Activitiesofdailyliving(FunctionalIndependenceMeasureSelf-Caresubscale)-MeanSD-Neuromuscular electrical stimulation (NMES)-Placebo/sham-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Physicalfunction-upperlimb(FuglMeyerAssessment-UpperExtremity)-MeanSD-Neuromuscular electrical stimulation (NMES)-Placebo/sham-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Brashear, 2002

Bibliographic Reference	Brashear, A.; Gordon, M. F.; Elovic, E.; Kassicieh, V. D.; Marciniak, C.; Do, M.; Lee, C. H.; Jenkins, S.; Turkel, C.; Botox Post-Stroke Spasticity Study, Group; Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke; New England Journal of Medicine; 2002; vol. 347 (no. 6); 395-400

Study details

Secondary publication of another included	No additional information

study- see primary study for details	
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	United States of America
Study setting	Outpatient follow up
Study dates	April 30, 1999 to February 29, 2000.
Sources of funding	Supported by Allergan.
Inclusion criteria	At least 2 years old; had a stroke at least 6 months earlier; had focal spasticity of the wrist and fingers, as demonstrated by a score of 3 or 4 for wrist flexor tone and a score of 2 or higher for finger flexor tone on the Ashworth scale, with 0 indicating normal muscle tone and 4 rigid flexion; evidence of difficulty in maintaining hygiene or dressing, pain or malposition of the wrist or fingers, as evidenced by a score of 2 or 3 on the Disability Assessment Scale, with 0 indicating no disability and 3 severe disability.
Exclusion criteria	A fixed contracture or profound muscle atrophy in the spastic limb; prior or planned treatment of the limb with any botulinum toxin serotype or with phenol, alcohol or surgery; a change in oral medication for spasticity in the previous three months; treatment with intrathecal baclofen; treatment with agents affecting neuromuscular transmission; people who were pregnant, lactating or planning to become pregnant during the course of the study.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	No additional information.

Intervention(s)	Botulinum toxin type A (BOTOX) N=64 Botulinum toxin A (Botox), 200-240 units delivered as one session. 50 units injected in each of four wrist and finger muscles (50 units per muscle) with optional injections in one or two thumb muscles (20 units per muscle). Concomitant therapy: No additional information.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Severe (or MAS 3)
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	No additional information.
Comparator	Placebo N=62

	Placebo (Botulinum toxin A vehicle only) delivered identically to the botulinum toxin type A group. The appearance was identical to the botulinum toxin type A injections. Concomitant therapy: No additional information.
Number of participants	126
Duration of follow-up	12 weeks
Indirectness	No additional information
Additional comments	No additional information

Study arms

Onaotulinum toxin type A (BOTOX) (N = 64)
Botulinum toxin A (Botox), 200-240 units delivered as one session. 50 units injected in each of four wrist and finger muscles (50 units per muscle) with optional injections in one or two thumb muscles (20 units per muscle). Concomitant therapy: No additional information.

Placebo (N = 62)
Placebo (Botulinum toxin A vehicle only) delivered identically to the botulinum toxin type A group. The appearance was identical to the botulinum toxin type A injections. Concomitant therapy: No additional information.

1 **Characteristics**

2 ***Arm-level characteristics***

Characteristic	Onaotulinum toxin type A (BOTOX) (N = 64)	Placebo (N = 62)
% Female Sample size	n = 36 ; % = 56	n = 27 ; % = 44
Mean age (SD) (years) Range	23 to 87	23 to 88
Mean age (SD) (years) Mean (SD)	61 (NR)	62 (NR)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
White Sample size	n = 53 ; % = 83	n = 46 ; % = 74
Black Sample size	n = 7 ; % = 11	n = 14 ; % = 23
Hispanic Sample size	n = 3 ; % = 5	n = 1 ; % = 2
Asian Sample size	n = 0 ; % = 0	n = 1 ; % = 2

Characteristic	Onaotulinum toxin type A (BOTOX) (N = 64)	Placebo (N = 62)
Other Sample size	*empty data*	n = 0 ; % = 0
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Severity of spasticity Sample size	n = NR ; % = NR	n = NR ; % = NR
Time period after stroke (years) Mean (SD)	4.6 (NR)	4.9 (NR)
Type of spasticity Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- Baseline
- 12 week (</=6 months)

Continuous outcomes

Outcome	Onaotulinum toxin type A (BOTOX), Baseline, N = 64	Onaotulinum toxin type A (BOTOX), 12 week, N = 64	Placebo, Baseline, N = 62	Placebo, 12 week, N = 62
Spasticity outcome measure (Ashworth scale) Scale range: 0-4. Change scores. Combination of wrist, finger and thumb flexor scores. Reported as mean 95% confidence interval, converted to mean SD to combine scores. Mean (SD)	2.87 (NR)	-0.92 (1.19)	2.82 (NR)	-0.67 (1.14)
Activities of daily living (Disability Assessment Scale) Scale range: 0-3. Change scores. Mean (95% CI)	2.7 (NR to NR)	-0.88 (-1.12 to -0.63)	2.52 (NR to NR)	-0.46 (-0.67 to -0.24)

Spasticity outcome measure (Ashworth scale) - Polarity - Higher values are better

Activities of daily living (Disability Assessment Scale) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuousoutcomes-Spasticityoutcomemeasure(Ashworthscale)-MeanSD-Botulinum toxin type A (BOTOX)-Placebo-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Activitiesofdailyliving(DisabilityAssessmentScale)-MeanNineFivePercentCI-Botulinum toxin type A (BOTOX)-Placebo-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Calvo, 2022

Bibliographic Reference	Calvo S; Brandín-de la Cruz N; Jiménez-Sánchez C; Bravo-Esteban E; Herrero P; Effects of dry needling on function, hypertonia and quality of life in chronic stroke: a randomized clinical trial.; Acupuncture in medicine : journal of the British Medical Acupuncture Society; 2022; vol. 40 (no. 4)

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	NCT03546517
Study type	Randomised controlled trial (RCT)

Study location	Spain
Study setting	NR
Study dates	NR
Sources of funding	The authors received no financial support for the research, authorship and/or publication of this article.
Inclusion criteria	Inclusion in the study was based on the following criteria: (1) age 40–90 years with hemiparesis resulting from stroke of more than 6months evolution based on a diagnosis confirmed by a neurologist; (2) ability to follow instructions and reply to assessment questionnaires; and (3) presence of hypertonia ⩾1 in at least one of the muscles of the upper extremity evaluated according to a Modified Modified Ashworth Scale (MMAS) score.
Exclusion criteria	Individuals were excluded if they had: (1) grade 0 (no increase in muscle tone) or 4 (rigidity) hypertonia according to the MMAS; (2) previous treatment with BTX-A or other pharmacological agents for hypertonia at any time, or in the previous 6months; (3) other concomitant neurodegenerative conditions; (4) fear of needles; (5) any contraindication to treatment with DN; or (6) cognitive decline (score ⩽24 points on mini-mental examination test). The withdrawal criteria consisted of the failure to attend assessments.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	Participants were recruited from the Aragon Association of Stroke in Zaragoza (Spain).
Intervention(s)	Acupuncture/dry needling (dry needling) N=11 Participants received a single session of dry needling in the biceps brachii, brachialis, flexor digitorum superficialis and profundus, extensor digitorum, adductor pollicis and triceps brachii muscles. The Dry Needling for Hypertonia and Spasticity technique was applied on the most nodular area of the muscular trigger point, with the muscle placed in a position of sub-maximal stretch and sought to elicit a local twitch response. The application was performed with repeated needle insertions in the muscle at approximately 1Hz, until all LTRs disappeared or substantially decreased. Treatment was discontinued if the participant asked to stop because of intolerable pain. There was only one insertion point per muscle. Treatments and assessments were always performed at the same time and site to maximally standardize participant conditions. Each session lasted about 60min. All participants were treated by a skilled physiotherapist (SC) trained in DN who was not blinded, and were evaluated by another physiotherapist (NB) who was blinded.

	Concomitant therapy: No additional information.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mild (or MAS 1)
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	Dry needling
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	NR
Comparator	Placebo/sham (Sham dry needling) N=12 The SG received the same treatments with sham DN (considered a non-active treatment for MTrPs, as they were neither reached nor needled). Sham needles were placed superficially so people could perceive a needle prick but without going beyond the skin layer. Subsequently, the physiotherapist mimicked needle manipulation. Otherwise the protocol was the same as for the dry needling group. Treatments and assessments were always performed at the same time and site to maximally standardize participant conditions. Each session lasted about 60min. All participants were treated by a skilled

	physiotherapist (SC) trained in DN who was not blinded, and were evaluated by another physiotherapist (NB) who was blinded. Concomitant therapy: No additional information.
Number of participants	23
Duration of follow-up	2 weeks
Indirectness	NR
Additional comments	NR

Study arms

Acupuncture/dry needling (dry needling) (N = 11)
Participants received a single session of dry needling in the biceps brachii, brachialis, flexor digitorum superficialis and profundus, extensor digitorum, adductor pollicis and triceps brachii muscles. The Dry Needling for Hypertonia and Spasticity technique was applied on the most nodular area of the muscular trigger point, with the muscle placed in a position of sub-maximal stretch and sought to elicit a local twitch response. The application was performed with repeated needle insertions in the muscle at approximately 1Hz, until all LTRs disappeared or substantially decreased. Treatment was discontinued if the participant asked to stop because of intolerable pain. There was only one insertion point per muscle. Treatments and assessments were always performed at the same time and site to maximally standardize participant conditions. Each session lasted about 60min. All participants were treated by a skilled physiotherapist (SC) trained in DN who was not blinded, and were evaluated by another physiotherapist (NB) who was blinded.
Concomitant therapy: No additional information.

Placebo/sham (Sham dry needling) (N = 12)

The SG received the same treatments with sham DN (considered a non-active treatment for MTrPs, as they were neither reached nor needled). Sham needles were placed superficially so people could perceive a needle prick but without going beyond the skin layer. Subsequently, the physiotherapist mimicked needle manipulation. Otherwise the protocol was the same as for the dry needling group. Treatments and assessments were always performed at the same time and site to maximally standardize participant conditions. Each session lasted about 60min. All participants were treated by a skilled physiotherapist (SC) trained in DN who was not blinded, and were evaluated by another physiotherapist (NB) who was blinded. Concomitant therapy: No additional information.

Characteristics

Arm-level characteristics

Characteristic	Acupuncture/dry needling (dry needling) (N = 11)	Placebo/sham (Sham dry needling) (N = 12)
% Female Sample size	n = 6 ; % = 55	n = 3 ; % = 25
Mean age (SD) (years) Mean (SD)	63.6 (9)	58.3 (19.3)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Severity of spasticity Mean (SD)	1.33 (1.23)	1.37 (1.14)

Characteristic	Acupuncture/dry needling (dry needling) (N = 11)	Placebo/sham (Sham dry needling) (N = 12)
Time period after stroke years Mean (SD)	7.5 (5.9)	4.6 (4)
Type of spasticity Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 2 week

Continuous outcomes

Outcome	Acupuncture/dry needling (dry needling), Baseline, N = 11	Acupuncture/dry needling (dry needling), 2 week, N = 11	Placebo/sham (Sham dry needling), Baseline, N = 12	Placebo/sham (Sham dry needling), 2 week, N = 12
Spasticity outcome measures (MAS) Scale range: 1-4. Change scores. Calculated by averaging the values for elbow flexors, extensors, wrist dorsal flexors, plantar flexors and thumb adductors together. Mean (SD)	1.33 (1.23)	-0.46 (0.72)	1.37 (1.14)	-0.25 (0.55)

Spasticity outcome measures (MAS) - Polarity - Lower values are better

Dichotomous outcomes and baseline values for continuous outcomes where mean differences are reported (baseline values)

Outcome	Acupuncture/dry needling (dry needling), Baseline, N = 11	Acupuncture/dry needling (dry needling), 2 week, N = 11	Placebo/sham (Sham dry needling), Baseline, N = 12	Placebo/sham (Sham dry needling), 2 week, N = 12
Withdrawal due to adverse events No of events	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0
Person/participant health related quality of life (EQ5D) Scale range: -0.11-1. Final values. Values reported in the study as pre-test and follow up-test but these appear to look incorrect (or people had very low quality of life values at baseline and after the test). These may be change values after the post test and follow up test instead but mislabeled. Mean (SD)	0.09 (0.43)	0.18 (0.47)	0.01 (0.16)	0.005 (0.06)
Physical function - upper limb (Fugl Meyer Assessment - Upper Extremity) Scale range: 0-66. Final values. Mean (SD)	33.91 (19.48)	41.09 (19.75)	27.83 (18.51)	30.83 (16.75)

Withdrawal due to adverse events - Polarity - Lower values are better

Person/participant health related quality of life (EQ5D) - Polarity - Higher values are better

Physical function - upper limb (Fugl Meyer Assessment - Upper Extremity) - Polarity - Higher values are better

Continuous outcomes (mean difference)

Outcome	Acupuncture/dry needling (dry needling) vs Placebo/sham (Sham dry needling), Baseline, N2 = 11, N1 = 12	Acupuncture/dry needling (dry needling) vs Placebo/sham (Sham dry needling), 2 week, N2 = 11, N1 = 12
Person/participant health related quality of life (EQ5D) Scale range: -0.11-1. Change scores. Mean (95% CI)	NA (NA to NA)	0.09 (0.03 to 0.2)
Physical function - upper limb (Fugl Meyer Assessment - Upper Extremity) Scale range: 0-66. Change scores. Mean (95% CI)	NA (NA to NA)	4.18 (-0.34 to 8.7)

Person/participant health related quality of life (EQ5D) - Polarity - Higher values are better
Physical function - upper limb (Fugl Meyer Assessment - Upper Extremity) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuousoutcomes-Spasticityoutcomemeasures(MAS)-MeanSD-Acupuncture/dry needling (dry needling)-Placebo/sham (Sham dry needling)-t2

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Withdrawalduetoadverseevents-NoOfEvents-Acupuncture/dry needling (dry needling)-Placebo/sham (Sham dry needling)-t2

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes(meandifference)-Person/participanthealthrelatedqualityoflife(EQ5D)-MeanNineFivePercentCI-Acupuncture/dry needling (dry needling)-Placebo/sham (Sham dry needling)-t2

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes(meandifference)-Physicalfunction-upperlimb(FuglMeyerAssessment-UpperExtremity)-MeanNineFivePercentCI-Acupuncture/dry needling (dry needling)-Placebo/sham (Sham dry needling)-t2

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Childers, 2004

Bibliographic Reference	Childers, M. K.; Brashear, A.; Jozefczyk, P.; Reding, M.; Alexander, D.; Good, D.; Walcott, J. M.; Jenkins, S. W.; Turkel, C.; Molloy, P. T.; Dose-dependent response to intramuscular botulinum toxin type A for upper-limb spasticity in patients after a stroke; Archives of Physical Medicine & Rehabilitation; 2004; vol. 85 (no. 7); 1063-9

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	19 outpatient clinics across the United States (MO, IN, PA, NY, CA, NC)
Study setting	Outpatient clinics
Study dates	No additional information
Sources of funding	'A commercial party with a direct financial interest in the results of the research supporting this article has conferred or will confer a financial benefit on the author or 1 or more of the authors'
Inclusion criteria	Stroke diagnosed by a neurologist

	Occurrence of a stroke at least 6 weeks prior to study enrolment Focal spasticity of an upper limb shown by excessive wrist flexor muscle tone score of 3 or higher (very severe) and elbow flexor tone score of 2 or more (severe) as measured by the Modified Ashworth Scale Able to give informed consent and comply with study instructions
Exclusion criteria	Fixed contracture or profound atrophy in the affected limb Previous or current treatment with any botulinum toxin serotype, phenol or surgery Current plaster casting for spasticity of the study limb Current treatment with agents that affect neuromuscular transmission Pulmonary functional testing (FEV1, FVC) less than 65% of predicted value Participation in another clinical trial within 30 days of study entry Diagnosis of myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis or any other condition that might interfere with the study Known sensitivity to any components of the study medication Women were excluded if pregnant, breastfeeding or planning pregnancy during the course of the study
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	Participants recruited from 19 medical centres outpatient departments
Intervention(s)	All study drugs and placebo were identical. Each vial of BTX contained 100U of BTX with 0.5mg of human serum albumin and 0.9mg of sodium chloride. Injection volume was the same between all injections (4mL) by adding additional saline.

	Investigators could implement concurrent therapies after the first week after injection (with the exception of stabilisation devices such as splits, casts and orthotic devices). Use of antispasticity was not restricted and investigators were permitted to add, change the dose or stop the antispasticity medication at their discretion. Muscles chosen for injection were the flexor carpi ulnaris, flexor carpi radialis, biceps brachii, flexor digitorum profundus and the flexor digitorum sublimus. The second treatment cycle (if given) was identical to the first in dose and location of injections. Subjects were eligible for a second treatment cycle 12 weeks or more after the first only if they showed MAS scores of 2 or higher at the wrist and/or elbow flexor muscles and pulmonary function measurements did not decrease by >15% from baseline.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mixed
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months) Range of 0.9 to 226.9 months after stroke. Mean time after stroke was 25.8 months.
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)

Population subgroups	No additional information
Comparator	Placebo was identical in appearance to the BTX injections and contained 0.5mg of serum albumin and 0.9mg of sodium chloride.
Number of participants	70 randomised, 56 completed treatment, 49 analysed
Duration of follow-up	24 weeks
Indirectness	None
Additional comments	Efficacy data included for patients who received study medication and completed at least 6 weeks of visits One-way analysis of covariance for MAS (including time since onset of stroke as covariate) FIM, SF36, global assessments, functional disability and pain assessed via one-way analysis of variance Adverse effect incidence was calculated from the number of participants exposed to the study drug using Fisher's exact

Study arms

Onabotulinum Toxin A (BOTOX) (N = 44)

Combined data for 90U and 180U BTX intramuscular injection arms. 360U intervention arm was omitted due to exceeding maximum recommended dose stated in protocol.

Placebo (N = 26)

1 **Characteristics**

2 ***Arm-level characteristics***

Characteristic	Onabotulinum Toxin A (BOTOX) (N = 44)	Placebo (N = 26)
% Female Sample size	n = 13 ; % = 30	n = 13 ; % = 50
Mean age (SD) (years) Age reported as mean (range) - intervention mean calculated as weighted mean from combined intervention arms Nominal	60.2	60.6
Mean age (SD) (years) Age reported as mean (range) - intervention mean calculated as weighted mean from combined intervention arms Range	30.4 to 79.4	33.8 to 76
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Severity of spasticity Nominal	NR	NR

Characteristic	Onabotulinum Toxin A (BOTOX) (N = 44)	Placebo (N = 26)
Time period after stroke (Months) Reported as mean (range) - intervention mean calculated as weighted mean from combined intervention arms Nominal	30	26.6
Time period after stroke (Months) Reported as mean (range) - intervention mean calculated as weighted mean from combined intervention arms Range	0.9 to 226.9	2.1 to 211.7
Type of spasticity Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 24 week

Continuous Outcomes

Outcome	Onabotulinum Toxin A (BOTOX), Baseline, N = 44	Onabotulinum Toxin A (BOTOX), 24 week, N = 31	Placebo, Baseline, N = 26	Placebo, 24 week, N = 18

Dichotomous Outcomes

Outcome	Onabotulinum Toxin A (BOTOX), Baseline, N = 44	Onabotulinum Toxin A (BOTOX), 24 week, N = 31	Placebo, Baseline, N = 26	Placebo, 24 week, N = 18
Withdrawal due to adverse events No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Withdrawal due to adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

DichotomousOutcomes-Withdrawalduetoadverseevents-NoOfEvents-Intervention-Placebo-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Cousins, 2010

Bibliographic Reference	Cousins, E.; Ward, A.; Roffe, C.; Rimington, L.; Pandyan, A.; Does low-dose botulinum toxin help the recovery of arm function when given early after stroke? A phase II randomized controlled pilot study to estimate effect size; Clinical Rehabilitation; 2010; vol. 24 (no. 6); 501-13

1 **Study details**

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	United Kingdom
Study setting	Stroke unit of the University Hospital of North Staffordshire, a large teaching hospital.
Study dates	No additional information.
Sources of funding	The study received support from the North Staffordshire Medical Institute and an unrestricted educational grant from Allergan Ltd.
Inclusion criteria	People within three weeks of a first stroke affecting upper limb function; adults; unable to score the maximum on the easiest test of the Grasp subsection of the Action Research Arm Test (i.e. they were unable to, or experienced difficulty with lifting a 2cm cube onto a shelf with their affected hand).
Exclusion criteria	Any neurological or musculoskeletal condition that affected upper limb function prior to the stroke, if they had a brainstem stroke, if the stroke affected both hemisphere, or if they were unconscious or moribund.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	People were recruited from the stroke unit of the University Hospital of North Staffordshire within three weeks of their first stroke affecting upper limb function.

Intervention(s)	Onabotulinum toxin A (BOTOX) N=19 Half (9 people) or a quarter (10 people) of the usual dose of botulinum toxin type A. The standard doses considered for this study were 100 IU for biceps brachii, 60 IU for brachialis, 50 IU for brachioradialis, 50 IU for flexor digitorum superficialis and 50 IU for flexor digitorum profundus. The dose was calculated by the muscle mass. Using the average muscle mass, the average dose given for the half dose group would be 50 U of BOTOX, but would be increased to 62.5 units for people with an upper arm muscle area in the upper 25th percentile, and reduced to 37.5 units if muscle mass was in the lower 25th percentile. Concomitant therapy: No additional information.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Not stated/unclear
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	No additional information.

Comparator	Placebo N=11 Saline injections corresponding to the amount provided in the botulinum toxin groups. Concomitant therapy: No additional information.
Number of participants	30
Duration of follow-up	20 weeks
Indirectness	No additional information
Additional comments	Missing data were handled in the following manner. Where data was available either side of a missing data point, the mean of the two data points on either side of the missing one was calculated, and used. Where a participant had data post intervention but had subsequently been lost to follow-up, the last data point available was used for the subsequent missed assessments.

Study arms

Onabotulinum toxin A (BOTOX) (N = 19)
Half (9 people) or a quarter (10 people) of the usual dose of botulinum toxin type A. The standard doses considered for this study were 100 IU for biceps brachii, 60 IU for brachialis, 50 IU for brachioradialis, 50 IU for flexor digitorum superficialis and 50 IU for flexor digitorum profundus. The dose was calculated by the muscle mass. Using the average muscle mass, the average dose given for the half dose group would be 50 U of BOTOX, but would be increased to 62.5 units for people with an upper arm muscle area in the upper 25th percentile, and reduced to 37.5 units if muscle mass was in the lower 25th percentile. Concomitant therapy: No additional information.

Placebo (N = 11)
Saline injections corresponding to the amount provided in the botulinum toxin groups. Concomitant therapy: No additional information.

Characteristics

Study-level characteristics

Characteristic	Study (N = 30)
% Female Sample size	n = 17 ; % = 57
Mean age (SD) (years) Mean (SD)	69 (11.8)
Ethnicity Sample size	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR
Severity of spasticity Sample size	n = NR ; % = NR
Time period after stroke (days) Mean (SD)	23 (9)
Type of spasticity Sample size	n = NR ; % = NR

Outcomes

Study timepoints

- Baseline
- 20 week (<6 months)

Continuous outcomes

Outcome	Onabotulinum toxin A (BOTOX), Baseline, N = 16	Onabotulinum toxin A (BOTOX), 20 week, N = 16	Placebo, Baseline, N = 7	Placebo, 20 week, N = 7
Physical function - upper limb- ARAT Scale range: 0-57. Change scores. Intervention group half dose and quarter dose groups were combined in the analysis. Change score half dose = 11.0 (18.2). Change score quarter dose = 6.4 (7.5). Mean (SD)	0.6 (1.6)	9 (14.7)	1.3 (2)	12.8 (20)

Physical function - upper limb- ARAT - Polarity - Higher values are better

Dichotomous outcomes

Outcome	Onabotulinum toxin A (BOTOX), Baseline, N = 19	Onabotulinum toxin A (BOTOX), 20 week, N = 19	Placebo, Baseline, N = 11	Placebo, 20 week, N = 11
Withdrawal due to adverse events Botulinum toxin: 2 restroked after baseline assessment. Placebo: 2 dead, 2 required treatment with botulinum toxin, 1 subsequent subdural haemorrhage No of events	n = NA ; % = NA	n = 2 ; % = 11	n = NA ; % = NA	n = 5 ; % = 45

Withdrawal due to adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuousoutcomes-Physicalfunction-upperlimb-ARAT-MeanSD-Onabotulinum toxin A (BOTOX)-Placebo-t20

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Withdrawalduetoadverseevents-NoOfEvents-Onabotulinum toxin A (BOTOX)-Placebo-t20

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Creamer, 2018

Bibliographic Reference	Creamer, M.; Cloud, G.; Kossmehl, P.; Yochelson, M.; Francisco, G. E.; Ward, A. B.; Wissel, J.; Zampolini, M.; Abouihia, A.; Berthuy, N.; Calabrese, A.; Loven, M.; Saltuari, L.; Intrathecal baclofen therapy versus conventional medical management for severe poststroke spasticity: results from a multicentre, randomised, controlled, open-label trial (SISTERS); Journal of Neurology, Neurosurgery & Psychiatry; 2018; vol. 89 (no. 6); 642-650

1 **Study details**

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	Effect of intrathecal baclofen on pain and quality of life in poststroke spasticity: A Randomized Trial (SISTERS) Stroke; 2018; vol. 49 (no. 9); 2129-2137. Creamer 2018 2899 Effect of Intrathecal Baclofen on Pain and Quality of Life in Poststroke Spasticity Stroke; 2018; vol. 49 (no. 9); 2129-2137 Creamer 2018 2857
Trial name / registration number	NCT01032239
Study type	Randomised controlled trial (RCT)
Study location	Multicentre: 11 European centers (Austria, Belgium, Germany, Italy, the Netherlands, Spain, UK, Slovenia) and 7 US centres.
Study setting	Rehabilitation hospitals
Study dates	No additional information
Sources of funding	This work was supported by Medtronic International Trading Sàrl. MC, MZ and LS report personal fees from Medtronic during the conduct of the study. GEF reports grants from Allergan, Ipsen, Merz and Mallinckrodt during the conduct of the study. JW reports personal fees from Medtronic during the conduct of the study, and personal fees from Allergan, Merz, Ipsen, and Medtronic outside the submitted work. AA, NB, AC and ML are all employees of Medtronic and report personal fees from Medtronic during the conduct of the study.

Inclusion criteria	Men or women aged 18-75 years with a poststroke duration >6 months and generalised spasticity, who had not reached their therapy goal with other treatment interventions (eg, physiotherapy, botulinum toxin injection and oral medication). All people had spasticity in at least two extremities and an Ashworth Scale score at least 3 in a minimum of two muscle groups of the lower extremities on the affected body side.
Exclusion criteria	Known baclofen sensitivity; uncontrolled refractory epilepsy; active systemic infection; presence of a cardiac pacemaker, implantable cardioverter defibrillator, implantable neurostimulator, or drug delivery device; use of oral vitamin K antagonists; use of botulinum toxin within the 4 months prior to inclusion; and inability/unwillingness of the patient/family to participate in long-term ITB therapy management.
Stratification - Type of spasticity	Generalised spasticity
Recruitment / selection of participants	No additional information
Intervention(s)	Intrathecal baclofen N=31 Lioresal Intrathecal (baclofen injection, Novartis (Europe)/Saol Therapeutics (US)) was used for intrathecal baclofen therapy. People underwent an intrathecal baclofen therapy trial between days 1 and 10 during the run-in phase to evaluate drug response. People could continued their oral antispastic medications during this phase. At the test visit, the Ashworth Scale was measured prior to and at several points during intrathecal baclofen therapy administration. People fulfilling the test success criterion (1-point drop in the Ashworth Scale score in three muscle groups in the affected lower extremity) were implanted between days 2 and 25 with the marketed SynchroMed II infusion system (Medtronic). After implant, patients underwent a 6-week titration period during which the intrathecal baclofen dose was increased until the desired clinical effect was achieved or reduced for side-effect management; oral antispastics were gradually reduced with complete discontinuation by week 6. People randomised to intrathecal baclofen who were not implanted remained on oral antispastic medication and physiotherapy until the study end. Concomitant therapy: No additional information.
Subgroup 1: Severity of spasticity (as	Not stated/unclear

stated by category or as measured by modified Ashworth scale [MAS])	
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	not applicable
Population subgroups	No additional information
Comparator	Usual care N=29 This arm received a combination of oral antispastic medication (at least one of oral baclofen, tinzanidine, diazepam/other benzodiazepines, or dantrolene) and physiotherapy throughout the study. Oral antispastic medications were prescribed by the investigator at randomisation, medications were then reassessed at the end of the run-in phase at the second assessment visit, and could be adjusted as deemed necessary by the investigator at any time during the trial, in accordance with usual clinical practice and the needs of the individual patient. Concomitant therapy: No additional information.
Number of participants	60

Duration of follow-up	6 months
Indirectness	No additional information
Additional comments	Intention to treat (modified intention to treat and per protocol analyses were also conducted).

Study arms

Intrathecal baclofen (N = 31)
Lioresal Intrathecal (baclofen injection, Novartis (Europe)/Saol Therapeutics (US)) was used for intrathecal baclofen therapy. People underwent an intrathecal baclofen therapy trial between days 1 and 10 during the run-in phase to evaluate drug response. People could continued their oral antispastic medications during this phase. At the test visit, the Ashworth Scale was measured prior to and at several points during intrathecal baclofen therapy administration. People fulfilling the test success criterion (1-point drop in the Ashworth Scale score in three muscle groups in the affected lower extremity) were implanted between days 2 and 25 with the marketed SynchroMed II infusion system (Medtronic). After implant, patients underwent a 6-week titration period during which the intrathecal baclofen dose was increased until the desired clinical effect was achieved or reduced for side-effect management; oral antispastics were gradually reduced with complete discontinuation by week 6. People randomised to intrathecal baclofen who were not implanted remained on oral antispastic medication and physiotherapy until the study end. Concomitant therapy: No additional information.

Usual care (N = 29)
This arm received a combination of oral antispastic medication (at least one of oral baclofen, tinzanidine, diazepam/other benzodiazepines, or dantrolene) and physiotherapy throughout the study. Oral antispastic medications were prescribed by the investigator at randomisation, medications were then reassessed at the end of the run-in phase at the second assessment visit, and could be adjusted as deemed necessary by the investigator at any time during the trial, in accordance with usual clinical practice and the needs of the individual patient. Concomitant therapy: No additional information.

1 **Characteristics**

2 ***Arm-level characteristics***

Characteristic	Intrathecal baclofen (N = 31)	Usual care (N = 29)
% Female Sample size	n = 7 ; % = 22.6	n = 11 ; % = 37.9
Mean age (SD) (years) Mean (SD)	56.1 (11.1)	55.7 (8.6)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 23 ; % = 74.2	n = 23 ; % = 79.3
Other Sample size	n = 8 ; % = 25.8	n = 6 ; % = 20.7
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Severity of spasticity Mean (SD)	NR (NR)	NR (NR)
Time period after stroke (years) Mean (SD)	4.95 (3.56)	4.55 (3.73)

Characteristic	Intrathecal baclofen (N = 31)	Usual care (N = 29)
Type of spasticity Sample size	n = NA ; % = NA	n = NA ; % = NA

Outcomes

Study timepoints

- Baseline
- 6 month (≤6 months)

Continuous outcomes

Outcome	Intrathecal baclofen, Baseline, N = 31	Intrathecal baclofen, 6 month, N = 25	Usual care, Baseline, N = 29	Usual care, 6 month, N = 26
Spasticity outcome measures (Ashworth Scale) Scale range: 0-4. Change scores. Reported values for lower extremity and upper extremity separately. These were combined for analysis. Lower extremity baclofen: -0.99 (0.75). Upper extremity baclofen: -0.66 (0.59). Lower extremity usual care: -0.43 (0.72). Upper extremity usual care: -0.17 (0.70). Mean (SD)	NR (NR)	-0.83 (0.7)	NR (NR)	-0.3 (0.72)
Activities of daily living (Functional Independence Measure total score) Scale range: 18-126. Change scores. Mean (SD)	89.23 (28.76)	2.68 (10.31)	96.1 (19.45)	-2.58 (11)

Outcome	Intrathecal baclofen, Baseline, N = 31	Intrathecal baclofen, 6 month, N = 25	Usual care, Baseline, N = 29	Usual care, 6 month, N = 26
Person/participant generic health-related quality of life (EQ-5D-3L) Scale range: -0.11-1. Change scores. Mean (SD)	0.32 (0.4)	0.09 (0.26)	0.54 (0.3)	0.01 (0.16)
Pain (NRS) Scale range: 0-10. Change scores. Mean (SD)	4.14 (3.57)	-1.17 (3.17)	2.96 (2.66)	0 (3.29)
Stroke-specific Patient Reported Outcome Measures (SS-QOL) Scale range: 1-5. Change scores. Mean (SD)	3.1 (0.73)	0.26 (0.58)	3.23 (0.64)	0.05 (0.58)

1 Spasticity outcome measures (Ashworth Scale) - Polarity - Lower values are better
2 Activities of daily living (Functional Independence Measure total score) - Polarity - Higher values are better
3 Person/participant generic health-related quality of life (EQ-5D-3L) - Polarity - Higher values are better
4 Pain (NRS) - Polarity - Lower values are better
5 Stroke-specific Patient Reported Outcome Measures (SS-QOL) - Polarity - Higher values are better

6 ***Dichotomous outcomes***

Outcome	Intrathecal baclofen, Baseline, N = 31	Intrathecal baclofen, 6 month, N = 31	Usual care, Baseline, N = 29	Usual care, 6 month, N = 29
Withdrawal due to adverse events Intrathecal baclofen: 1 died after pump implantation No of events	n = NA ; % = NA	n = 1 ; % = 3.2	n = NA ; % = NA	n = 0 ; % = 0

7 Withdrawal due to adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuousoutcomes-Spasticityoutcomemeasures(AshworthScale)-MeanSD-Intrathecal baclofen-Usual care-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Activitiesofdailyliving(FunctionalIndependenceMeasuretotalscore)-MeanSD-Intrathecal baclofen-Usual care-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Withdrawalduetoadverseevents-NoOfEvents-Intrathecal baclofen-Usual care-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Person/participantgenerichealth-relatedqualityoflife(EQ-5D-3L)-MeanSD-Intrathecal baclofen-Usual care-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Pain(NRS)-MeanSD-Intrathecal baclofen-Usual care-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Stroke-specificPatientReportedOutcomeMeasures(SS-QOL)-MeanSD-Intrathecal baclofen-Usual care-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Creamer, 2018

Bibliographic Reference	Creamer, M.; Cloud, G.; Kossmehl, P.; Yochelson, M.; Francisco, G. E.; Ward, A. B.; Wissel, J.; Zampolini, M.; Abouihia, A.; Calabrese, A.; Saltuari, L.; Effect of Intrathecal Baclofen on Pain and Quality of Life in Poststroke Spasticity; Stroke; 2018; vol. 49 (no. 9); 2129-2137

Study details

Secondary publication of another included study- see primary study for details	Intrathecal baclofen therapy versus conventional medical management for severe poststroke spasticity: results from a multicentre, randomised, controlled, open-label trial (SISTERS) Journal of Neurology, Neurosurgery & Psychiatry; 2018; vol. 89 (no. 6); 642-650. Creamer 2018 2897

Creamer, 2018

Bibliographic Reference	Creamer, M.; Cloud, G.; Kossmehl, P.; Yochelson, M.; Francisco, G. E.; Ward, A. B.; Wissel, J.; Zampolini, M.; Abouihia, A.; Calabrese, A.; Saltuari, L.; Effect of intrathecal baclofen on pain and quality of life in poststroke spasticity: A Randomized Trial (SISTERS); Stroke; 2018; vol. 49 (no. 9); 2129-2137

Study details

Secondary publication of another included study- see primary study for details	Intrathecal baclofen therapy versus conventional medical management for severe poststroke spasticity: results from a multicentre, randomised, controlled, open-label trial (SISTERS) Journal of Neurology, Neurosurgery & Psychiatry; 2018; vol. 89 (no. 6); 642-650. Creamer 2018 2897

Daly, 2011

Bibliographic Reference	Daly, J. J.; Zimbelman, J.; Roenigk, K. L.; McCabe, J. P.; Rogers, J. M.; Butler, K.; Burdsall, R.; Holcomb, J. P.; Marsolais, E. B.; Ruff, R. L.; Recovery of coordinated gait: randomized controlled stroke trial of functional electrical stimulation (FES) versus no FES, with weight-supported treadmill and over-ground training; Neurorehabilitation & Neural Repair; 2011; vol. 25 (no. 7); 588-96

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	No additional information
Study dates	No additional information
Sources of funding	Funding from the Department of Veterans Affairs, Office of Rehabilitation Research and Development (grant numbers: B2226R, A3102R, B5080S)
Inclusion criteria	>6 months since stroke onset

	Inability to execute normal swing phase in the sagittal plane using hip, knee and ankle flexion Hyperflexion or hyperextension of knee during stance Passive joint range of motion of hip, knee and ankle equal to normal excursion needed for walking Not participating in gait rehabilitation
Exclusion criteria	Inability to follow 2-level commands Pacemaker Peripheral neuropathy Debilitating illness
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	No additional information
Intervention(s)	Four sessions per week (1.5 hours each) for 12 weeks. Sessions included strengthening and coordination exercise, bodyweight supported treadmill training and over-ground gait training. Bodyweight supported treadmill training began at 30%BW supported, progressing to 0% according to ability to maintain normal, neutral alignment of torso and stance limb. Walking speed was increased up to 0.894m/s, as tolerated. Over ground gait training included training in torso, pelvic, knee and ankle position control during loading and weight bearing; swing hip, knee and ankle flexion; and terminal swing knee extension/ankle dorsiflexion. Home exercises emphasised coordination exercises for one hour per day. Intramuscular functional electrical stimulation was administered through a V-40 stimulator worn on the belt with a custom pattern downloaded to each participants stimulator for gait practise. Electrodes were implanted at the motor point in 8 muscles including; the tibialis anterior, peroneus longus, gastrocnemius lateral head, biceps femoris short head, semimembranosis, semitendenosis, vastus lateralis and gluteus medius, and remained in place for the duration of the treatment. The electrical stimulation parameters included amplitude of 4-20mA, pulse width 1-150uS, frequency 15-50Hz. Stimulation was used to treat pelvic stability during stance phase, knee extension at loading, ankle dorsiflexion during

	swing, knee flexion at toe-off and knee flexion and extension during swing. The level of stimulation was incrementally reduced as volitional control improved.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mixed
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	not applicable
Population subgroups	No additional information
Comparator	Four sessions per week (1.5 hours each) for 12 weeks. Sessions included strengthening and coordination exercise, bodyweight supported treadmill training and over-ground gait training. Bodyweight supported treadmill training began at 30%BW supported, progressing to 0% according to ability to maintain normal, neutral alignment of torso and stance limb. Walking speed was increased up to 0.894m/s, as tolerated. Over ground gait training included training in torso, pelvic, knee and ankle position control during loading and weight bearing; swing hip, knee and ankle flexion; and terminal swing knee extension/ankle dorsiflexion. Home exercises emphasised coordination exercises for one hour per day. The programs were identical to the intervention group, with the comparison group receiving no intramuscular functional electrical stimulation.
Number of participants	18 in treatment group and 19 in comparison group at 6-month follow up

Duration of follow-up	6 months
Indirectness	None
Additional comments	Plum ordinal regression model with Wilcoxon signed rank test in secondary analysis to determine within group pre vs post treatment effect

Study arms

Functional Electrical Stimulation (N = 20)
Intramuscular Functional electrical stimulation in addition to gait training

No Treatment (N = 24)
Gait training with no electrical stimulation

Characteristics

Arm-level characteristics

Characteristic	**Functional Electrical Stimulation (N = 20)**	**No Treatment (N = 24)**
% Female Sample size	n = 5 ; % = 25	n = 7 ; % = 29
Mean age (SD) (years) Nominal	59	62
Ethnicity	NR	NR

Characteristic	Functional Electrical Stimulation (N = 20)	No Treatment (N = 24)
Nominal		
Comorbidities Nominal	NR	NR
Severity of spasticity Fugl-Meyer Lower Limb Scale Median (IQR)	21.5 (18.75 to 24.25)	19.5 (17.13 to 21.88)
Time period after stroke Nominal	NR	NR
Type of spasticity Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 3 month

Continuous Outcomes

Outcome	Functional Electrical Stimulation, Baseline, N = 20	Functional Electrical Stimulation, 3 month, N = 20	No Treatment, Baseline, N = 24	No Treatment, 3 month, N = 24
Physical Function (Lower Limb) (6 minute walk distance) (meters) Final scores Mean (SD)	161.54 (80)	218.89 (107.4)	126.85 (93.2)	171.37 (125.2)

Physical Function (Lower Limb) (6 minute walk distance) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Functional Electrical Stimulation, Baseline, N = 20	Functional Electrical Stimulation, 3 month, N = 20	No Treatment, Baseline, N = 24	No Treatment, 3 month, N = 24
Withdrawal due to Adverse Effects No of events	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0

Withdrawal due to Adverse Effects - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Physical Function (Lower Limb) (6 minute walk distance)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-WithdrawalduetoAdverseEffects-NoOfEvents-Functional Electrical Stimulation-No Treatment-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

de Jong, 2013

Bibliographic Reference	de Jong, L. D.; Dijkstra, P. U.; Gerritsen, J.; Geurts, A. C.; Postema, K.; Combined arm stretch positioning and neuromuscular electrical stimulation during rehabilitation does not improve range of motion, shoulder pain or function in patients after stroke: a randomised trial; Journal of Physiotherapy; 2013; vol. 59 (no. 4); 245-54

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NTR1748

Study type	Randomised controlled trial (RCT)
Study location	The Netherlands
Study setting	Neurological unit of rehabilitation centres
Study dates	August 2008 to September 2010
Sources of funding	Financial support from Fonds NutsOhra [SNO-T-0702-72] and Stichting Beatrixoord Noord-Nederland
Inclusion criteria	First ever or recurrent stroke (except subarachnoid haemorrhages) between 2 and 8 weeks post-stroke >18 years of age Paralysis or severe paralysis of affected arm scoring 1-3 on the recovery stages of Brunnstrom (1970) No planned date of discharge within 4 weeks
Exclusion criteria	Contraindications for electrical stimulation (e.g. metal implants, cardiac pacemaker) Pre-existing impairments of the affected arm (pre-existing contracture not an exclusion criteria) Severe cognitive deficits and/or severe language comprehension difficulties (defined as <3/4 correct verbal responses and/or <3 correct visual graphic rating scale scores on the AbilityQ (Turner-Stokes and Rusconi, 2003) Moderate to good arm motor control (>18 points on the FMA arm score)
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	Consecutive newly admitted patients on the neurological unit of rehabilitation centres were approached. Patients were initially screened by a physician for inclusion criteria. Exclusion criteria were assessed by a local trial co-ordinator

Intervention(s)	All patients received multidisciplinary stroke rehabilitation (daily training of daily living by rehabilitation nurses, occupational therapists, physiotherapists and speech therapists). Rehabilitation was not standardised, but was delivered in accordance with the recommendations of the Dutch stroke guidelines. Patients underwent additional allocated treatment twice daily for 45 minutes on weekdays for 8 weeks, resulting in 60 hours of positioning. The intervention group received arm stretching positioning with simultaneous four-channel motor amplitude NMES. All procedures were performed by the local trial coordinator or instructed nursing staff. Compliance was monitored through a patient record sheet. Prescription of pain and spasticity medication was also monitored during the 8-week intervention period.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mixed Initial FMA score between 0 and 18
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	No additional information
Comparator	All patients received multidisciplinary stroke rehabilitation (daily training of daily living by rehabilitation nurses, occupational therapists, physiotherapists and speech therapists). Rehabilitation was not standardised, but was delivered in accordance with the recommendations of the Dutch stroke guidelines. Patients underwent additional allocated treatment twice daily for 45 minutes on weekdays for 8 weeks, resulting in 51 hours of NMES/TENS. The control group received a sham stretch procedure with simultaneous sham conventional TENS with minimal sensory stimulation by using a similar treatment

	protocol, electrical stimulator and electrode placement to the intervention group. All procedures were performed by the local trial coordinator or instructed nursing staff. Compliance was monitored through a patient record sheet. Prescription of pain and spasticity medication was also monitored during the 8-week intervention period.
Number of participants	23 in treatment group, 23 in control
Duration of follow-up	20 weeks
Indirectness	None
Additional comments	Analysed with intention to treat (minus 2 dropouts) using multilevel regression analysis. Then analysed again including the 2 dropouts using the last observation carried forward approach (ITT results reported)

Study arms

Neuromuscular Electrical Stimulation (N = 23)
Simultaneous neuromuscular electrical stimulation

Sham (N = 23)
Sham stretching procedure

Characteristics

Arm-level characteristics

Characteristic	Neuromuscular Electrical Stimulation (N = 23)	Sham (N = 23)
% Female	n = 8 ; % = 35	n = 11 ; % = 48
Sample size		

Characteristic	Neuromuscular Electrical Stimulation (N = 23)	Sham (N = 23)
Mean age (SD) (years) Mean (SD)	56.6 (14.2)	58.4 (9.6)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Severity of spasticity FMA Score Sample size	n = NR ; % = NR	n = NR ; % = NR
0-11 Points Sample size	n = 19 ; % = 83	n = 17 ; % = 74
12-18 Points Sample size	n = 4 ; % = 17	n = 6 ; % = 26
Time period after stroke (days) Mean (SD)	43.7 (13.3)	43.3 (15.5)
Type of spasticity Nominal	NR	NR

1

Outcomes

Study timepoints

- Baseline
- 20 week (<6 months. 12 weeks after end of 8-week treatment period)

Continuous Outcomes

Outcome	Neuromuscular Electrical Stimulation, Baseline, N = 17	Neuromuscular Electrical Stimulation, 20 week, N = 17	Sham, Baseline, N = 23	Sham, 20 week, N = 22
Spasticity outcome measures (Leeds Adult/Arm Spasticity Impact Scale) Scale range: 0-100. Final values. Values calculated from individual patient data reported in the additional information for the study. Data available for 17 people in the intervention arm and 22 people in the comparator arm. Mean (SD)	57.9 (19.6)	68.6 (17.6)	62.3 (15.4)	66.7 (20.7)
Physical function - upper limb (Fugl Meyer Upper Extremity) Scale range: 0-66. Final values. Values calculated from individual patient data reported in the additional information for the study. Data available for 17 people in the intervention arm and 22 people in the comparator arm. Mean (SD)	9.4 (8.3)	21.6 (16.1)	9.8 (7.9)	21.7 (16.1)
Pain (Visual analogue scale) Scale range: 0-10. Final values. Values calculated from individual patient data reported in the additional information for	3.9 (2.2)	5.7 (2.9)	4.4 (2.6)	4.4 (2.2)

Outcome	Neuromuscular Electrical Stimulation, Baseline, N = 17	Neuromuscular Electrical Stimulation, 20 week, N = 17	Sham, Baseline, N = 23	Sham, 20 week, N = 22
the study. Data available for 7 people in the intervention arm and 7 people in the comparator arm. Mean (SD)				

Spasticity outcome measures (Leeds Adult/Arm Spasticity Impact Scale) - Polarity - Higher values are better
Physical function - upper limb (Fugl Meyer Upper Extremity) - Polarity - Higher values are better
Pain (Visual analogue scale) - Polarity - Lower values are better

Dichotomous outcomes

Outcome	Neuromuscular Electrical Stimulation, Baseline, N = 24	Neuromuscular Electrical Stimulation, 20 week, N = 24	Sham, Baseline, N = 24	Sham, 20 week, N = 24
Withdrawal due to adverse events Intervention arm: 3 shoulder pain, 1 death, 1 severe shoulder subluxation. Control: 1 readmission to hospital, 1 forearm pain, 2 recurrent stroke. No of events	n = NA ; % = NA	n = 5 ; % = 21	n = NA ; % = NA	n = 4 ; % = 17
Hospitalisation Control: 1 readmission to hospital No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 1 ; % = 4
Additional health care contacts (prescription of pain medication) No of events	n = NA ; % = NA	n = 16 ; % = 73	n = NA ; % = NA	n = 11 ; % = 48

Outcome	Neuromuscular Electrical Stimulation, Baseline, N = 24	Neuromuscular Electrical Stimulation, 20 week, N = 24	Sham, Baseline, N = 24	Sham, 20 week, N = 24
Additional health care contacts (prescription of spasticity medication) No of events	n = NA ; % = NA	n = 5 ; % = 23	n = NA ; % = NA	n = 2 ; % = 9

Withdrawal due to adverse events - Polarity - Lower values are better
Hospitalisation - Polarity - Lower values are better
Additional health care contacts (prescription of pain medication) - Polarity - Lower values are better
Additional health care contacts (prescription of spasticity medication) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

ContinuousOutcomes-Spasticityoutcomemeasures(LeedsAdult/ArmSpasticityImpactScale)-MeanSD-Treatment-Control -t20

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Only concern is adherence to the intervention - suitable detail is given to suggest this is not a major cause for concern)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Physicalfunction-upperlimb(FuglMeyerUpperExtremity)-MeanSD-Treatment-Control -t20

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Only concern is adherence to the intervention - suitable detail is given to suggest this is not a major cause for concern)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Pain(Visualanaloguescale)-MeanSD-Treatment-Control -t20

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Withdrawalduetoadverseevents-NoOfEvents-Treatment-Control -t20

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Only concern is adherence to the intervention - suitable detail is given to suggest this is not a major cause for concern)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Hospitalisation-NoOfEvents-Treatment-Control -t20

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Only concern is adherence to the intervention - suitable detail is given to suggest this is not a major cause for concern)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Additionalhealthcarecontacts(prescriptionofpainmedication)-NoOfEvents-Treatment-Control -t20

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Only concern is adherence to the intervention - suitable detail is given to suggest this is not a major cause for concern)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Additionalhealthcarecontacts(prescriptionofspasticitymedication)-NoOfEvents-Treatment-Control -t20

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Only concern is adherence to the intervention - suitable detail is given to suggest this is not a major cause for concern)*
Overall bias and Directness	Overall Directness	Directly applicable

Ding, 2015

Bibliographic Reference	Ding, X. D.; Zhang, G. B.; Chen, H. X.; Wang, W.; Song, J. H.; Fu, D. G.; Color Doppler ultrasound-guided botulinum toxin type A injection combined with an ankle foot brace for treating lower limb spasticity after a stroke; European Review for Medical & Pharmacological Sciences; 2015; vol. 19 (no. 3); 406-11

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	No additional information
Study dates	October 2006 to October 2012
Sources of funding	No additional information
Inclusion criteria	First onset of stroke confirmed by computed tomography or magnetic resonance imaging and referred to the diagnostic criteria for cerebral infarction and cerebral haemorrhage as per the Guidelines for Diagnosis of Cerebrovascular Diseases developed at the Fourth National Conference on Cerebrovascular Disease in 1995

	Extensor spasm pattern of the lower limbs with spastic varus or foot drop not controlled with traditional physical therapy and medication Composite Spasticity Scale score ≥10 <75 years of age with good cognitive function, agree to participate in the study and sign an informed consent before enrolment
Exclusion criteria	Severe cognitive dysfunction >75 years of age Severe cardiopulmonary dysfunction Flexor spasm pattern of the lower limbs Complications of rheumatoid arthritis, fractures, joint contractures, injury or infection of injection sites, or other diseases that affect limb functions Intake of drugs aggravating neuromuscular junction transmission disorder in the past week Experience of nerve injury or surgical treatment on the target limbs Presence of asthma or allergic reactions Unwillingness to participate
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	Patients with lower limb spasticity recruited from department of neurology
Intervention(s)	BTX-A lyophilized powder (100u/ampule, diluted with 4ml 0.9% saline into 25u/ml) drawn into 1ml syringes. Depth of injection was determined by ultrasound and was administered with an electrical stimulation needle. Needle administered to

	muscle where spasms were most obvious (on an individual basis) with stratified injection according to the thickness of the muscle. Additionally received the same therapy as control group: conventional therapy and rehabilitation training including Bobath concept, range of motion training, walking, massage, physiotherapy and occupational therapy, activities of daily living training etc. *Additional study arm (n=35) receiving same care as treatment group, with additional ankle brace was excluded due to incomparability with control group (no ankle brace given in control)
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Not stated/unclear Composite Spasticity Scale score greater than 10
Subgroup 2: Time period after stroke when trial starts	Not stated/unclear 'First onset of stroke' - course of disease reported in table with no units (could be days or months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb
Population subgroups	No additional information
Comparator	Conventional therapy and rehabilitation training including Bobath concept, range of motion training, walking, massage, physiotherapy and occupational therapy, activities of daily living training etc.
Number of participants	33 in control group

	35 in treatment group
Duration of follow-up	6 months
Indirectness	None
Additional comments	Variance analysis used to compare distribution of sex, disease and hemiplegic side on three groups. T-test or F-test used to compare outcomes between groups. *No indication of method for missing data

Study arms

Intramuscular Onaotulinum Toxin Type A (BOTOX) (N = 35)
Conventional therapy, rehabilitation training and botulinum toxin type A injection

Usual Care (N = 33)
Conventional therapy and rehabilitation training

Characteristics

Study-level characteristics

Characteristic	**Study (N = 68)**
Ethnicity Nominal	NR

Characteristic	Study (N = 68)
Comorbidities Nominal	NR
Severity of spasticity Nominal	NR
Time period after stroke Nominal	NR
Type of spasticity Nominal	NR

Arm-level characteristics

Characteristic	Intramuscular Onaotulinum Toxin Type A (BOTOX) (N = 35)	Usual Care (N = 33)
% Female Sample size	n = 19 ; % = 54	n = 18 ; % = 55
Mean age (SD) (years) Mean (SD)	62.76 (11.52)	64.23 (12.38)

Outcomes

Study timepoints

- Baseline

- 6 month

Continuous Outcomes

Outcome	Intramuscular Onaotulinum Toxin Type A (BOTOX), Baseline, N = 33	Intramuscular Onaotulinum Toxin Type A (BOTOX), 6 month, N = NR	Usual Care, Baseline, N = 35	Usual Care, 6 month, N = NR
Activities of daily living Functional Independence Measure (scale 18-126, final scores) range: Mean (SD)	47.6 (12.1)	72.4 (10.8)	45.7 (10.2)	60.3 (10.5)
Physical function (lower limb) Fugl-Meyer Assessment (scale range 0-34, final scores) Mean (SD)	9.34 (1.37)	17.61 (3.98)	8.42 (2.42)	7.65 (1.07)
Spasticity Clinical Spasticity Influx (Final scores) Mean (SD)	12.1 (1.91)	5.92 (1.12)	12.7 (1.54)	10.12 (1.56)

Activities of daily living - Polarity - Higher values are better
Physical function (lower limb) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Activities of daily living

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Physical function (lower limb)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Spasticity (Clinical Spasticity Influx)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Ding, 2017

Bibliographic Reference	Ding, X.; Huang, L.; Wang, Q.; Liu, Y.; Zhong, J.; Chen, H.; Clinical study of botulinum toxin A injection combined with spasmodic muscle therapeutic instrument on lower limb spasticity in patients with stroke; Experimental & Therapeutic Medicine; 2017; vol. 13 (no. 6); 3319-3326

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Xiangyang No. 1 People's Hospital, China
Study setting	No additional information
Study dates	December 2013 - December 2014
Sources of funding	No additional information
Inclusion criteria	Initial onset, unilateral lesion that was diagnosed by computed tomography or magnetic resonance imaging The course of disease was 3-6 months, aged ≤70 years Without severe cognitive dysfunction (Mini-Mental State Examination, MMSE; ≥24), patients who understood and cooperated with treatment Not injecting botulinum toxin in the prior 2 weeks or the effect of other anti-vasospasm drugs was not obvious

	Partial body paralysis, modified Ashworth scale score of lower limb local muscle spasm ≥2 Vital signs were stable, without other severe liver disease and history of epilepsy
Exclusion criteria	Subarachnoid hemorrhage Patients with multiple cerebral infarction or cerebral hemorrhage Lower limb joint contracture combined with severe heart, liver, kidney disease and infection Patients who took drugs which aggravated neuromuscular junction transmission dysfunction (such as quinine, aminoglycoside antibiotics and morphine) Target limb of patients with nerve injury or who underwent operational treatment (such as nerve block) Patients with infection at injection site
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	Patients with stroke hospitalized in the Department of Neurology
Intervention(s)	**Botulinum Toxin A Injection** Normal saline (4 μl) was used to dilute 100 U BTX-A to reach 25 U/1 ml. The injection was carried out under ultrasonic guidance. The operation was conducted in an ultrasonography room. The ultrasonic probe was stained with appropriate coupling agent, entangled with sterile gum cover and placed at the marked positions of target muscle to be injected. The direction of the probe was perpendicular to the long axis of lower limb, to confirm the position and the range of target muscle through ultrasonography (if necessary, the target muscle was stretched to further confirm the changes of its dynamic constriction) and to clearly display muscle by adjusting the depth and other parameters of ultrasonic apparatus. Tibialis posterior, gastrocnemius muscle and soleus were selected as injection points according to the malformation manifestation of patients. Each target muscle was injected at 3-5 points, with a total dose of 350 units.

	Spasmodic Muscle Therapeutic Instrument The instrument entered into the interface of built-in prescriptions and the prescription parameters were seen on the screen. Fixation of electrodes: output of the two electrode slices from path A was placed at tendons at both ends of spasmodic muscle and the two electrode slices of path B were placed at both ends of the muscle belly of its antagonist (adjoining skin with flannelette surface). After electrodes were ensured to be in good contact with the skin, they could be fixed with a bandage. When starting, the 'on/off' button was pressed, therapeutic instrument showed the 'saved' at the lower right corner of interface, accompanied with buzzing, then entered into working state and displayed working interface. Determination of output current intensity: In case of adjusting output current, it was required to continually ask the reactions of the patients, until the obvious contraction of the patient's muscle. Since the human body is rather sensitive to current at the beginning, the current needed fine adjustment within 1-2 min after being adjusted so as to try to increase output current. In case it was unbearable for patients, the appropriate key was used to decrease the output current. End of treatment: the time was counted during the therapeutic process. When the time showed 0, output stopped and the instrument was buzzing. Treatment course: One treatment course was 10 days, with a total of three treatment courses.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mixed
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb

Population subgroups	No additional information
Comparator	Botulinum toxin A injection alone (administered with same protocol as intervention group)
Number of participants	80; 41 in intervention, 39 in comparator
Duration of follow-up	12 weeks
Indirectness	No further information
Additional comments	Data were analysed by t-test. Countable data were tested by Chi-square.

Study arms

Functional Electrical Stimulation + Onaotulinum Toxic A Injection (BOTOX) (N = 41)
BTX-A injection and spasmodic muscle therapeutic instrument treatment

Onaotulinum Toxin A (BOTOX) Injection Only (N = 39)

Characteristics

Arm-level characteristics

Characteristic	Functional Electrical Stimulation + Onaotulinum Toxic A Injection (BOTOX) (N = 41)	Onaotulinum Toxin A (BOTOX) Injection Only (N = 39)
% Female	n = 20 ; % = 49	n = 19 ; % = 49
Sample size		

Characteristic	Functional Electrical Stimulation + Onaotulinum Toxic A Injection (BOTOX) (N = 41)	Onaotulinum Toxin A (BOTOX) Injection Only (N = 39)
Mean age (SD) (years) Mean (SD)	61.23 (6.2)	62.52 (7.1)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Severity of spasticity Modified Ashworth Scale Mean (SD)	4.19 (0.57)	4.01 (0.52)
Time period after stroke (days) Mean (SD)	127.6 (27.6)	125.5 (31.3)
Type of spasticity Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Functional Electrical Stimulation + Onaotulinum Toxic A Injection (BOTOX), Baseline, N = 41	Functional Electrical Stimulation + Onaotulinum Toxic A Injection (BOTOX), 12 week, N = NR	Onaotulinum Toxin A (BOTOX) Injection Only, Baseline, N = 39	Onaotulinum Toxin A (BOTOX) Injection Only, 12 week, N = NR
Physical function (lower limb) Fugl-Meyer Assessment (scale range 0-34; Final scores) Mean (SD)	7.19 (0.87)	25.16 (0.78)	7.23 (0.77)	16.88 (0.66)
Spasticity Modified Ashworth Scale (scale range 0-4; Final scores) Mean (SD)	4.19 (0.57)	2.26 (0.58)	4.01 (0.52)	2.88 (0.6)
Activities of daily living Modified Barthel Index (scale range 0-100; Final scores) Mean (SD)	24.86 (6.97)	82.17 (10.58)	26.53 (8.75)	61.87 (7.96)

Physical function (lower limb) - Polarity - Higher values are better
Spasticity - Polarity - Lower values are better
Activities of daily living - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Physical function (lower limb)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Spasticity

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Activities of daily living

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Elovic, 2016

Bibliographic Reference	Elovic, E. P.; Munin, M. C.; Kanovsky, P.; Hanschmann, A.; Hiersemenzel, R.; Marciniak, C.; Randomized, placebo-controlled trial of incobotulinumtoxina for upper-limb post-stroke spasticity; Muscle & Nerve; 2016; vol. 53 (no. 3); 415-21

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT0139 2300, EudraCT 2010-023043-15
Study type	Randomised controlled trial (RCT)
Study location	46 sites in the Czech Republic, Germany, Hungary, India, Poland, Russia, and the USA.
Study setting	No additional information
Study dates	September 2011 - February 2014
Sources of funding	Sponsored by Merz Pharmaceuticals GmbH
Inclusion criteria	Adults (age 18–80 years) Spasticity of the upper-limb due to stroke (>3 months after last stroke)

	Participants had to have a flexed elbow, flexed wrist, and clenched fist clinical pattern of spasticity with muscle tone >2 on the Ashworth scale (AS) at each site. Clinical need for a total dose of 400 U of incobotulinumtoxin A into the affected upper-limb, according to the experience-based opinion of the investigator
Exclusion criteria	Spasticity due to etiologies other than stroke Bilateral upper-limb paresis, paralysis, or tetraparesis Fixed contracture in the affected joints Severe atrophy in the target limb muscles Previous treatment with phenol Received treatment with any botulinum toxin formulation in any body region for any indication in the previous 12 months.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	No additional information
Intervention(s)	At baseline, the investigator decided, based on his/her judgment and clinical experience, on 1 primary target clinical pattern (PTCP) that included flexed elbow, flexed wrist, or clenched fist. The PTCP was treated with a predefined fixed dose (flexed elbow, 200 U; flexed wrist, 150 U; clenched fist, 100 U). For the muscle groups other than the PTCP, investigators decided upon the dose and number of injection sites per muscle within predefined ranges, based on their clinical judgment and the individual condition of the subject. Doses complied with the dose ranges approved for incobotulinumtoxin A in Europe. The total dose was fixed at 400 U of incobotulinumtoxin A (using a 2.0 ml per 100 U dilution). The maximum injection volume per injection site was 1.0 ml, corresponding to 50 U of incobotulinumtoxin A. Injections were to be guided by electromyography and/or electrical nerve stimulation. Ultrasound guidance was allowed as a supplementary technique at the discretion of the investigator. All muscle groups with an AS score >2 and the corresponding clinical pattern had to be treated.

Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mixed Ashworth score ≥2
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months) At least 3 months after last stroke (median 28 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	No additional information
Comparator	Same as intervention, with an 8.0ml placebo in place of incobotulinumtoxin A.
Number of participants	259; 171 in intervention, 88 in placebo
Duration of follow-up	48 weeks
Indirectness	No additional information
Additional comments	Ashworth scale assessed using ANCOVA with comparison of least squares mean and missing values imputed according to last observation carried forward approach.

	*Analysis split into full analysis set and safety evaluation set due to changes to protocol after randomization of first 58 participants. All participants were included in safety analysis, and only those randomized after protocol adjustment were included in all other outcome assessments.

Study arms

Incobotulinum toxin A (Xeomin) (N = 171)

Placebo (N = 88)

Characteristics

Arm-level characteristics

Characteristic	**Incobotulinum toxin A (Xeomin) (N = 171)**	**Placebo (N = 88)**
% Female Sample size	n = 74 ; % = 43.3	n = 38 ; % = 43.2
Mean age (SD) Years Mean (SD)	55.4 (11.7)	57.1 (10.8)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 136 ; % = 79.5	n = 73 ; % = 83

Characteristic	Incobotulinum toxin A (Xeomin) (N = 171)	Placebo (N = 88)
Black or African American Sample size	n = 6 ; % = 3.5	n = 2 ; % = 2.3
Asian Sample size	n = 27 ; % = 15.8	n = 13 ; % = 14.8
Other Sample size	n = 2 ; % = 1.2	n = 0 ; % = 0
Comorbidities Nominal	NR	NR
Severity of spasticity Nominal	NR	NR
Time period after stroke (Months) Median (range) Nominal	28	27.8
Time period after stroke (Months) Median (range) Range	4 to 227	3 to 412
Type of spasticity Clinical pattern of upper limb spasticity Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Incobotulinum toxin A (Xeomin) (N = 171)	Placebo (N = 88)
Adducted or internally rotated shoulder Sample size	n = 87 ; % = 50.9	n = 49 ; % = 55.7
Flexed elbow Sample size	n = 171 ; % = 100	n = 88 ; % = 100
Pronated forearm Sample size	n = 151 ; % = 88.3	n = 75 ; % = 85.2
Flexed wrist Sample size	n = 171 ; % = 100	n = 88 ; % = 100
Thumb-in-palm Sample size	n = 104 ; % = 60.8	n = 52 ; % = 59.1
Clenched fist Sample size	n = 171 ; % = 100	n = 88 ; % = 100
Intrinsic plus hand Sample size	n = 22 ; % = 12.9	n = 5 ; % = 5.7

Outcomes

Study timepoints

- Baseline
- 4 week

- 48 week

Continuous Outcomes

Outcome	Incobotulinum toxin A (Xeomin), Baseline, N = 171	Incobotulinum toxin A (Xeomin), 4 week, N = 171	Incobotulinum toxin A (Xeomin), 48 week, N =	Placebo, Baseline, N = 88	Placebo, 4 week, N = 88	Placebo, 48 week, N =
Spasticity Ashworth Scale (scale range 0-4; change scores; least squares mean method) Mean (SE)	NA (NA)	-0.9 (0.06)	NA (NA)	NA (NA)	-0.5 (0.08)	NA (NA)

Spasticity - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	Incobotulinum toxin A (Xeomin), Baseline, N = 171	Incobotulinum toxin A (Xeomin), 4 week, N = 171	Incobotulinum toxin A (Xeomin), 48 week, N = 171	Placebo, Baseline, N = 88	Placebo, 4 week, N = 88	Placebo, 48 week, N = 88
Withdrawal due to Adverse Effects Nominal	NA	NA	0	NA	NA	0
Withdrawal due to Adverse Effects No of events	n = NA ; % = NA	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = NA ; % = NA	n = 0 ; % = 0

Withdrawal due to Adverse Effects - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Spasticity

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Withdrawal due to Adverse Effects

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-WithdrawalduetoAdverseEffects-NoOfEvents-Incobotulinum toxin A (Xeomin)-Placebo-t48

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Esquenazi, 2019

Bibliographic Reference	Esquenazi, A.; Wein, T. H.; Ward, A. B.; Geis, C.; Liu, C.; Dimitrova, R.; Optimal Muscle Selection for OnabotulinumtoxinA Injections in Poststroke Lower-Limb Spasticity: A Randomized Trial; American Journal of Physical Medicine & Rehabilitation; 2019; vol. 98 (no. 5); 360-368

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT01575054
Study type	Randomised controlled trial (RCT)
Study location	60 sites in North America, Europe and Asia
Study setting	Multicenter trial, outpatient follow up.
Study dates	May 23, 2012 and July 1, 2015.
Sources of funding	AE has received research support from and acted as a consultant for Allergan and Ipsen. THW has received research funds from Allergan plc, Merz, National Institutes of Health, Accorda, and Boehringer Ingelheim, acted as a consultant for Allergan plc and Ispen, and received honoraria for accredited CME from Bayer and Boehringer Ingelheim. ABWis a speaker and consultant for Allergan plc and Ipsen. CG has received research support from and is a speaker/consultant for Allergan plc. CL and RD are employees of Allergan plc, and RD holds stock in the company. This study and analysis were sponsored by Allergan plc (Dublin, Ireland). The study sponsor was involved in the study design, data collection, data

	analysis, data interpretation, and writing of the article. Assistance with medical writing was provided by Complete Healthcare Communications, LLC (West Chester, PA).
Inclusion criteria	Adults (18-85 years) with post-stroke lower limb spasticity (MAS score at least 3) with equinus (plantar flexion of the ankle) or equinovarus foot deformity and most recent stroke occuring 3 monthso f more before screening was enrolled. People were botulinum toxin treatment naive or treated with botulinum toxin 20 weeks or more before study day 1 for spasticity in the study limb or 12 weeks or more before study day 1 for other indications.
Exclusion criteria	Lower limb spasticity from a cause other than stroke; spasticity that required treatment in the contralateral leg; fixed contracture of the ankle in the study leg; profound atrophy of the muscles to be injected; previous surgical intervention, phenol block, ethanol block, or muscle afferent block before screening in muscles eligible for treatment or 6 months or less before screening for any other upper- or lower-limb muscles; nonambulatory; had the study limb casted 6 months or less before study day 1 or planned to cast the limb during the double-blind phase; had an infection of the skin, soft tissue, or joint in the injection area; had an intrathecal baclofen pump; were pregnant; had a known allergy or sensitivity to study medication.
Stratification - Type of spasticity	Mixed spasticity While some had focal spasticity, the majority has left sided or right sided spasticity affecting both the arm and leg
Recruitment / selection of participants	No additional information
Intervention(s)	Onabotulinum toxin A N=233 Intramuscular injection of onabotulinum toxin A. 100 U onabotulinum toxin type A, in 0.5 mg of human albumin and 0.9mg of sodium chloride (per the standard dosage forumaltion) was reconstituted in 4mL of preservative-free sterile saline (0.9% sodium chloride) per 100 U vial. The dose for each muscle was evenly distributed across the number of specified injection sites for that muscle, including three sites for each mandatory ankle muscle (i.e. medial and lateral gastrocnemius, soleus, tibialis posterior). An optional dose of 100 U or less was injected into additional muscles (i.e., FDL, flexor digitorum brevis, FHL, extensor hallucis, rectus femoris) if clinically indicated. Muscles were injected using instrumented muscle localisation techniques (i.e., electromyography, electrical stimulation, sonography). People received 400 U of onabotulinum toxin A or less at approximately 12 week intervals (the initial 12 week period was double blind, while time after that was a part of an open label trial. Only the evidence for the double blind period was included in this analysis).

	Concomitant therapy: People receiving muscle relaxants or oral medication for spasticity were on a stable dose for 2 months or more before study day 1. Those receiving antiepileptic medications were on a stable dose for 1 month or more before study day 1. People on a stable program of physical therapy including the use of static or dynamic splints 14 days or more before study treatment could be enrolled if the program was not expected to change during the double-blind phase of the study.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Severe (or MAS 3)
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb
Population subgroups	No additional information
Comparator	Placebo N=235 A matching placebo (0.9% sodium chloride solution only) was injected instead of onabotulinum toxin A.

	Concomitant therapy: People receiving muscle relaxants or oral medication for spasticity were on a stable dose for 2 months or more before study day 1. Those receiving antiepileptic medications were on a stable dose for 1 month or more before study day 1. People on a stable program of physical therapy including the use of static or dynamic splints 14 days or more before study treatment could be enrolled if the program was not expected to change during the double-blind phase of the study.
Number of participants	468
Duration of follow-up	12 weeks (double blind phase only - the study continued in an open blind phase until 60 weeks. However, only the double blind phase will be included in this review).
Indirectness	No additional information.
Additional comments	Intention to treat. Some outcomes are extracted from clinicaltrials.gov where not reported in the rubric of the study. https://clinicaltrials.gov/ct2/show/results/NCT01575054. Date accessed: 08/11/2021. This will be noted in the comments for the outcome.

Study arms

Onabotulinum toxin A (BOTOX) (N = 233)

Intramuscular injection of onabotulinum toxin A. 100 U onabotulinum toxin type A, in 0.5 mg of human albumin and 0.9mg of sodium chloride (per the standard dosage forumaltion) was reconstituted in 4mL of preservative-free sterile saline (0.9% sodium chloride) per 100 U vial. The dose for each muscle was evenly distributed across the number of specified injection sites for that muscle, including three sites for each mandatory ankle muscle (i.e. medial and lateral gastrocnemius, soleus, tibialis posterior). An optional dose of 100 U or less was injected into additional muscles (i.e., FDL, flexor digitorum brevis, FHL, extensor hallucis, rectus femoris) if clinically indicated. Muscles were injected using instrumented muscle localisation techniques (i.e., electromyography, electrical stimulation, sonography). People received 400 U of onabotulinum toxin A or less at approximately 12 week intervals (the initial 12 week period was double blind, while time after that was a part of an open label trial. Only the evidence for the double blind period was included in this analysis). Concomitant therapy: People receiving muscle relaxants or oral medication for spasticity were on a stable dose for 2 months or more before study day 1. Those receiving antiepileptic medications were on a stable dose for 1 month or more before study day 1. People on a stable program of physical therapy including the use of static or dynamic splints 14 days or more before study treatment could be enrolled if the program was not expected to change during the double-blind phase of the study.

Placebo (N = 235)
A matching placebo (0.9% sodium chloride solution only) was injected instead of onabotulinum toxin A. Concomitant therapy: People receiving muscle relaxants or oral medication for spasticity were on a stable dose for 2 months or more before study day 1. Those receiving antiepileptic medications were on a stable dose for 1 month or more before study day 1. People on a stable program of physical therapy including the use of static or dynamic splints 14 days or more before study treatment could be enrolled if the program was not expected to change during the double-blind phase of the study.

Characteristics

Arm-level characteristics

Characteristic	Onabotulinum toxin A (BOTOX) (N = 233)	Placebo (N = 235)
% Female Sample size	n = 85 ; % = 37	n = 80 ; % = 34
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 184 ; % = 79	n = 194 ; % = 82.6
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Severity of spasticity Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Onabotulinum toxin A (BOTOX) (N = 233)	Placebo (N = 235)
Baseline modified Ashworth scale = 3 Sample size	n = 215 ; % = 92.3	n = 219 ; % = 93.2
Time period after stroke (Months) Mean (SD)	67.1 (74.4)	61.6 (73.9)
Type of spasticity Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- Baseline
- 6 week (The study reports most outcomes at 6 weeks rather than the 12 week follow up period for the end of the study. </=6 months.)
- 12 week (Adverse events only. </=6 months.)

Continuous outcomes

Outcome	Onabotulinum toxin A (BOTOX), Baseline, N = 233	Onabotulinum toxin A (BOTOX), 6 week, N = 233	Onabotulinum toxin A (BOTOX), 12 week, N = 233	Placebo, Baseline, N = 235	Placebo, 6 week, N = 235	Placebo, 12 week, N = 235
Spasticity outcome measure (Modified Ashworth Scale) Scale range: 0-5. Mean difference with confidence	NR (NR)	-0.2 (0.01)	NR (NR)	NR (NR)	NA (NA)	NR (NR)

Outcome	Onabotulinum toxin A (BOTOX), Baseline, N = 233	Onabotulinum toxin A (BOTOX), 6 week, N = 233	Onabotulinum toxin A (BOTOX), 12 week, N = 233	Placebo, Baseline, N = 235	Placebo, 6 week, N = 235	Placebo, 12 week, N = 235
intervals calculated from p value (p = 0.010). Mean (p value)						
Pain (numeric rating scale) Scale range: 0-10. Change scores. Data gathered from clinicaltrials.gov reports. Mean (SD)	NR (NR)	-0.8 (2.3)	NR (NR)	NR (NR)	-1.1 (2.38)	NR (NR)

1 Spasticity outcome measure (Modified Ashworth Scale) - Polarity - Lower values are better
2 Pain (numeric rating scale) - Polarity - Lower values are better

3 ***Dichotomous outcome***

Outcome	Onabotulinum toxin A (BOTOX), Baseline, N = 233	Onabotulinum toxin A (BOTOX), 6 week, N = 233	Onabotulinum toxin A (BOTOX), 12 week, N = 233	Placebo, Baseline, N = 235	Placebo, 6 week, N = 235	Placebo, 12 week, N = 235
Withdrawal due to adverse events Reasons not provided. No deaths occurred during the double blind study. No of events	n = NA ; % = NA	n = NA ; % = NA	n = 5 ; % = 2	n = NA ; % = NA	n = NA ; % = NA	n = 2 ; % = 1

4 Withdrawal due to adverse events - Polarity - Lower values are better

5

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuousoutcomes-Spasticityoutcomemeasure(ModifiedAshworthScale)-MeanPValue-Onabotulinum toxin A-Placebo-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Pain(numericratingscale)-MeanSD-Onabotulinum toxin A-Placebo-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcome-Withdrawalduetoadverseevents-NoOfEvents-Onabotulinum toxin A-Placebo-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Ghannadi, 2020

Bibliographic Reference	Ghannadi, S.; Shariat, A.; Ansari, N. N.; Tavakol, Z.; Honarpishe, R.; Dommerholt, J.; Noormohammadpour, P.; Ingle, L.; The Effect of Dry Needling on Lower Limb Dysfunction in Poststroke Survivors; Journal of Stroke & Cerebrovascular Diseases; 2020; vol. 29 (no. 6); 104814

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Iran
Study setting	No additional information
Study dates	No additional information
Sources of funding	No additional information
Inclusion criteria	Aged between 18 and 75 years First hemiplegic ischemic stroke

	Stroke occurred at least six months prior to trial recruitment Able to walk without support for at least 10 meters Modified Modified Ashworth Scale spasticity score ≥1 Ambulation ability ≥3 based on the Functional Ambulation Classification test Taking no antispasmodic drug Able to understand and follow instructions
Exclusion criteria	Contraindications to dry needling Have cognitive alterations History of diabetes or neurological pain Fixed muscle contractures at the ankle joint Currently receiving other treatment protocols
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	No additional information
Intervention(s)	A qualified sports medicine specialist delivered the DN in three sessions spaced across one week, with at least 48 hours between treatment sessions. The protocol was performed using disposable sterile stainless-steel needles (size, 0.30 mm×50 mm) with patients in the prone position with their ankles hanging from the bed. The fast-in and fast-out technique was adopted and each muscle was needled for one minute. The depth of needling was determined according to the clinician’s judgment. For dry needling of the lateral head of the gastrocnemius muscle, a pillow was placed under the patient's leg, and the muscle was needled 2 cm lateral to the middle of the proximal segment of a line connecting the heel

	to the popliteal crease. A point located 2 cm medial to the one third of distal segment was needled for the medial head of the gastrocnemius muscle.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mixed MMAS score ≥1
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	Dry needling
Subgroup 4: For focal and multifocal spasticity only, area affected	not applicable
Population subgroups	No additional information
Comparator	The sham treatment was applied exactly at the same area of the standard dry needling, with blunted dry needling.
Number of participants	24; 12 per group
Duration of follow-up	One-month
Indirectness	No additional information
Additional comments	No additional information

Study arms

Dry Needling (N = 12)

Sham (N = 12)

Characteristics

Arm-level characteristics

Characteristic	**Dry Needling (N = 12)**	**Sham (N = 12)**
% Female Sample size	n = 2 ; % = 17	n = 5 ; % = 42
Mean age (SD) (years) Mean (SD)	58 (6.6)	55.9 (12.1)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Severity of spasticity Nominal	NR	NR

Characteristic	Dry Needling (N = 12)	Sham (N = 12)
Time period after stroke Mean (SD)	23.9 (13.2)	26.4 (12.1)
Type of spasticity Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 1 month

Continuous Outcomes

Outcome	Dry Needling , Baseline, N = 12	Dry Needling , 1 month, N = 12	Sham, Baseline, N = 12	Sham, 1 month, N = 12
Physical Function - Lower Limb (Minutes) 10m Walk (final scores) Mean (SD)	19.09 (18.05)	12.27 (11.88)	20.27 (15.07)	18.42 (15.47)
Spasticity Modified Modified Ashworth Scale (scale range 0-4; final scores) Mean (SD)	2.25 (0.87)	1.33 (0.89)	2.5 (0.67)	2.33 (0.78)

Outcome	Dry Needling , Baseline, N = 12	Dry Needling , 1 month, N = 12	Sham, Baseline, N = 12	Sham, 1 month, N = 12
Activities of daily living Barthel Index (scale range 0-100; final scores) Mean (SD)	67.5 (10.55)	78.75 (10.25)	70.83 (11.44)	73.34 (11.47)

Physical Function - Lower Limb - Polarity - Lower values are better
Spasticity - Polarity - Lower values are better
Activities of daily living - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Activities of Daily Living

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Spasticity

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Physical Function - Lower Limb

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Gong, 2009

Bibliographic Reference	Gong, W.; Zhang, T.; Cui, L.; Yang, Y.; Sun, X.; Electro-acupuncture at Zusanli (ST 36) to improve lower extremity motor function in sensory disturbance patients with cerebral stroke: A randomized controlled study of 240 cases; Neural Regeneration Research; 2009; vol. 4 (no. 11); 935-940

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)

Study location	China
Study setting	The Department of Neurological Rehabilitation, China Rehabilitation Research Centre (inpatient)
Study dates	September 2006 to June 2008
Sources of funding	Supported by the Foundation from China Rehabilitation Research Centre, No. 2007-15.
Inclusion criteria	People diagnosed with cerebral infarction or haemorrhage, and diagnoses were in accordance with diagnosis of Cerebrovascular Disease published by the Chinese Neurosurgery Department Association, Chinese Thoracic Surgery Association in 1996; cerebral infarction or cerebral haemorrhage in the internal carotid system, which was confirmed by computer tomography or magnetic resonance imaging; initial onset, or prior onset but no remaining neurological dysfunction; right-handed; stable disease state, with a Brunnstrom stage of III, IV or V and a functional ambulation classification of three or greater.
Exclusion criteria	Patients with subarachnoid haemorrhage, secondary cerebral stroke, or patients with lumbar disease, bone and joint disease of the lower limbs, other pre-existing nervous system diseases, or disturbed vestibular or cerebellum function; unstable or deteriorating disease state, such as re-occurrence of cerebral infarction or cerebral haemorrhage; recent seizures that were not effectively controlled; primary organ dysfunction or failure, including heart, lung, live or kidney; patients who were not effectively evaluated for neurological functions due to cognitive and communication disorders; all left-handed patients.
Stratification - Type of spasticity	Generalised spasticity Unclear. Is focussed on lower limb spasticity. Treated as generalised as the effect appeared to be aiming at a more broad effect than just this foci.
Recruitment / selection of participants	People who were hospitalised at the Department of Neurological Rehabilitation
Intervention(s)	Electroacupuncture N=124 Activation of the Zusanli (ST 36) electro-acupuncture point. Perpendicular acupuncture 3.0-4.0 cm deep. The acupuncture methods (yunzhen) included perpendicular needling and twirling, with lifting and thrusting needles. An electrode from the 6805 All-type electric acupuncture instrument was connected to the needle handle, when people developed needle sensation (deqi). The other electrode was placed on the ankle-joint (close to the Jiexi acupoint). Once connected, the instrument was turned on. A stimulation pattern, consisting of distant and dense 50-Hz waves, was used to elicit slight

	dorsal extension of the foot. Acupuncture was administered 5 times per week, once per day, 30 minutes per session and the intervention was 6 weeks in total. Concomitant therapy: Drugs related to motor function, such as muscle relaxants, were not administered to either group.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Not stated/unclear
Subgroup 2: Time period after stroke when trial starts	Not stated/unclear
Subgroup 3: Acupuncture/dry needling	Acupuncture
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb
Population subgroups	No additional information
Comparator	Usual care/no treatment N=116 No acupuncture treatment.

	Concomitant therapy: Drugs related to motor function, such as muscle relaxants, were not administered to either group.
Number of participants	240
Duration of follow-up	6 weeks (end of treatment)
Indirectness	No additional information
Additional comments	ITT (no loss to follow up).

Study arms

Electroacupuncture (N = 124)
Activation of the Zusanli (ST 36) electro-acupuncture point. Perpendicular acupuncture 3.0-4.0 cm deep. The acupuncture methods (yunzhen) included perpendicular needling and twirling, with lifting and thrusting needles. An electrode from the 6805 All-type electric acupuncture instrument was connected to the needle handle, when people developed needle sensation (deqi). The other electrode was placed on the ankle-joint (close to the Jiexi acupoint). Once connected, the instrument was turned on. A stimulation pattern, consisting of distant and dense 50-Hz waves, was used to elicit slight dorsal extension of the foot. Acupuncture was administered 5 times per week, once per day, 30 minutes per session and the intervention was 6 weeks in total. Concomitant therapy: Drugs related to motor function, such as muscle relaxants, were not administered to either group.

Usual care/no treatment (N = 116)
No acupuncture treatment. Concomitant therapy: Drugs related to motor function, such as muscle relaxants, were not administered to either group.

1 **Characteristics**

2 ***Arm-level characteristics***

Characteristic	Electroacupuncture (N = 124)	Usual care/no treatment (N = 116)
% Female Sample size	n = 61 ; % = 49	n = 58 ; % = 50
Mean age (SD) (years) Mean (SD)	57.8 (NR)	58.2 (NR)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Severity of spasticity Sample size	n = NR ; % = NR	n = NR ; % = NR
Time period after stroke Sample size	n = NR ; % = NR	n = NR ; % = NR
Type of spasticity Sample size	n = NR ; % = NR	n = NR ; % = NR

3

Outcomes

Study timepoints

- Baseline
- 6 week (End of intervention. </=6 months.)

Continuous outcomes

Outcome	Electroacupuncture, Baseline, N = 124	Electroacupuncture, 6 week, N = 124	Usual care/no treatment, Baseline, N = 116	Usual care/no treatment, 6 week, N = 116
Spasticity outcome measures (Composite Spasticity Scale) Scale range: 0-16 (<7 = no spasm, 7-9 = mild spasms, 10-12 = moderate spasms, 13-16 = severe spasms). Final values. Mean (SD)	10 (2.27)	7.62 (1.45)	9.54 (2.85)	7.31 (1.32)
Physical function - lower limb (Fugl-Meyer lower extremity) Scale range: 0-34. Final values. Mean (SD)	15.43 (2.09)	17.38 (3.59)	15.15 (2.77)	16.13 (3.4)

Spasticity outcome measures (Composite Spasticity Scale) - Polarity - Lower values are better

Physical function - lower limb (Fugl-Meyer lower extremity) - Polarity - Higher values are better

Dichotomous outcome

Outcome	Electroacupuncture, Baseline, N = 124	Electroacupuncture, 6 week, N = 124	Usual care/no treatment, Baseline, N = 116	Usual care/no treatment, 6 week, N = 116
Discontinuation due to adverse events No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Discontinuation due to adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuousoutcomes-Spasticityoutcomemeasures(CompositeSpasticityScale)-MeanSD-Electroacupuncture-Usual care/no treatment-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Physicalfunction-lowerlimb(Fugl-Meyerlowerextremity)-MeanSD-Electroacupuncture-Usual care/no treatment-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcome-Discontinuationduetoadverseevents-NoOfEvents-Electroacupuncture-Usual care/no treatment-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Gracies, 2015

Bibliographic Reference	Gracies, J. M.; Brashear, A.; Jech, R.; McAllister, P.; Banach, M.; Valkovic, P.; Walker, H.; Marciniak, C.; Deltombe, T.; Skoromets, A.; Khatkova, S.; Edgley, S.; Gul, F.; Catus, F.; De Fer, B. B.; Vilain, C.; Picaut, P.; International Abobotulinumtoxin, A. Adult Upper Limb Spasticity Study Group; Safety and efficacy of abobotulinumtoxinA for hemiparesis in adults with upper limb spasticity after stroke or traumatic brain injury: a double-blind randomised controlled trial; Lancet Neurology; 2015; vol. 14 (no. 10); 992-1001

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT01313299

Study type	Randomised controlled trial (RCT)
Study location	Belgium, Czech Republic, France, Hungary, Italy, Poland, Russia, Slovakia and the USA.
Study setting	34 centres, outpatient follow up
Study dates	August 4th 2011 to September 4th 2013
Sources of funding	The manuscript was written with editorial assistance from Martin Gilmour (ESP Bioscience, Crowthorne, UK), funded by Ipsen. The clinical research organisation responsible for the study was INC Research. J-MG served as a consultant and received research grant support from Allergan, Ipsen, and Merz. AB served as a consultant for Concerta, Ipsen, and Allergan, and she has received research and salary support from the National Institute of Neurological Disorders and Stroke. AB was paid by the Wake Forest School of Medicine and the research funds go to the Wake Forest School of Medicine. MB has received training fees and meeting sponsorship from Ipsen and Merz. HW has received consultancy stipends from Merz and Ipsen. CM has received research grant support through her institution from Allergan, Ipsen, and Merz, and was on an advisory board for Ipsen but did not receive any compensation. TD served as a consultant for Allergan, Ipsen, and Merz. SK received training fees and meeting sponsorship from Ipsen, Merz, and Allergan. FG has received compensation from Ipsen for being an advisory board member and support from Allergan for consultancy, speaking engagements, and preceptorship. PM has received compensation for consulting, speakers' bureaus, and conducting clinical trials for Allergan, Ipsen, and Merz. RJ has received grants from the Czech Science Foundation, Czech Ministry of Health, Czech Ministry of Education, and Charles University, Prague and honorarium from Ipsen for consultations and lectures. SE has received grants from Ipsen. All non-Ipsen authors (J-MG, AB, RJ, PM, MB, PV, HW, CM, TD, AS, SK, SE, FG) also received compensation from Ipsen for conducting this clinical trial. BBDF, CV, and PP are employees or contractors of Ipsen, and FC is a former employee of Ipsen. The other authors declare no competing interests.
Inclusion criteria	Age 18-80 years; hemiparesis for at least 6 months after a stroke or traumatic brain injury (<10% had a traumatic brain injury); modified Ashworth scale score in the primary target muscle group of at least 2 for patients who had no previous botulinum toxin A injection in the paretic limb or at least 3 for patients with previous injections of botulinum toxin A in the paretic limb; Disability Assessment Scale score of at least 2 on the principal target of treatment (one of four functional domains: dressing, hygiene, limb position and pain); spasticity angle of at least 10 degrees in the primary target muscle group; mean Modified Frenchay Scale score of 1-8 (over a total possible score of 10).
Exclusion criteria	Major limitations in the passive range of motion in the paretic limb; physiotherapy initiated less than 4 weeks before the expected enrolment; treatment with botulinum toxin A of any type in the previous 4 months; anticipated botulinum toxin A treatment in the lower limb during the study; previous surgery, or administration of alcohol or phenol in the study limb; any medical disorder increasing the risk of botulinum-toxin-A-related adverse events; major neurological impairment (other than hemiparesis) that could negatively affect functional performance.

Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	People were recruited from 34 centres in nine countries.
Intervention(s)	Abobotulinum toxin type A N=162 Abobotulinum toxin type A either 500 U or 1000 U. Each vial was diluted with 2.5mL of saline and the resulting solutions from the two vials were combined in one 5mL syringe. People received 5 mL of reconstituted treatment into the primary target muscle group and at least two other upper limb muscles in a single injection session using electrical stimulation as the only accepted technique for targeting the muscle for consistency within the study. Mandatory volumes for the primary target muscle group were 2-3 mL for elbow flexors (2 mL for brachialis and an additional 1 mL for brachioradialis if injected), 2mL for wrist flexors (1 mL each for flexor carpi radialis and flexor carpi ulnaris), and 2mL for extrinsic finger flexors (1mL each for flexor digitorum profundus and flexor digitorum superficialis). After injecting the primary target muscle group, the remainder of the 5mL was injected in the additional upper limb muscles selected. Concomitant therapy: Presence of absence of concomitant physiotherapy throughout the trial was recorded; if patients received physiotherapy before enrolment, the regimen was kept unchanged during the trial. Concomitant medications were to be maintained at a stable dose during the study.
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)

Population subgroups	No additional information.
Comparator	Placebo N=81 Placebo injection only using the same methods. Concomitant therapy: Presence of absence of concomitant physiotherapy throughout the trial was recorded; if patients received physiotherapy before enrolment, the regimen was kept unchanged during the trial. Concomitant medications were to be maintained at a stable dose during the study.
Number of participants	243
Duration of follow-up	4 weeks
Indirectness	The study includes people with traumatic brain injury. However, from the information reported, this accounts for 23 participants (9.7%) and so the study will not be downgraded for indirectness due to this.
Additional comments	Intention to treat.

Study arms

Abobotulinum toxin type A (N = 162)

Abobotulinum toxin type A either 500 U (n=81) or 1000 U (n=81). Each vial was diluted with 2.5mL of saline and the resulting solutions from the two vials were combined in one 5mL syringe. People received 5 mL of reconstituted treatment into the primary target muscle group and at least two other upper limb muscles in a single injection session using electrical stimulation as the only accepted technique for targeting the muscle for consistency within the study. Mandatory volumes for the primary target muscle group were 2-3 mL for elbow flexors (2 mL for brachialis and an additional 1 mL for brachioradialis if injected), 2mL for wrist flexors (1 mL each for flexor carpi radialis and flexor carpi ulnaris), and 2mL for extrinsic finger flexors (1mL each for flexor digitorum profundus and flexor digitorum superficialis). After injecting the primary target muscle group, the remainder of the 5mL was injected in the additional upper

limb muscles selected. Concomitant therapy: Presence of absence of concomitant physiotherapy throughout the trial was recorded; if patients received physiotherapy before enrolment, the regimen was kept unchanged during the trial. Concomitant medications were to be maintained at a stable dose during the study.

Placebo (N = 81)

Placebo injection only using the same methods. Concomitant therapy: Presence of absence of concomitant physiotherapy throughout the trial was recorded; if patients received physiotherapy before enrolment, the regimen was kept unchanged during the trial. Concomitant medications were to be maintained at a stable dose during the study.

Characteristics

Arm-level characteristics

Characteristic	Abobotulinum toxin type A (N = 162)	Placebo (N = 81)
% Female Sample size	n = 55 ; % = 35	n = 30 ; % = 38
Mean age (SD) (years) Mean (SD)	52.8 (13.3)	52.7 (13.9)
Ethnicity Sample size	n = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Severity of spasticity	3.9 (0.5)	3.9 (0.4)

Characteristic	Abobotulinum toxin type A (N = 162)	Placebo (N = 81)
Mean (SD)		
Time period after stroke Mean (SD)	5.2 (4.3)	4.9 (4.7)
Type of spasticity Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- Baseline
- 4 week (End of intervention. </=6 months)

Continuous outcomes

Outcome	Abobotulinum toxin type A, Baseline, N = 159	Abobotulinum toxin type A, 4 week, N = 159	Placebo, Baseline, N = 79	Placebo, 4 week, N = 79
Spasticity outcome measures (Derived Modified Ashworth Scale) Scale range: 0-5. Change scores. Mean (SD)	3.9 (3.6)	-1.3 (1.1)	3.9 (0.4)	-0.3 (0.6)
Activities of daily living (Disability Assessment Scale) Scale range: 0-3. Change scores.	2.6 (0.5)	-0.7 (0.8)	2.6 (0.5)	-0.5 (0.7)

Outcome	Abobotulinum toxin type A, Baseline, N = 159	Abobotulinum toxin type A, 4 week, N = 159	Placebo, Baseline, N = 79	Placebo, 4 week, N = 79
Mean (SD)				
Person/participant health related quality of life - EQ-5D VAS added after GRADE Mean (SD)	NR (NR)	2.7 (17.4)	NR (NR)	2 (19.6)

Spasticity outcome measures (Derived Modified Ashworth Scale) - Polarity - Lower values are better
Activities of daily living (Disability Assessment Scale) - Polarity - Lower values are better
Person/participant health related quality of life - EQ-5D VAS - Polarity - Higher values are better

Dichotomous outcome

Outcome	Abobotulinum toxin type A, Baseline, N = 159	Abobotulinum toxin type A, 4 week, N = 159	Placebo, Baseline, N = 79	Placebo, 4 week, N = 79
Withdrawal due to adverse events Botulinum toxin 1000U = 1. Botulinum toxin 500U = 1. Placebo = 3. No of events	n = NA ; % = NA	n = 2 ; % = 1	n = NA ; % = NA	n = 3 ; % = 4

Withdrawal due to adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuousoutcomes-Strokeoutcomemeasures(DerivedModifiedAshworthScale)-MeanSD-Abobotulinum toxin type A-Placebo-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Activitiesofdailyliving(DisabilityAssessmentScale)-MeanSD-Abobotulinum toxin type A-Placebo-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcome-Withdrawalduetoadverseevents-NoOfEvents-Abobotulinum toxin type A-Placebo-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Person/participanthealthrelatedqualityoflife-EQ-5DVAS-MeanSD-Abobotulinum toxin type A-Placebo-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Gurcan, 2015

Bibliographic Reference	Gurcan, A.; Selcuk, B.; Onder, B.; Akyuz, M.; Akbal Yavuz, A.; Evaluation of clinical and electrophysiological effects of electrical stimulation on spasticity of plantar flexor muscles in patients with stroke; Turkiye fiziksel tip ve rehabilitasyon dergisi; 2015; vol. 61 (no. 4); 307-313

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	Turkey
Study setting	Inpatients (people hospitalised and enrolled in a rehabilitation program)
Study dates	September 2009 to February 2010.

Sources of funding	No financial support.
Inclusion criteria	People with stroke in subacute and chronic phases who were hospitalised and enrolled in a rehabilitation program; spasticity of the lower extremity, particularly in the plantar flexors; not given any other treatment for spasticity.
Exclusion criteria	Ankle contractures; a history of diabetes mellitus and similar systemic disease that could cause peripheral neuropathy; history and clinical finding of radiculopathy in the lower extremity.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	People hospitalised and enrolled in a rehabilitation program.
Intervention(s)	Transcutaneous electrical nerve stimulation (TENS) N=19 TENS for 20 minutes per day for 15 days (5 days per week for 3 weeks) in additional to conventional treatment. Electrodes were placed in the medial and lateral gastrocnemius bodies about one-hand width below the popliteal line. The Intelect TENS (D) 77724 device was used. This device had dual-channel outputs, and the stretch of current could be independently adjusted for each channel. For electrical stimulation, biphasic square waves with a frequency of 20 Hz and current width of 300 microseconds were used. The strength of the applied current was 60-80 Ma, similar to that used for contractions. Concomitant therapy: All people were administered conventional treatment methods (range of joint motion, progressive resistive, stretching and neurophysiological exercises).
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Moderate (or MAS 2)

Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb
Population subgroups	No additional information.
Comparator	Usual care/no treatment N=13 Conventional treatment only. Concomitant therapy: All people were administered conventional treatment methods (range of joint motion, progressive resistive, stretching and neurophysiological exercises).
Number of participants	32
Duration of follow-up	3 weeks (end of intervention)
Indirectness	No additional information
Additional comments	ITT

1

Study arms

Transcutaneous electrical nerve stimulation (TENS) (N = 19)

TENS for 20 minutes per day for 15 days (5 days per week for 3 weeks) in additional to conventional treatment. Electrodes were placed in the medial and lateral gastrocnemius bodies about one-hand width below the popliteal line. The Intelect TENS (D) 77724 device was used. This device had dual-channel outputs, and the stretch of current could be independently adjusted for each channel. For electrical stimulation, biphasic square waves with a frequency of 20 Hz and current width of 300 microseconds were used. The strength of the applied current was 60-80 Ma, similar to that used for contractions. Concomitant therapy: All people were administered conventional treatment methods (range of joint motion, progressive resistive, stretching and neurophysiological exercises).

Usual care/no treatment (N = 13)

Conventional treatment only. Concomitant therapy: All people were administered conventional treatment methods (range of joint motion, progressive resistive, stretching and neurophysiological exercises).

Characteristics

Arm-level characteristics

Characteristic	**Transcutaneous electrical nerve stimulation (TENS) (N = 19)**	**Usual care/no treatment (N = 13)**
% Female Sample size	n = 5 ; % = 26	n = 9 ; % = 69
Mean age (SD) (years) Mean (SD)	57.42 (12.51)	58.38 (12.59)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Transcutaneous electrical nerve stimulation (TENS) (N = 19)	Usual care/no treatment (N = 13)
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Severity of spasticity Mean (SD)	2.42 (2.44)	2.69 (1.28)
Time period after stroke (Months) Mean (SD)	10.89 (16.85)	17.69 (20.96)
Type of spasticity Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- Baseline
- 3 week (End of intervention. </=6 months.)

Continuous outcomes

Outcome	Transcutaneous electrical nerve stimulation (TENS), Baseline, N = 19	Transcutaneous electrical nerve stimulation (TENS), 3 week, N = 19	Usual care/no treatment, Baseline, N = 13	Usual care/no treatment, 3 week, N = 13
Spasticity outcome measures (Modified Ashworth Scales) Scale range: 0-5. Final values. Mean (SD)	2.42 (2.44)	2.33 (2.41)	2.69 (1.28)	2.65 (1.38)
Activities of daily living (functional independence measure) Scale range: 18-126. Final values. Mean (SD)	83.1 (22.23)	86.1 (21.62)	87.7 (26.88)	89.53 (28.13)
Physical function - lower limb (10-m walking scale) (seconds? - based on how test is usually reported) Final values Mean (SD)	28.37 (10.9)	24.37 (8.12)	36.5 (30.04)	29.69 (23.7)

Spasticity outcome measures (Modified Ashworth Scales) - Polarity - Lower values are better
Activities of daily living (functional independence measure) - Polarity - Higher values are better
Physical function - lower limb (10-m walking scale) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuousoutcomes-Spasticityoutcomemeasures(ModifiedAshworthScales)-MeanSD-Transcutaneous electrical nerve stimulation (TENS)-Usual care/no treatment-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Activitiesofdailyliving(functionalindependencemeasure)-MeanSD-Transcutaneous electrical nerve stimulation (TENS)-Usual care/no treatment-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Physicalfunction-lowerlimb(10-mwalkingscale)-MeanSD-Transcutaneous electrical nerve stimulation (TENS)-Usual care/no treatment-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Hesse, 2012

Bibliographic Reference	Hesse, S.; Mach, H.; Frohlich, S.; Behrend, S.; Werner, C.; Melzer, I.; An early botulinum toxin A treatment in subacute stroke patients may prevent a disabling finger flexor stiffness six months later: a randomized controlled trial; Clinical Rehabilitation; 2012; vol. 26 (no. 3); 237-45

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT180311
Study type	Randomised controlled trial (RCT)
Study location	Germany.
Study setting	An inpatient rehabilitation centre focused on early stroke rehabilitation.
Study dates	Conducted over 12 months (no additional information)
Sources of funding	The Verein zur Forderung der Hirnforschung und Rehabilitation e.V. supported the study.
Inclusion criteria	Age <80 years; first time supratentorial stroke; 4-6 weeks after stroke onset; participating in a comprehensive inpatient rehabilitation programme; at least wheelchair mobilized and partly independent in the basic activities of living with a Barthel Index (0-100) >25; non-functional upper extremity with a Fugl-Meyer motor score (0-66) <20; no (MRC 0) volitional wrist or finger extensor activity; beginning finger and/or wrist flexor stiffness with a Modified Ashworth Scale score (0-5) of 1 or 2,

	tested when supine by an experienced rater in the morning; able to give written informed consent, approved by the local ethical committee.
Exclusion criteria	Oral antispastic medication prescribed at study onset; severe neglect syndrome, tested clinically and with the help of a cancellation test.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	People in an inpatient rehabilitation centre focused on early stroke rehabilitation.
Intervention(s)	Botulinum toxin type A (Xeomin) N=9 150 units botulinum toxin type A (Xeomin) injected into the deep and superficial finger (100 units) and wrist flexors (50 units). Ultrasound-guided injections. Rapid passive mobilisation of the wrist and finger joints for 20-30 minutes immediately followed the injection. Concomitant therapy: Comprehensive rehabilitation was provided to both groups. This consisted of a multiprofessional motor rehabilitation programme, including physiotherapy (45 minutes every workday) and occupational therapy (30 minutes every workday). Speech therapy, neuropsychology and spa therapy were administered according to individual needs. The therapy combined elements of the neurodevelopment technique and motor relearning programme.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mild (or MAS 1)
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)

Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	No additional information.
Comparator	Usual care/no treatment N=9 No injections. Concomitant therapy: Comprehensive rehabilitation was provided to both groups. This consisted of a multiprofessional motor rehabilitation programme, including physiotherapy (45 minutes every workday) and occupational therapy (30 minutes every workday). Speech therapy, neuropsychology and spa therapy were administered according to individual needs. The therapy combined elements of the neurodevelopment technique and motor relearning programme.
Number of participants	18
Duration of follow-up	4 weeks, 6 months.
Indirectness	No additional information
Additional comments	Unclear method of analysis. Appears to be per protocol.

1

Study arms

Incootulinum toxin type A (Xeomin) (N = 9)
150 units botulinum toxin type A (Xeomin) injected into the deep and superficial finger (100 units) and wrist flexors (50 units). Ultrasound-guided injections. Rapid passive mobilisation of the wrist and finger joints for 20-30 minutes immediately followed the injection. Concomitant therapy: Comprehensive rehabilitation was provided to both groups. This consisted of a multiprofessional motor rehabilitation programme, including physiotherapy (45 minutes every workday) and occupational therapy (30 minutes every workday). Speech therapy, neuropsychology and spa therapy were administered according to individual needs. The therapy combined elements of the neurodevelopment technique and motor relearning programme.

Usual care/no treatment (N = 9)
No injections. Concomitant therapy: Comprehensive rehabilitation was provided to both groups. This consisted of a multiprofessional motor rehabilitation programme, including physiotherapy (45 minutes every workday) and occupational therapy (30 minutes every workday). Speech therapy, neuropsychology and spa therapy were administered according to individual needs. The therapy combined elements of the neurodevelopment technique and motor relearning programme.

Characteristics

Arm-level characteristics

Characteristic	Incootulinum toxin type A (Xeomin) (N = 9)	Usual care/no treatment (N = 9)
% Female Sample size	n = 6 ; % = 67	n = 6 ; % = 67
Mean age (SD) (years) Mean (SD)	57 (11)	66 (11)
Ethnicity	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Incootulinum toxin type A (Xeomin) (N = 9)	Usual care/no treatment (N = 9)
Sample size		
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Severity of spasticity Mean (SD)	1.7 (0.5)	1.6 (0.5)
Time period after stroke (Weeks) Mean (SD)	5.8 (1.3)	5.6 (1.1)
Type of spasticity Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- Baseline
- 6 month (</=6 months)

Continuous outcomes

Outcome	Incootulinum toxin type A (Xeomin), Baseline, N = 9	Incootulinum toxin type A (Xeomin), 6 month, N = 9	Usual care/no treatment, Baseline, N = 9	Usual care/no treatment, 6 month, N = 8
Spasticity outcome measures (modified Ashworth scale) Scale range: 0-5. Final values. Mean (SD)	1.7 (0.5)	1.4 (0.7)	1.6 (0.5)	2.4 (0.9)
Activities of daily living (disability scale) Scale range: 0-24. Final values. Mean (SD)	9.1 (3.2)	5.7 (3.2)	9.2 (2.9)	10.9 (4.4)
Physical function - upper limb (Fugl-Meyer score) Scale range: 0-66. Final values. Mean (SD)	6.6 (3.9)	13.1 (4.9)	7.3 (2.7)	12.8 (5.8)

Spasticity outcome measures (modified Ashworth scale) - Polarity - Lower values are better

Activities of daily living (disability scale) - Polarity - Lower values are better

Physical function - upper limb (Fugl-Meyer score) - Polarity - Higher values are better

Discontinuation outcome

Outcome	Incootulinum toxin type A (Xeomin), Baseline, N = 9	Incootulinum toxin type A (Xeomin), 6 month, N = 9	Usual care/no treatment, Baseline, N = 9	Usual care/no treatment, 6 month, N = 9
Discontinuation due to adverse events No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Discontinuation due to adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuousoutcomes-Spasticityoutcomemeasures(modifiedAshworthscale)-MeanSD-Botulinum toxin type A (Xeomin)-Usual care/no treatment-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Activitiesofdailyliving(disabilityscale)-MeanSD-Botulinum toxin type A (Xeomin)-Usual care/no treatment-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Physicalfunction-upperlimb(Fugl-Meyerscore)-MeanSD-Botulinum toxin type A (Xeomin)-Usual care/no treatment-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Discontinuationoutcome-Discontinuationduetoadverseevents-NoOfEvents-Botulinum toxin type A (Xeomin)-Usual care/no treatment-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Hesse, 1998

Bibliographic Reference	Hesse, S.; Reiter, F.; Konrad, M.; Jahnke, M. T.; Botulinum toxin type A and short-term electrical stimulation in the treatment of upper limb flexor spasticity after stroke: a randomized, double-blind, placebo-controlled trial; Clinical Rehabilitation; 1998; vol. 12 (no. 5); 381-8

Study details

Secondary publication of another included	No additional information.

study- see primary study for details	
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	Germany
Study setting	Outpatient clinic
Study dates	No additional information
Sources of funding	This study was supported by a grant of Speywood Pharmaceuticals Ltd, UK, who supplied the botulinum toxin and placebo used in this study.
Inclusion criteria	At least 6 and no more than 12 months after stroke and to demonstrate severe upper limb flexor spasticity of at least grade 3 as measured by the modified Ashworth Score, tested for the elbow, wrist and finger joints. The affected extremity had to be nonfunctional with no possibility of any selective movement except protracting the shoulder girdle.
Exclusion criteria	People with fixed contractures; previous treatment with botulinum toxin type A, neurolytic or surgical procedures in the study limb; severe impairments of cognition and communication.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	No additional information.
Intervention(s)	Combination (Botulinum toxin type A [Dysport] and neuromuscular electrical stimulation [NMES]) N=6 1000 units of Botulinum Toxin type A (Dysport) (500 unit vials reconsistuted with 0.9% normal saline to make a total volume of 2.5mL per vial) injected under EMG guidance into the Mm. biceps brachii, brachialis (each 250 units), flexor carpi ulnaris,

	flexor carpi radialis, flexor digitorum profundus et superficialis (each 125 units) at two sites per muscle, close to the motor point. Alternating electrical stimulation of both the arm (Mm. biceps and triceps) and forearm (wrist and finger flexors and extensors) muscles for half an hour three times per day during the three days following the injection. An IJS dual channel stimulator with continuous trains (3s) of charge-balanced constant current pulses (20 Hz, 200 microseconds, 50-90 mA) was used for stimulation. Pairs of 5x5 self-adhesive PALS surface electrodes were attached either to the Mm. biceps and triceps brachii or to the wrist and finger flexors and extensors, the stimulus amplitude was adjusted so that a minimal movement effect in the elbow or wrist joints was visible. Concomitant therapy: All received an average of two physiotherapeutic treatment sessions for half an hour per week, which did not change during the course of the study. The amount of therapy did not differ across the groups and was unanimously applied by the Bobath techniques. None of the patients received a concomitant anti-spastic medication during the study. Botulinum toxin type A (Dysport) N=6 1000 units of Botulinum Toxin type A (Dysport) (500 unit vials reconsistuted with 0.9% normal saline to make a total volume of 2.5mL per vial) injected under EMG guidance into the Mm. biceps brachii, brachialis (each 250 units), flexor carpi ulnaris, flexor carpi radialis, flexor digitorum profundus et superficialis (each 125 units) at two sites per muscle, close to the motor point. Concomitant therapy: All received an average of two physiotherapeutic treatment sessions for half an hour per week, which did not change during the course of the study. The amount of therapy did not differ across the groups and was unanimously applied by the Bobath techniques. None of the patients received a concomitant anti-spastic medication during the study. Neuromuscular electrical stimulation and sham injection N=6

	0.9% normal saline injected under EMG guidance into the Mm. biceps brachii, brachialis, flexor carpi ulnaris, flexor carpi radialis, flexor digitorum profundus et superficialis at two sites per muscle, close to the motor point. Alternating electrical stimulation of both the arm (Mm. biceps and triceps) and forearm (wrist and finger flexors and extensors) muscles for half an hour three times per day during the three days following the injection. An IJS dual channel stimulator with continuous trains (3s) of charge-balanced constant current pulses (20 Hz, 200 microseconds, 50-90 mA) was used for stimulation. Pairs of 5x5 self-adhesive PALS surface electrodes were attached either to the Mm. biceps and triceps brachii or to the wrist and finger flexors and extensors, the stimulus amplitude was adjusted so that a minimal movement effect in the elbow or wrist joints was visible. Concomitant therapy: All received an average of two physiotherapeutic treatment sessions for half an hour per week, which did not change during the course of the study. The amount of therapy did not differ across the groups and was unanimously applied by the Bobath techniques. None of the patients received a concomitant anti-spastic medication during the study.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Severe (or MAS 3)
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)

Population subgroups	No additional information
Comparator	Combination vs. individual components Botulinum toxin vs. placebo Placebo injection N=6 0.9% normal saline injected under EMG guidance into the Mm. biceps brachii, brachialis, flexor carpi ulnaris, flexor carpi radialis, flexor digitorum profundus et superficialis at two sites per muscle, close to the motor point. Concomitant therapy: All received an average of two physiotherapeutic treatment sessions for half an hour per week, which did not change during the course of the study. The amount of therapy did not differ across the groups and was unanimously applied by the Bobath techniques. None of the patients received a concomitant anti-spastic medication during the study.
Number of participants	24
Duration of follow-up	12 weeks (follow up at 2 weeks, 6 weeks and 12 weeks)
Indirectness	No additional information
Additional comments	No additional information (no discontinuations).

1

Study arms

Combination (Onaotulinum toxin type A [Dysport] and neuromuscular electrical stimulation [NMES]) (N = 6)
1000 units of Botulinum Toxin type A (Dysport) (500 unit vials reconsistuted with 0.9% normal saline to make a total volume of 2.5mL per vial) injected under EMG guidance into the Mm. biceps brachii, brachialis (each 250 units), flexor carpi ulnaris, flexor carpi radialis, flexor digitorum profundus et superficialis (each 125 units) at two sites per muscle, close to the motor point. Alternating electrical stimulation of both the arm (Mm. biceps and triceps) and forearm (wrist and finger flexors and extensors) muscles for half an hour three times per day during the three days following the injection. An IJS dual channel stimulator with continuous trains (3s) of charge-balanced constant current pulses (20 Hz, 200 microseconds, 50-90 mA) was used for stimulation. Pairs of 5x5 self-adhesive PALS surface electrodes were attached either to the Mm. biceps and triceps brachii or to the wrist and finger flexors and extensors, the stimulus amplitude was adjusted so that a minimal movement effect in the elbow or wrist joints was visible. Concomitant therapy: All received an average of two physiotherapeutic treatment sessions for half an hour per week, which did not change during the course of the study. The amount of therapy did not differ across the groups and was unanimously applied by the Bobath techniques. None of the patients received a concomitant anti-spastic medication during the study.

Onabotulinum toxin type A (Dysport) (N = 6)
1000 units of Botulinum Toxin type A (Dysport) (500 unit vials reconsistuted with 0.9% normal saline to make a total volume of 2.5mL per vial) injected under EMG guidance into the Mm. biceps brachii, brachialis (each 250 units), flexor carpi ulnaris, flexor carpi radialis, flexor digitorum profundus et superficialis (each 125 units) at two sites per muscle, close to the motor point. Concomitant therapy: All received an average of two physiotherapeutic treatment sessions for half an hour per week, which did not change during the course of the study. The amount of therapy did not differ across the groups and was unanimously applied by the Bobath techniques. None of the patients received a concomitant anti-spastic medication during the study.

Neuromuscular electrical stimulation and sham injection (N = 6)
0.9% normal saline injected under EMG guidance into the Mm. biceps brachii, brachialis, flexor carpi ulnaris, flexor carpi radialis, flexor digitorum profundus et superficialis at two sites per muscle, close to the motor point. Alternating electrical stimulation of both the arm (Mm. biceps and triceps) and forearm (wrist and finger flexors and extensors) muscles for half an hour three times per day during the three days following the injection. An IJS dual channel stimulator with continuous trains (3s) of charge-balanced constant current pulses (20 Hz, 200 microseconds, 50-90 mA) was used for stimulation. Pairs of 5x5 self-adhesive PALS surface electrodes were attached either to the Mm. biceps and triceps brachii or to the wrist and finger flexors and extensors, the stimulus amplitude was

adjusted so that a minimal movement effect in the elbow or wrist joints was visible. Concomitant therapy: All received an average of two physiotherapeutic treatment sessions for half an hour per week, which did not change during the course of the study. The amount of therapy did not differ across the groups and was unanimously applied by the Bobath techniques. None of the patients received a concomitant anti-spastic medication during the study.

Placebo injection (N = 6)

0.9% normal saline injected under EMG guidance into the Mm. biceps brachii, brachialis, flexor carpi ulnaris, flexor carpi radialis, flexor digitorum profundus et superficialis at two sites per muscle, close to the motor point. Concomitant therapy: All received an average of two physiotherapeutic treatment sessions for half an hour per week, which did not change during the course of the study. The amount of therapy did not differ across the groups and was unanimously applied by the Bobath techniques. None of the patients received a concomitant anti-spastic medication during the study.

Characteristics

Study-level characteristics

Characteristic	**Study (N = 24)**
% Female Sample size	n = 5 ; % = 21
Mean age (SD) Range	32 to 73
Mean age (SD) Mean (SD)	52.3 (NR)
Ethnicity Sample size	n = NR ; % = NR

Characteristic	Study (N = 24)
Comorbidities Sample size	n = NR ; % = NR
Severity of spasticity Sample size	n = NR ; % = NR
Time period after stroke (Months) Range	6 to 11
Time period after stroke (Months) Mean (SD)	7.45 (NR)
Type of spasticity Sample size	n = NA ; % = NA

Outcomes

Study timepoints

- Baseline
- 12 week (</=6 months)

Continuous outcomes

Outcome	Combination (Onaotulinum toxin type A [Dysport] and neuromuscular electrical stimulation [NMES]), Baseline, N = 6	Combination (Onaotulinum toxin type A [Dysport] and neuromuscular electrical stimulation [NMES]), 12 week, N = 6	Onabotulinum toxin type A (Dysport), Baseline, N = 6	Onabotulinum toxin type A (Dysport), 12 week, N = 6	Neuromuscular electrical stimulation and sham injection, Baseline, N = 6	Neuromuscular electrical stimulation and sham injection, 12 week, N = 6	Placebo injection, Baseline, N = 6	Placebo injection, 12 week, N = 6
Spasticity outcome measures (modified Ashworth scale) Scale range: 0-5. Final values. Reported values for elbow, wrist and finger separately. Pooled together in the analysis. Mean (SD)	3.61 (0.89)	2.44 (0.66)	3.5 (1.21)	3.22 (1.18)	3.61 (1.04)	3.11 (1.13)	3.11 (0.93)	3.17 (0.95)

Spasticity outcome measures (modified Ashworth scale) - Polarity - Lower values are better

Dichotomous outcomes

Outcome	Combination (Onaotulinum toxin type A [Dysport] and neuromuscular electrical stimulation [NMES]), Baseline, N = 6	Combination (Onaotulinum toxin type A [Dysport] and neuromuscular electrical stimulation [NMES]), 12 week, N = 6	Onabotulinum toxin type A (Dysport), Baseline, N = 6	Onabotulinum toxin type A (Dysport), 12 week, N = 6	Neuromuscular electrical stimulation and sham injection, Baseline, N = 6	Neuromuscular electrical stimulation and sham injection, 12 week, N = 6	Placebo injection, Baseline, N = 6	Placebo injection, 12 week, N = 6
Withdrawal due to adverse events No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Withdrawal due to adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomousoutcomes-Withdrawalduetoadverseevents-CombinationcomparedtobotulinumtoxintypeA-NoOfEvents-Combination (Botulinum toxin type A [Dysport] and neuromuscular electrical stimulation [NMES])-Botulinum toxin type A (Dysport)-Neuromuscular electrical stimulation and sham injection-Placebo injection-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Withdrawalduetoadverseevents-CombinationcomparedtoNMES-NoOfEvents-Combination (Botulinum toxin type A [Dysport] and neuromuscular electrical stimulation [NMES])-Botulinum toxin type A (Dysport)-Neuromuscular electrical stimulation and sham injection-Placebo injection-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Withdrawalduetoadverseevents-BotulinumtoxintypeAcomparedtoNMES-NoOfEvents-Combination (Botulinum toxin type A [Dysport] and neuromuscular electrical stimulation [NMES])-Botulinum toxin type A (Dysport)-Neuromuscular electrical stimulation and sham injection-Placebo injection-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Withdrawalduetoadverseevents-BotulinumtoxintypeAcomparedtoplacebo-NoOfEvents-Combination (Botulinum toxin type A [Dysport] and neuromuscular electrical stimulation [NMES])-Botulinum toxin type A (Dysport)-Neuromuscular electrical stimulation and sham injection-Placebo injection-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Spasticityoutcomemeasures(modifiedAshworthscale)-CombinationcomparedtobotulinumtoxintypeA-MeanSD-Combination (Botulinum toxin type A [Dysport] and neuromuscular electrical stimulation [NMES])-Botulinum toxin type A (Dysport)-Neuromuscular electrical stimulation and sham injection-Placebo injection-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Spasticityoutcomemeasures(modifiedAshworthscale)-CombinationcomparedtoNMES-MeanSD-Combination (Botulinum toxin type A [Dysport] and neuromuscular electrical stimulation [NMES])-Botulinum toxin type A (Dysport)-Neuromuscular electrical stimulation and sham injection-Placebo injection-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Spasticityoutcomemeasures(modifiedAshworthscale)-BotulinumtoxintypeAcomparedtoNMES-MeanSD-Combination (Botulinum toxin type A [Dysport] and neuromuscular electrical stimulation [NMES])-Botulinum toxin type A (Dysport)-Neuromuscular electrical stimulation and sham injection-Placebo injection-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Spasticityoutcomemeasures(modifiedAshworthscale)-BotulinumtoxintypeAcomparedtoplacebo-MeanSD-Combination (Botulinum toxin type A [Dysport] and neuromuscular electrical stimulation [NMES])-Botulinum toxin type A (Dysport)-Neuromuscular electrical stimulation and sham injection-Placebo injection-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Hu, 2015

Bibliographic Reference	Hu, X. L.; Tong, R. K.; Ho, N. S.; Xue, J. J.; Rong, W.; Li, L. S.; Wrist Rehabilitation Assisted by an Electromyography-Driven Neuromuscular Electrical Stimulation Robot After Stroke; Neurorehabilitation & Neural Repair; 2015; vol. 29 (no. 8); 767-76

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)

Study location	Hong Kong
Study setting	People were screened from local districts (outpatient follow up)
Study dates	No additional information
Sources of funding	The study was financially supported by a GRF grant (PolyU 5318/09E) from the Research Grants Council and an ITF grant (ITS/033/12) from the Innovation and Technology Commission of the Hong Kong Special Administrative Region.
Inclusion criteria	Had unilateral ischaemic brain injury or intracerebral haemorrhage at least 6 months after the onset of single stroke without other diagnosed neurological deficits; had moderate level of motor impairment in the affected upper limb, assessed by Fugl-Meyer Assessment (9 < shoulder/elbow < 27; 6 < wrist/hand <18); had enough cognition to be able to follow the training protocol as assessed by the Mini Mental State Examination (MMSE >21); had detectable EMG signals (3 times of the standard deviation above the baseline) from the flexor carpi radialis and extensor carpi radialis.
Exclusion criteria	No additional information
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	No additional information
Intervention(s)	Neuromuscular electrical stimulation (NMES) N=11 Electromyography (EMG)-driven NMES robot for seven weeks. The NMES group received the interactive assistance from both the motor and the NMES parts at the same time during the tracking. In the case when robot gave 50% support, and NMES provided 50% assistance, the assistance from the motor was the half value as for the robot group; the assistance from the NMES was electrical stimulation on the agonist muscle with the intensity proportional to the voluntary EMG amplitude of the muscle. The maximum assistance from the NMES was the half value of the threshold to evoke maximal wrist flexion and extension when the forearm was put horizontally on a table with the wrist joint starts at its neutral position. Concomitant therapy: For both groups, each recruited subject received the wrist training with an intensity of 3 to 5 sessions/week for 20 sessions, finished within 7 weeks. In a training session, a subject was seated in front of a computer screen with the paretic arm attached on the robotic system, the shoulder abducted at around 80 degrees and extended 0 degrees, and the elbow flexed at 90 degrees. The wrist joint was in line with the rotation center of the motor system, and

	the palm was mounted on a manipulandum which could rotate with the motor. The shoulder and the forearm were fixed by belts during the experiment. The subject was instructed to conduct tracking tasks by wrist flexion/extension when following a moving cursor on the screen with a constant angular velocity of 10 degrees/seconds at the wrist joint, with a target to minimize the difference between the target and the actual wrist positions indicated by cursors as much as possible.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mild (or MAS 1)
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	No additional information
Comparator	Usual care/no treatment N=15 EMG-drive robot only (no NMES). Concomitant therapy: For both groups, each recruited subject received the wrist training with an intensity of 3 to 5 sessions/week for 20 sessions, finished within 7 weeks. In a training session, a subject was seated in front of a computer

	screen with the paretic arm attached on the robotic system, the shoulder abducted at around 80 degrees and extended 0 degrees, and the elbow flexed at 90 degrees. The wrist joint was in line with the rotation center of the motor system, and the palm was mounted on a manipulandum which could rotate with the motor. The shoulder and the forearm were fixed by belts during the experiment. The subject was instructed to conduct tracking tasks by wrist flexion/extension when following a moving cursor on the screen with a constant angular velocity of 10 degrees/seconds at the wrist joint, with a target to minimize the difference between the target and the actual wrist positions indicated by cursors as much as possible.
Number of participants	26
Duration of follow-up	3 months
Indirectness	No additional information
Additional comments	ITT (no discontinuations)

Study arms

Neuromuscular electrical stimulation (NMES) (N = 11)
Electromyography (EMG)-driven NMES robot for seven weeks. The NMES group received the interactive assistance from both the motor and the NMES parts at the same time during the tracking. In the case when robot gave 50% support, and NMES provided 50% assistance, the assistance from the motor was the half value as for the robot group; the assistance from the NMES was electrical stimulation on the agonist muscle with the intensity proportional to the voluntary EMG amplitude of the muscle. The maximum assistance from the NMES was the half value of the threshold to evoke maximal wrist flexion and extension when the forearm was put horizontally on a table with the wrist joint starts at its neutral position. Concomitant therapy: For both groups, each recruited subject received the wrist training with an intensity of 3 to 5 sessions/week for 20 sessions, finished within 7 weeks. In a training session, a subject was seated in front of a computer screen with the paretic arm attached on the robotic system, the shoulder abducted at around 80 degrees and extended 0 degrees, and the elbow flexed at 90 degrees. The wrist joint was in line with the rotation center of the motor system, and the palm was mounted on a manipulandum which could rotate with the motor. The shoulder and the forearm were fixed by belts during the experiment. The subject was instructed to conduct tracking tasks by wrist flexion/extension when following a moving cursor on the screen with a constant angular velocity of 10 degrees/seconds at the wrist joint, with a target to minimize the difference between the target and the actual wrist positions indicated by cursors as much as possible.

Usual care/no treatment (N = 15)
EMG-drive robot only (no NMES). Concomitant therapy: For both groups, each recruited subject received the wrist training with an intensity of 3 to 5 sessions/week for 20 sessions, finished within 7 weeks. In a training session, a subject was seated in front of a computer screen with the paretic arm attached on the robotic system, the shoulder abducted at around 80 degrees and extended 0 degrees, and the elbow flexed at 90 degrees. The wrist joint was in line with the rotation center of the motor system, and the palm was mounted on a manipulandum which could rotate with the motor. The shoulder and the forearm were fixed by belts during the experiment. The subject was instructed to conduct tracking tasks by wrist flexion/extension when following a moving cursor on the screen with a constant angular velocity of 10 degrees/seconds at the wrist joint, with a target to minimize the difference between the target and the actual wrist positions indicated by cursors as much as possible.

Characteristics

Arm-level characteristics

Characteristic	**Neuromuscular electrical stimulation (NMES) (N = 11)**	**Usual care/no treatment (N = 15)**
% Female Sample size	n = 5 ; % = 33	n = 3 ; % = 27
Mean age (SD) (years) Mean (SD)	45.6 (11.4)	49.2 (14.7)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Neuromuscular electrical stimulation (NMES) (N = 11)	Usual care/no treatment (N = 15)
Severity of spasticity Mean (SD)	1.45 (0.56)	1.35 (0.61)
Time period after stroke (years) Mean (SD)	4.2 (3.6)	4.7 (5.2)
Type of spasticity Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- Baseline
- 3 month (</=6 months)

Continuous outcomes

Outcome	Neuromuscular electrical stimulation (NMES), Baseline, N = 11	Neuromuscular electrical stimulation (NMES), 3 month, N = 11	Usual care/no treatment, Baseline, N = 15	Usual care/no treatment, 3 month, N = 15
Spasticity outcome measures (modified Ashworth scale) Scale range: 0-5. Final values. Values are reported as MAS elbow and MAS wrist. These	1.45 (0.56)	0.8 (0.55)	1.35 (0.61)	0.8 (0.54)

Outcome	Neuromuscular electrical stimulation (NMES), Baseline, N = 11	Neuromuscular electrical stimulation (NMES), 3 month, N = 11	Usual care/no treatment, Baseline, N = 15	Usual care/no treatment, 3 month, N = 15
are combined together to determine this outcome measure. Mean (SD)				
Physical function - upper limb (Fugl Meyer Assessment) Scale range: 0-66. Final values. Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Shoulder/elbow Scale range: 0-42. Final values. Mean (SD)	19.7 (3.3)	30.4 (6.1)	18.4 (4.4)	22 (5)
Wrist/hand Scale range: 0-24. Final values. Mean (SD)	10.4 (3.9)	16.2 (6.7)	11 (4.2)	12.2 (5)

1 Spasticity outcome measures (modified Ashworth scale) - Polarity - Lower values are better
2 Physical function - upper limb (Fugl Meyer Assessment) - Polarity - Higher values are better

3 ***Dichotomous outcome***

Outcome	Neuromuscular electrical stimulation (NMES), Baseline, N = 11	Neuromuscular electrical stimulation (NMES), 3 month, N = 11	Usual care/no treatment, Baseline, N = 15	Usual care/no treatment, 3 month, N = 15
Withdrawal due to adverse events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Outcome	Neuromuscular electrical stimulation (NMES), Baseline, N = 11	Neuromuscular electrical stimulation (NMES), 3 month, N = 11	Usual care/no treatment, Baseline, N = 15	Usual care/no treatment, 3 month, N = 15
No of events				

Withdrawal due to adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuousoutcomes-Spasticityoutcomemeasures(modifiedAshworthscale)-MeanSD-Neuromuscular electrical stimulation (NMES)-Usual care/no treatment-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Physicalfunction-upperlimb(FuglMeyerAssessment)-Shoulder/elbow-MeanSD-Neuromuscular electrical stimulation (NMES)-Usual care/no treatment-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Physicalfunction-upperlimb(FuglMeyerAssessment)-Wrist/hand-MeanSD-Neuromuscular electrical stimulation (NMES)-Usual care/no treatment-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcome-Withdrawalduetoadverseevents-NoOfEvents-Neuromuscular electrical stimulation (NMES)-Usual care/no treatment-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Huang, 2020

Bibliographic Reference	Huang, Y.; Nam, C.; Li, W.; Rong, W.; Xie, Y.; Liu, Y.; Qian, Q.; Hu, X.; A comparison of the rehabilitation effectiveness of neuromuscular electrical stimulation robotic hand training and pure robotic hand training after stroke: A randomized controlled trial; Biomedical Signal Processing and Control; 2020; vol. 56 (no. no pagination)

Study details

Secondary publication of another included	No additional information

study- see primary study for details	
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT02117089
Study type	Randomised controlled trial (RCT)
Study location	Hong Kong
Study setting	People from local districts
Study dates	No additional information
Sources of funding	This project was funded by PolyU Central Fund1-ZE4R ITS/073/16 and NSFC81771959.
Inclusion criteria	The participants were at least 6 months after the onset of a singular and unilateral brain lesion due to stroke; both the metacarpophalangeal and proximal interphalangeal joints could be extended to 180 degrees passively; muscle spasticity during extension at the finger joints and the wrist joint was below 3 as measured by the Modified Ashworth Scale, ranged from 0 (no increase in muscle tone) to 4 (affected part rigid); detectable voluntary EMG signals from the driving muscle on the affected side (three times the standard deviation (SD) above the EMG baseline).
Exclusion criteria	Visual deficit and not able to understand and follow simple instructions as assessed by the Mini-Mental State Examination (MMSE ≤21).
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	No additional information.
Intervention(s)	Neuromuscular electrical stimulation (NMES) N=15

	The NMES robot group. Synchronized support from the NMES and the robot were provided. Therapy delivered as 3-5 sessions/week for 20 sessions, finished within 7 consecutive weeks. The NMES electrode pair (30mm diameter) was attached over the ED muscle to provide stimulation during finger extension. The outputs of NMES were square pulses with a constant amplitude of 70V, a stimulation frequency of 40Hz, and a manually adjustable pulse width in the range of 0-300 microseconds. Before the training, the pulse width was set at the minimum intensity, which achieved a fully extended position of the fingers in each patient. During the training, NMES would be triggered by the EMG from the ED muscle first and then provided stimulation to the ED muscle to assist hand-opening motions for the entire phase of finger extension, while no assistance from NMES was provided during finger flexion to avoid the possible increase of finger spasticity after stimulation. Concomitant therapy: In each session, the participants were first required to perform a maximum voluntary contraction test for the following five target muscles: APB, ED, flexor digitorum, biceps brachii and triceps brachii muscles. Each MVC test on each target muscle was maintained for 5 seconds and repeated twice. Following this, the participants were asked to use their paretic limbs (without assistance from NMES or the robot hand) to perform bare-hand evaluation tasks, which included lateral and vertical arm reaching-grasping tasks. For the lateral task, participants were asked to hold a sponge (thickness 5cm, weight 30g) and move it 50cm horizontally from one side of a table to the other. Then, to release it, grasp it again, and finally move it back to its original position. For the vertical task, each participant was asked to grasp the sponge fromt he middle of a lower layer of a shelf, and then raise up it to a vertical distance of 17cm and position it in the middle of upper layer of the shelf. After this people were asked to pick the sponge up and position it back at the starting point. Both lateral and vertical tasks were repeated three times. To avoid muscle fatigue, there was a 2-min break between two consecutive contractions for both the MVC test and the barehand evaluation tasks. After this, people were instructed to carry out repetitive upper-limb movements as in the lateral and vertical tasks in the evaluation with assistance from either the EMG-driven robotic hand or the EMG-driven NMES robotic hand. In each training session, the participants performed 30-minutes lateral and vertical tasks respectively, with a 10-minute break between the two tasks to avoid muscle fatigue.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mild (or MAS 1)

Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	No additional information
Comparator	Usual care/no treatment N=15 Robot group only. Same parameters as the NMES group, but without the NMES. Therapy delivered as 3-5 sessions/week for 20 sessions, finished within 7 consecutive weeks. Concomitant therapy: In each session, the participants were first required to perform a maximum voluntary contraction test for the following five target muscles: APB, ED, flexor digitorum, biceps brachii and triceps brachii muscles. Each MVC test on each target muscle was maintained for 5 seconds and repeated twice. Following this, the participants were asked to use their paretic limbs (without assistance from NMES or the robot hand) to perform bare-hand evaluation tasks, which included lateral and vertical arm reaching-grasping tasks. For the lateral task, participants were asked to hold a sponge (thickness 5cm, weight 30g) and move it 50cm horizontally from one side of a table to the other. Then, to release it, grasp it again, and finally move it back to its original position. For the vertical task, each participant was asked to grasp the sponge fromt he middle of a lower layer of a shelf, and then raise up it to a vertical distance of 17cm and position it in the middle of upper layer of the shelf. After this people were asked to pick the sponge up and position it back at the starting point. Both lateral and vertical tasks were repeated three times. To avoid muscle fatigue, there was a 2-min break between two consecutive contractions for both the MVC test and the barehand evaluation tasks. After this, people were instructed to carry out repetitive upper-limb movements as in the lateral and vertical tasks in the evaluation with assistance from either the EMG-

	driven robotic hand or the EMG-driven NMES robotic hand. In each training session, the participants performed 30-minutes lateral and vertical tasks respectively, with a 10-minute break between the two tasks to avoid muscle fatigue.
Number of participants	30
Duration of follow-up	3 months
Indirectness	No additional information
Additional comments	ITT (no discontinuations)

Study arms

Neuromuscular electrical stimulation (NMES) (N = 15)
The NMES robot group. Synchronized support from the NMES and the robot were provided. Therapy delivered as 3-5 sessions/week for 20 sessions, finished within 7 consecutive weeks. The NMES electrode pair (30mm diameter) was attached over the ED muscle to provide stimulation during finger extension. The outputs of NMES were square pulses with a constant amplitude of 70V, a stimulation frequency of 40Hz, and a manually adjustable pulse width in the range of 0-300 microseconds. Before the training, the pulse width was set at the minimum intensity, which achieved a fully extended position of the fingers in each patient. During the training, NMES would be triggered by the EMG from the ED muscle first and then provided stimulation to the ED muscle to assist hand-opening motions for the entire phase of finger extension, while no assistance from NMES was provided during finger flexion to avoid the possible increase of finger spasticity after stimulation. Concomitant therapy: In each session, the participants were first required to perform a maximum voluntary contraction test for the following five target muscles: APB, ED, flexor digitorum, biceps brachii and triceps brachii muscles. Each MVC test on each target muscle was maintained for 5 seconds and repeated twice. Following this, the participants were asked to use their paretic limbs (without assistance from NMES or the robot hand) to perform bare-hand evaluation tasks, which included lateral and vertical arm reaching-grasping tasks. For the lateral task, participants were asked to hold a sponge (thickness 5cm, weight 30g) and move it 50cm horizontally from one side of a table to the other. Then, to release it, grasp it again, and finally move it back to its original position. For the vertical task, each participant was asked to grasp the sponge fromt he middle of a lower layer of a shelf, and then raise up it to a vertical distance of 17cm and position it in the middle of upper layer of the shelf. After this people were asked to pick the sponge up and position it back at the starting point. Both lateral and vertical tasks were repeated three times. To avoid muscle fatigue, there was a 2-min break between two consecutive contractions for both the MVC test and the

barehand evaluation tasks. After this, people were instructed to carry out repetitive upper-limb movements as in the lateral and vertical tasks in the evaluation with assistance from either the EMG-driven robotic hand or the EMG-driven NMES robotic hand. In each training session, the participants performed 30-minutes lateral and vertical tasks respectively, with a 10-minute break between the two tasks to avoid muscle fatigue.

Usual care/no treatment (N = 15)

Robot group only. Same parameters as the NMES group, but without the NMES. Therapy delivered as 3-5 sessions/week for 20 sessions, finished within 7 consecutive weeks. Concomitant therapy: In each session, the participants were first required to perform a maximum voluntary contraction test for the following five target muscles: APB, ED, flexor digitorum, biceps brachii and triceps brachii muscles. Each MVC test on each target muscle was maintained for 5 seconds and repeated twice. Following this, the participants were asked to use their paretic limbs (without assistance from NMES or the robot hand) to perform bare-hand evaluation tasks, which included lateral and vertical arm reaching-grasping tasks. For the lateral task, participants were asked to hold a sponge (thickness 5cm, weight 30g) and move it 50cm horizontally from one side of a table to the other. Then, to release it, grasp it again, and finally move it back to its original position. For the vertical task, each participant was asked to grasp the sponge fromt he middle of a lower layer of a shelf, and then raise up it to a vertical distance of 17cm and position it in the middle of upper layer of the shelf. After this people were asked to pick the sponge up and position it back at the starting point. Both lateral and vertical tasks were repeated three times. To avoid muscle fatigue, there was a 2-min break between two consecutive contractions for both the MVC test and the barehand evaluation tasks. After this, people were instructed to carry out repetitive upper-limb movements as in the lateral and vertical tasks in the evaluation with assistance from either the EMG-driven robotic hand or the EMG-driven NMES robotic hand. In each training session, the participants performed 30-minutes lateral and vertical tasks respectively, with a 10-minute break between the two tasks to avoid muscle fatigue.

Characteristics

Arm-level characteristics

Characteristic	Neuromuscular electrical stimulation (NMES) (N = 15)	Usual care/no treatment (N = 15)
% Female	n = 3 ; % = 20	n = 3 ; % = 20

Characteristic	Neuromuscular electrical stimulation (NMES) (N = 15)	Usual care/no treatment (N = 15)
Sample size		
Mean age (SD) (years) Mean (SD)	57.33 (9.19)	60.07 (6.88)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Severity of spasticity Sample size	n = NR ; % = NR	n = NR ; % = NR
Time period after stroke Mean (SD)	8.27 (*empty data*)	6.2 (3.41)
Type of spasticity Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- Baseline
- 3 month (</= 6 months)

Continuous outcomes

Outcome	Neuromuscular electrical stimulation (NMES), Baseline, N = 15	Neuromuscular electrical stimulation (NMES), 3 month, N = 15	Usual care/no treatment, Baseline, N = 15	Usual care/no treatment, 3 month, N = 15
Spasticity outcome measures (modified Ashworth scale) Scale range: 0-5. Reported for finger, wrist and elbow separately. Therefore, the values were converted to mean (SD) and then combined for including in this report. Mean (SD)	1.59 (1.11)	0.54 (0.7)	1.55 (1.11)	1.19 (1.03)
Physical function - upper limb (Fugl Meyer Assessment) Scale range: 0-66. Final values. Mean (95% CI)	27.07 (21.22 to 32.91)	43.73 (37.1 to 50.37)	26.93 (21.69 to 32.18)	34.93 (29.75 to 40.11)
Activities of daily living (functional independence measure) Scale range: 18-126. Final values. Mean (95% CI)	64.93 (63.69 to 66.18)	65.87 (64.8 to 66.93)	65 (63.84 to 66.16)	65.93 (64.78 to 67.09)

Spasticity outcome measures (modified Ashworth scale) - Polarity - Lower values are better

Physical function - upper limb (Fugl Meyer Assessment) - Polarity - Higher values are better

Activities of daily living (functional independence measure) - Polarity - Higher values are better

Dichotomous outcome

Outcome	Neuromuscular electrical stimulation (NMES), Baseline, N = 15	Neuromuscular electrical stimulation (NMES), 3 month, N = 15	Usual care/no treatment, Baseline, N = 15	Usual care/no treatment, 3 month, N = 15
Withdrawal due to adverse events No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Withdrawal due to adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuousoutcomes-Spasticityoutcomemeasures(modifiedAshworthscale)-MeanSD-Neuromuscular electrical stimulation (NMES)-Usual care/no treatment-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Physicalfunction-upperlimb(FuglMeyerAssessment)-MeanNineFivePercentCI-Neuromuscular electrical stimulation (NMES)-Usual care/no treatment-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Activitiesofdailyliving(functionalindependencemeasure)-MeanNineFivePercentCI-Neuromuscular electrical stimulation (NMES)-Usual care/no treatment-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcome-Withdrawalduetoadverseevents-NoOfEvents-Neuromuscular electrical stimulation (NMES)-Usual care/no treatment-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Jung, 2017

Bibliographic Reference	Jung, K. S.; In, T. S.; Cho, H. Y.; Effects of sit-to-stand training combined with transcutaneous electrical stimulation on spasticity, muscle strength and balance ability in patients with stroke: A randomized controlled study; Gait & Posture; 2017; vol. 54; 183-187

1 **Study details**

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Republic of Korea
Study setting	Rehabilitation centers (outpatient follow up)
Study dates	No additional information
Sources of funding	This work was supported by the 2016 Gimcheon University Research Grant, and also this work was supported by the Gachon University research fund of 2015 (GCU-2015-0060).
Inclusion criteria	First episode of unilateral stroke with hemiparalysis caused by hemicerebrum damage; MRI to confirm stroke; able to understand and follow verbal commands; able to independently stand up from a chair without using hand; moderate to severe spasticity in the affected ankle plantar flexors with composite spasticity score of at least 10; motor recovery of the lower extremity by Brunnstrom stage is at 3; National Institute of Health Stroke Scale score <20.
Exclusion criteria	Hemianopia, dizziness, or other symptoms indicating vestibular impairment; medical history of lesion of peroneal nerve; neglect and sensory loss; orthopedic disease influencing sit-to-stand movement; contraindications of TENS; previous experiences with TENS therapy.
Stratification - Type of spasticity	Focal spasticity

Recruitment / selection of participants	People were recruited from a rehabilitation center
Intervention(s)	Transcutaneous electrical nerve stimulation (TENS) N=20 Before each physical therapy session (see concomitant therapy), TENS for 30 minutes (five times a week for six weeks). TENS electrodes were attached over the peroneal nerve on the affected side. In the TENS group, electrical stimulation was applied to the peroneal nerve using a TENS machine (TENS-7000, Koalaty Products Inc., USA). The intensity of the stimulation delivered was two times the sensory threshold without muscle contraction. Pulse width of 200 microseconds was delivered at a frequency of 100 Hz. Sensory threshold was defined as the minimal tingling sensation felt by the person. The people were asked to inform the mediator if they felt any discomfort or involuntary muscle contraction following TENS. The mediator also observed whether motion due to muscle contraction occurred in the person. Concomitant therapy: Sit-to-stand training for 15 minutes a day, five times a week for six weeks. Otherwise, all people received conventional therapy for an additional hour a day, five times a week for six weeks.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Moderate (or MAS 2) Defined as moderate to severe
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and	Lower limb

multifocal spasticity only, area affected	
Population subgroups	No additional information
Comparator	Placebo/sham therapy N=21 Sham TENS. The same protocol as the TENS group. However, the electrodes did not provide any electrical current when attached. Concomitant therapy: Sit-to-stand training for 15 minutes a day, five times a week for six weeks. Otherwise, all people received conventional therapy for an additional hour a day, five times a week for six weeks.
Number of participants	41
Duration of follow-up	6 weeks (end of intervention)
Indirectness	No additional information
Additional comments	Unclear method of analysis. Appears to be completers analysed only.

Study arms

Transcutaneous electrical nerve stimulation (TENS) (N = 20)

Before each physical therapy session (see concomitant therapy), TENS for 30 minutes (five times a week for six weeks). TENS electrodes were attached over the peroneal nerve on the affected side. In the TENS group, electrical stimulation was applied to the peroneal nerve using a TENS machine (TENS-7000, Koalaty Products Inc., USA). The intensity of the stimulation delivered was two times the sensory threshold without muscle contraction. Pulse width of 200 microseconds was delivered at a frequency of 100 Hz. Sensory threshold was defined as the minimal tingling sensation felt by the person. The people were asked to inform the mediator if

they felt any discomfort or involuntary muscle contraction following TENS. The mediator also observed whether motion due to muscle contraction occurred in the person. Concomitant therapy: Sit-to-stand training for 15 minutes a day, five times a week for six weeks. Otherwise, all people received conventional therapy for an additional hour a day, five times a week for six weeks.

Placebo/sham therapy (N = 21)

Sham TENS. The same protocol as the TENS group. However, the electrodes did not provide any electrical current when attached. Concomitant therapy: Sit-to-stand training for 15 minutes a day, five times a week for six weeks. Otherwise, all people received conventional therapy for an additional hour a day, five times a week for six weeks.

Characteristics

Arm-level characteristics

Characteristic	Transcutaneous electrical nerve stimulation (TENS) (N = 20)	Placebo/sham therapy (N = 21)
% Female Sample size	n = 9 ; % = 45	n = 8 ; % = 38
Mean age (SD) (years) Mean (SD)	56.2 (10.4)	56.3 (10.2)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Transcutaneous electrical nerve stimulation (TENS) (N = 20)	Placebo/sham therapy (N = 21)
Severity of spasticity CSS score (spasticity) Mean (SD)	11.5 (1.7)	11.9 (1.8)
Time period after stroke (Months) Mean (SD)	6.5 (2.7)	6.6 (2.5)
Type of spasticity Sample size	n = NA ; % = NA	n = NA ; % = NA

Outcomes

Study timepoints

- Baseline
- 6 week (End of intervention. </=6 months)

Continuous outcomes

Outcome	Transcutaneous electrical nerve stimulation (TENS), Baseline, N = 20	Transcutaneous electrical nerve stimulation (TENS), 6 week, N = 20	Placebo/sham therapy, Baseline, N = 21	Placebo/sham therapy, 6 week, N = 20
Spasticity outcome measures (Composite Spasticity Scale) Scale range: 0-16 (0-9 indicates mild spasticity, 10-12 indicates moderate	11.5 (*empty data*)	8.9 (1.7)	11.9 (1.8)	10.8 (1.8)

Outcome	Transcutaneous electrical nerve stimulation (TENS), Baseline, N = 20	Transcutaneous electrical nerve stimulation (TENS), 6 week, N = 20	Placebo/sham therapy, Baseline, N = 21	Placebo/sham therapy, 6 week, N = 20
spasticity, 13-16 indicates severe spasticity). Final values. Mean (SD)				

Spasticity outcome measures (Composite Spasticity Scale) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuousoutcomes-Spasticityoutcomemeasures(CompositeSpasticityScale)-MeanSD-Transcutaneous electrical nerve stimulation (TENS)-Placebo/sham therapy-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Jung, 2020

Bibliographic Reference	Jung, K. S.; Jung, J. H.; In, T. S.; Cho, H. Y.; Effectiveness of Heel-Raise-Lower Exercise after Transcutaneous Electrical Nerve Stimulation in Patients with Stroke: A Randomized Controlled Study; Journal of Clinical Medicine; 2020; vol. 9 (no. 11); 31

1 **Study details**

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	KCT0005217
Study type	Randomised controlled trial (RCT)
Study location	Republic of Korea
Study setting	The K Hospital in South Korea (inpatients)
Study dates	No additional information
Sources of funding	This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (No. 2017R1C1B5075810).
Inclusion criteria	A diagnosis of stroke; first episode of unilateral stroke with hemiparalysis caused by hemicerebrum damage; subacute patients with an onset period of less than 12 months; ability to communicate; ability to walk 10 m independently; moderate to severe spasticity of the paretic ankle (composite spasticity score at least 10); a medically stable status.
Exclusion criteria	History of peroneal nerve lesions; neglect and sensory loss; orthopedic disease that can influence walking; have previous received TENS; contraindications to TENS.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	People were recruited from people admitted to the K Hospital in South Korea.

Intervention(s)	Transcutaneous electrical nerve stimulation (TENS) N=20 A TENS machine (TENS-7000, Koalaty Products Inc., Tampa, FL, USA) was used to provide electrical stimulation for 30 minutes before the heel-raise-lower exercise training. The electrode was attached to the affected peroneal nerve. The TENS group received stimulation at twice the intensity of producing a tingling sensation, to the extent that muscle contractions did not occur. The pulse width and frequency were set to 200 microseconds and 100 Hz respectively. The participants were instructed to immediately report any involuntary muscle contraction or discomfort. Concomitant therapy: Both groups placed their forefeet on a block with a height that allowed heel contact with the floor according to the extensibility of the plantar flexors during the heel-raise-lower exercise. The participants performed repeated concentric and eccentric contractions of the plantar flexors by raising both heels as high as possible and lowering them slowly for approximately 2s. To promote the contraction of the affected plantar flexors, the participants were instructed to symmetrically support their weight during exercise. Since the speed is different for each person, the amount of exercise was set with the goal of repeating 100 times rather than time in order to equalize the amount of exercise. Training was conducted 5 times a week for 6 weeks. At the beginning of training, most started on a block with a height of 5cm, which was gradually increased as sessions progressed.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Moderate (or MAS 2) Moderate to severe
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable

Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb
Population subgroups	No additional information
Comparator	Placebo/sham therapy N=20 Electrodes were attached to the same location as the TENS group. The researcher showed the person that they had turned on the TENS apparatus and gave the subject a very fine electrical stimulation that they could feel. When the person could feel the stimulation, the research turned off power to the apparatus while hiding the TENS in the box, and explained that a microcurrent of TENS was being applied to the subject. Concomitant therapy: Both groups placed their forefeet on a block with a height that allowed heel contact with the floor according to the extensibility of the plantar flexors during the heel-raise-lower exercise. The participants performed repeated concentric and eccentric contractions of the plantar flexors by raising both heels as high as possible and lowering them slowly for approximately 2s. To promote the contraction of the affected plantar flexors, the participants were instructed to symmetrically support their weight during exercise. Since the speed is different for each person, the amount of exercise was set with the goal of repeating 100 times rather than time in order to equalize the amount of exercise. Training was conducted 5 times a week for 6 weeks. At the beginning of training, most started on a block with a height of 5cm, which was gradually increased as sessions progressed.
Number of participants	40
Duration of follow-up	6 weeks (end of intervention)
Indirectness	No additional information
Additional comments	ITT (no loss to follow up)

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Study arms

Transcutaneous electrical nerve stimulation (TENS) (N = 20)

A TENS machine (TENS-7000, Koalaty Products Inc., Tampa, FL, USA) was used to provide electrical stimulation for 30 minutes before the heel-raise-lower exercise training. The electrode was attached to the affected peroneal nerve. The TENS group received stimulation at twice the intensity of producing a tingling sensation, to the extent that muscle contractions did not occur. The pulse width and frequency were set to 200 microseconds and 100 Hz respectively. The participants were instructed to immediately report any involuntary muscle contraction or discomfort. Concomitant therapy: Both groups placed their forefeet on a block with a height that allowed heel contact with the floor according to the extensibility of the plantar flexors during the heel-raise-lower exercise. The participants performed repeated concentric and eccentric contractions of the plantar flexors by raising both heels as high as possible and lowering them slowly for approximately 2s. To promote the contraction of the affected plantar flexors, the participants were instructed to symmetrically support their weight during exercise. Since the speed is different for each person, the amount of exercise was set with the goal of repeating 100 times rather than time in order to equalize the amount of exercise. Training was conducted 5 times a week for 6 weeks. At the beginning of training, most started on a block with a height of 5cm, which was gradually increased as sessions progressed.

Placebo/sham therapy (N = 20)

Electrodes were attached to the same location as the TENS group. The researcher showed the person that they had turned on the TENS apparatus and gave the subject a very fine electrical stimulation that they could feel. When the person could feel the stimulation, the research turned off power to the apparatus while hiding the TENS in the box, and explained that a microcurrent of TENS was being applied to the subject. Concomitant therapy: Both groups placed their forefeet on a block with a height that allowed heel contact with the floor according to the extensibility of the plantar flexors during the heel-raise-lower exercise. The participants performed repeated concentric and eccentric contractions of the plantar flexors by raising both heels as high as possible and lowering them slowly for approximately 2s. To promote the contraction of the affected plantar flexors, the participants were instructed to symmetrically support their weight during exercise. Since the speed is different for each person, the amount of exercise was set with the goal of repeating 100 times rather than time in order to equalize the amount of exercise. Training was conducted 5 times a week for 6 weeks. At the beginning of training, most started on a block with a height of 5cm, which was gradually increased as sessions progressed.

1 **Characteristics**

2 ***Arm-level characteristics***

Characteristic	Transcutaneous electrical nerve stimulation (TENS) (N = 20)	Placebo/sham therapy (N = 20)
% Female Sample size	n = 6 ; % = 30	n = 8 ; % = 40
Mean age (SD) (years) Mean (SD)	53.1 (7.9)	52.7 (11.5)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Severity of spasticity Composite Spasticity Score Mean (SD)	11.5 (1.6)	11.9 (2.1)
Time period after stroke (Months) Mean (SD)	6.8 (2.5)	7 (2.6)
Type of spasticity Sample size	n = NR ; % = NR	n = NR ; % = NR

3

Outcomes

Study timepoints

- Baseline
- 6 week (End of intervention. </=6 months.)

Continuous outcomes

Outcome	Transcutaneous electrical nerve stimulation (TENS), Baseline, N = 20	Transcutaneous electrical nerve stimulation (TENS), 6 week, N = 20	Placebo/sham therapy, Baseline, N = 20	Placebo/sham therapy, 6 week, N = 20
Spasticity outcome measures (Composite Spasticity Score) Scale range: 0-16. Change scores. Mean (SD)	11.5 (1.6)	-2 (1.1)	11.9 (2.1)	-0.4 (0.9)
Physical function - lower limb (10 meter walk test time) (seconds) Change scores. Mean (SD)	24.7 (4)	-5.3 (1.4)	25.2 (4.8)	-2.7 (1.2)

Spasticity outcome measures (Composite Spasticity Score) - Polarity - Lower values are better

Physical function - lower limb (10 meter walk test time) - Polarity - Lower values are better

Dichotomous outcome

Outcome	Transcutaneous electrical nerve stimulation (TENS), Baseline, N = 20	Transcutaneous electrical nerve stimulation (TENS), 6 week, N = 20	Placebo/sham therapy, Baseline, N = 20	Placebo/sham therapy, 6 week, N = 20
Discontinuation due to adverse events No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Discontinuation due to adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuousoutcomes-Spasticityoutcomemeasures(CompositeSpasticityScore)-MeanSD-Transcutaneous electrical nerve stimulation (TENS)-Placebo/sham therapy-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Physicalfunction-lowerlimb(10meterwalktesttime)-MeanSD-Transcutaneous electrical nerve stimulation (TENS)-Placebo/sham therapy-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcome-Discontinuationduetoadverseevents-NoOfEvents-Transcutaneous electrical nerve stimulation (TENS)-Placebo/sham therapy-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Kaji, 2010

Bibliographic Reference	Kaji, R.; Osako, Y.; Suyama, K.; Maeda, T.; Uechi, Y.; Iwasaki, M.; Group, G. S. K. Spasticity Study; Botulinum toxin type A in post-stroke lower limb spasticity: a multicenter, double-blind, placebo-controlled trial; Journal of Neurology; 2010; vol. 257 (no. 8); 1330-7

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with	No additional information.

this study included in review	
Trial name / registration number	NCT00460655.
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	People from 19 Japanese medical institutions
Study dates	May 2007 and April 2008
Sources of funding	This study was sponsored by GlaxoSmithKline K.K. Dr. Kaji served on the steering committee of GSK1358820 Spasticity Study and received grants from GlaxoSmithKline K.K. He also receives honoraria for speaker's bureau activities from Eisai Co., Ltd. Yuka Osako, Kazuaki Suyama, Toshio Maeda, Dr. Uechi, and Dr. Iwasaki are employed by GlaxoSmithKline K.K.
Inclusion criteria	Male or female patients aged 20-80 years and weighing at least 50 kg were eligible if they had a stroke at least 6 months prior to treatment and had equinus deformity (plantar flexion of the ankle) as demonstrated by a score of >3 for ankle flexors on the Modified Ashworth Scale.
Exclusion criteria	Bilateral hemiplegia or quadriplegia; fixed contractures in the ankle; profound atrophy of the muscles to be injected; prior treatment with surgery; phenol/ethanol block, muscle afferent block, intrathecal baclofen or any botulinum toxin serotype; current use of peripheral muscle relaxants; people who were pregnant, lactating, potentially pregnant or planning to become pregnant during the course of the study.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	No additional information.
Intervention(s)	Botulinum toxin type A (Botox) N=58 A single injection of 300 U of botulinum toxin type A injected as 75 units into the following locations: medial head of gastrocnemius, lateral head of gastrocnemius and soleus muscle and tibialis posterior muscle (divided into three sites per

	muscle). An EMG or a nerve stimulator, and an EMG injection needle were used to identify the proper muscles and facilitate injection in all patients. Concomitant therapy: No additional information.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Severe (or MAS 3)
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb
Population subgroups	No additional information.
Comparator	Placebo N=62 Same locations and amount of solution injected as the botulinum toxin group but only inserting physiological saline.

	Concomitant therapy: No additional information.
Number of participants	120
Duration of follow-up	12 weeks (follow up at weeks 1, 4, 6, 8 and 12)
Indirectness	No additional information
Additional comments	Intention to treat

Study arms

Botulinum toxin type A (Botox) (N = 58)
A single injection of 300 U of botulinum toxin type A injected as 75 units into the following locations: medial head of gastrocnemius, lateral head of gastrocnemius and soleus muscle and tibialis posterior muscle (divided into three sites per muscle). An EMG or a nerve stimulator, and an EMG injection needle were used to identify the proper muscles and facilitate injection in all patients Concomitant therapy: No additional information.

Placebo (N = 62)
Same locations and amount of solution injected as the botulinum toxin group but only inserting physiological saline. Concomitant therapy: No additional information.

1 **Characteristics**

2 ***Arm-level characteristics***

Characteristic	Botulinum toxin type A (Botox) (N = 58)	Placebo (N = 62)
% Female Sample size	n = 8 ; % = 14	n = 16 ; % = 26
Mean age (SD) (years) Mean (SD)	62.4 (8.7)	62.5 (9.3)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Japanese Sample size	n = 58 ; % = 100	n = 62 ; % = 100
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Severity of spasticity Modified Ashworth scale Mean (SD)	3.28 (0.45)	3.24 (0.43)
Time period after stroke (Months) Mean (SD)	80.8 (72.8)	72 (60.3)
Type of spasticity Sample size	n = NA ; % = NA	n = NA ; % = NA

Outcomes

Study timepoints

- Baseline
- 12 week (</=45 minutes)

Continuous outcomes

Outcome	Botulinum toxin type A (Botox), Baseline, N = 58	Botulinum toxin type A (Botox), 12 week, N = 58	Placebo, Baseline, N = 62	Placebo, 12 week, N = 62
Spasticity outcome measures (modified Ashworth scale) Scale range: 0-5. Change scores. Mean (SD)	3.28 (0.45)	-0.56 (0.69)	3.24 (0.43)	-0.4 (0.58)

Spasticity outcome measures (modified Ashworth scale) - Polarity - Lower values are better

Dichotomous outcomes

Outcome	Botulinum toxin type A (Botox), Baseline, N = 58	Botulinum toxin type A (Botox), 12 week, N = 58	Placebo, Baseline, N = 62	Placebo, 12 week, N = 62
Withdrawal due to adverse events No of events	n = NA ; % = NA	n = 3 ; % = 5	n = NA ; % = NA	n = 0 ; % = 0

Withdrawal due to adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuousoutcomes-Spasticityoutcomemeasures(modifiedAshworthscale)-MeanSD-Botulinum toxin type A (Botox)-Placebo-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Withdrawalduetoadverseevents-NoOfEvents-Botulinum toxin type A (Botox)-Placebo-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Kaji, 2010

Bibliographic Reference	Kaji, R.; Osako, Y.; Suyama, K.; Maeda, T.; Uechi, Y.; Iwasaki, M.; Group, G. S. K. Spasticity Study; Botulinum toxin type A in post-stroke upper limb spasticity; Current Medical Research & Opinion; 2010; vol. 26 (no. 8); 1983-92

Study details

Secondary publication of another included study- see primary study for details	No additional information.

Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT00460564
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	19 Japanese medical institutions
Study dates	May 2007 and April 2008.
Sources of funding	This study was sponsored by GlaxoSmithKline K.K. R.K. has disclosed that he has served on the steering committee of the GSK1358820 Spasticity Study and received grants from GlaxoSmithKline. K.K. He has also disclosed that he received honoraria for speaker's bureau activities from Eisai Co. Ltd. Y.O., K.S., T.M., Y.U. and M.I. have disclosed that they are employees of GlaxoSmithKline K.K.
Inclusion criteria	Male or female patients aged 20-80 years and at least 40kg in weight if they had a stroke at least 6 months prior to treatment; had focal spasticity of both the wrist and fingers, 3 or 4 for wrist flexors and 2 or higher for finger flexors on the Modified Ashworth Scale (MAS) of muscle tone; 2 or 3 on the Disability Assessment Scale (DAS) for at least one of four areas of functional disability (hygiene, pain, dressing and limb position).
Exclusion criteria	Bilateral hemiplegia or quadriplegia; fixed contractures in the wrist or fingers; prior treatment with phenol/ethanol block; muscle afferent block (MAB), intrathecal baclofen or any botulinum toxin serotype; current use of peripheral muscle relaxants.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	No additional information.
Intervention(s)	Botulinum toxin type A (Botox) N=72

	Combination of higher dose (n=51) and lower dose (n=21) botulinum toxin type A. People were given either a single injection of 200 U (in 4mL solution, higher-dose) or 120 U (in 2.4 mL solution, lower-dose) were injected into each of flexor carpi radialis, flexor carpi ulnaris, flexor digitorum profundus and flexor digitorum superficialis to improve wrist and finger flexion. For people with thumb spasticity (MAS score of at least 2 on the treatment day), an additional 40 U (in 0.8mL, higher-dose) or 30 U (in 0.6mL, lower-dose) of botulinum toxin was injected into each of the flexor pollicis longus and adductor pollicis to improve thumb flexion. An electromyograph or a nerve stimulator, and an EMG injection needle were used to identify proper muscles and facilitate injection in all patients. Concomitant therapy: No additional information.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Severe (or MAS 3)
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	No additional information.

Comparator	Placebo N=37 Placebo injections corresponding to the relevant doses of the botulinum toxin injections (higher dose n = 26, lower dose n = 11). Injection was with 0.9% normal saline using the same methods. Concomitant therapy: No additional information.
Number of participants	109
Duration of follow-up	12 weeks (follow up at weeks 1, 4, 6, 8 and 12)
Indirectness	No additional information
Additional comments	Intention to treat

Study arms

Botulinum toxin type A (Botox) (N = 72)
Combination of higher dose (n=51) and lower dose (n=21) botulinum toxin type A. People were given either a single injection of 200 U (in 4mL solution, higher-dose) or 120 U (in 2.4 mL solution, lower-dose) were injected into each of flexor carpi radialis, flexor carpi ulnaris, flexor digitorum profundus and flexor digitorum superficialis to improve wrist and finger flexion. For people with thumb spasticity (MAS score of at least 2 on the treatment day), an additional 40 U (in 0.8mL, higher-dose) or 30 U (in 0.6mL, lower-dose) of botulinum toxin was injected into each of the flexor pollicis longus and adductor pollicis to improve thumb flexion. An electromyograph or a nerve stimulator, and an EMG injection needle were used to identify proper muscles and facilitate injection in all patients.
Concomitant therapy: No additional information.

Placebo (N = 37)
Placebo injections corresponding to the relevant doses of the botulinum toxin injections (higher dose n = 26, lower dose n = 11). Injection was with 0.9% normal saline using the same methods. Concomitant therapy: No additional information.

Characteristics

Arm-level characteristics

Characteristic	Botulinum toxin type A (Botox) (N = 72)	Placebo (N = 37)
% Female Sample size	n = 17 ; % = 24	n = 18 ; % = 49
Mean age (SD) (years) Mean (SD)	63.3 (9.4)	63.2 (10.6)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Japanese Sample size	n = 72 ; % = 100	n = 37 ; % = 100
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Severity of spasticity Sample size	n = NR ; % = NR	n = NR ; % = NR
Time period after stroke (Months)	63.3 (9.4)	63.2 (10.6)

Characteristic	Botulinum toxin type A (Botox) (N = 72)	Placebo (N = 37)
Mean (SD)		
Type of spasticity Sample size	n = NA ; % = NA	n = NA ; % = NA

Outcomes

Study timepoints

- Baseline
- 12 week (</=6 months)

Continuous outcomes

Outcome	Botulinum toxin type A (Botox), Baseline, N = 72	Botulinum toxin type A (Botox), 12 week, N = 72	Placebo, Baseline, N = 37	Placebo, 12 week, N = 37
Spasticity outcome measures (modified Ashworth scale) Scale range: 0-5. Change scores. The study reports the values for the wrist, finger and thumb separately which are pooled for the analysis. Mean (SD)	3.04 (0.68)	-0.62 (0.79)	3.05 (0.54)	-0.19 (0.5)
Activities of daily living (Disability Assessment Scale) Scale range: 0-3. Change scores. Mean (SD)	2.3 (0.66)	-0.66 (0.67)	2.3 (0.47)	-0.2 (0.53)

Spasticity outcome measures (modified Ashworth scale) - Polarity - Lower values are better
Activities of daily living (Disability Assessment Scale) - Polarity - Lower values are better

Dichotomous outcomes

Outcome	Botulinum toxin type A (Botox), Baseline, N = 72	Botulinum toxin type A (Botox), 12 week, N = 72	Placebo, Baseline, N = 37	Placebo, 12 week, N = 37
Withdrawal due to adverse events Botulinum toxin (high dose): 3. Placebo (high dose): 1. No of events	n = NA ; % = NA	n = 3 ; % = 4	n = NA ; % = NA	n = 1 ; % = 3

Withdrawal due to adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuousoutcomes-Spasticityoutcomemeasures(modifiedAshworthscale)-MeanSD-Botulinum toxin type A (Botox)-Placebo-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Activitiesofdailyliving(DisabilityAssessmentScale)-MeanSD-Botulinum toxin type A (Botox)-Placebo-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Withdrawalduetoadverseevents-NoOfEvents-Botulinum toxin type A (Botox)-Placebo-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Kanovsky, 2009

Bibliographic Reference	Kanovsky, P.; Slawek, J.; Denes, Z.; Platz, T.; Sassin, I.; Comes, G.; Grafe, S.; Efficacy and safety of botulinum neurotoxin NT 201 in poststroke upper limb spasticity; Clinical Neuropharmacology; 2009; vol. 32 (no. 5); 259-65

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.

Trial name / registration number	NCT00465738
Study type	Randomised controlled trial (RCT)
Study location	Czech Republic, Hungary and Poland
Study setting	23 sites in 3 European countries, outpatient setting
Study dates	June 2006 to January 2007
Sources of funding	This study was supported by Merz Pharmaceuticals GmbH, Frankfurt.
Inclusion criteria	Adults with a history of stroke (at least 6 months before enrollment) resulting in focal spasticity of wrist and finger flexors (as demonstrated by the presence of the respective clinical patterns and a score of at least 2 on the Ashworth scale); a score of 2 or higher on the Disability Assessment Scale in 1 of 4 domains chosen as the principal therapeutic target.
Exclusion criteria	Spasticity of any other origin than stroke; bilateral upper limb paresis; botulinum toxin treatment within the last 4 months; previous or planned treatment with phenol or alcohol injection or surgery in the target limb; fixed contracture; other muscle hypertonia; neuromuscular disorders such as Lambert-Eaton syndrome, myasthenia gravis or amyotrophic lateral sclerosis; current treatment with intrathecal baclofen; severe atrophy of the target muscles; hypersensitivity to the study medications; female subjects of childbearing potential if they were without adequate contraception, pregnant or lactating.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	No additional information.
Intervention(s)	Botulinum toxin type A (Xeomin) N=73 Xeomin (named NT 201 in the study) up to a maximum of 400 U. Administered in a single set of intramuscular injections for upper limb spasticity. The appropriate localisation of the needle in the muscle targeted for treatment was assured by means of electrical stimulation or recording of electromyographic signal (EMG). Each muscle for the clinical patterns flexed wrist and clenched fist had to be treated. Other spastic upper limb muscle groups were treated as individually needed. Flexors of elbow and thumb as well as forearm pronators had to be treated only in the presence of a corresponding clinical pattern (flexed elbow, thumb-in-palm and pronated forearm) and if the Ashworth Scale score in that muscle group was at least 2. The choice of muscle to be treated within the muscle groups of forearm, pronators and thumb flexors was based on the

	investigator's clinical judgement. In the group of elbow flexors, treatment of biceps and at least 1 additional muscle was mandatory. In case of a lower Ashworth Scale score with present corresponding clinical pattern, treatment was at the investigator's discretion. If all listed muscle groups showed a clinical pattern and an Ashworth Scale score of 3 or higher, the investigator decided which muscles within a muscle group had priority for treatment, to not exceed the maximum dose of 400 U. Concomitant therapy: Antispastic medications with centrally acting muscle relaxants and/or benzodiazepine medication and physical and occupational therapy regimens were permitted if they had been stable in the 2 weeks before screening. No treatment changes were allowed during the study. Physical and occupational therapies were not allowed on study visit days before outcome assessments.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Moderate (or MAS 2)
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	No additional information

Comparator	Placebo N=75 Injection with matching placebo administered in the same manner. Concomitant therapy: Antispastic medications with centrally acting muscle relaxants and/or benzodiazepine medication and physical and occupational therapy regimens were permitted if they had been stable in the 2 weeks before screening. No treatment changes were allowed during the study. Physical and occupational therapies were not allowed on study visit days before outcome assessments.
Number of participants	148
Duration of follow-up	12 weeks
Indirectness	No additional information
Additional comments	Intention to treat

Study arms

Botulinum toxin type A (Xeomin) (N = 73)
Xeomin (named NT 201 in the study) up to a maximum of 400 U. Administered in a single set of intramuscular injections for upper limb spasticity. The appropriate localisation of the needle in the muscle targeted for treatment was assured by means of electrical stimulation or recording of electromyographic signal (EMG). Each muscle for the clinical patterns flexed wrist and clenched fist had to be treated. Other spastic upper limb muscle groups were treated as individually needed. Flexors of elbow and thumb as well as forearm pronators had to be treated only in the presence of a corresponding clinical pattern (flexed elbow, thumb-in-palm and pronated forearm) and if the Ashworth Scale score in that muscle group was at least 2. The choice of muscle to be treated within the muscle groups of forearm, pronators and thumb flexors was based on the investigator's clinical judgement. In the group of elbow flexors, treatment of biceps and at least 1 additional muscle was mandatory. In case of a lower Ashworth Scale score with present corresponding clinical pattern, treatment was at the investigator's discretion. If all listed muscle groups showed a clinical pattern and

an Ashworth Scale score of 3 or higher, the investigator decided which muscles within a muscle group had priority for treatment, to not exceed the maximum dose of 400 U. Concomitant therapy: Antispastic medications with centrally acting muscle relaxants and/or benzodiazepine medication and physical and occupational therapy regimens were permitted if they had been stable in the 2 weeks before screening. No treatment changes were allowed during the study. Physical and occupational therapies were not allowed on study visit days before outcome assessments.

Placebo (N = 75)

Injection with matching placebo administered in the same manner. Concomitant therapy: Antispastic medications with centrally acting muscle relaxants and/or benzodiazepine medication and physical and occupational therapy regimens were permitted if they had been stable in the 2 weeks before screening. No treatment changes were allowed during the study. Physical and occupational therapies were not allowed on study visit days before outcome assessments.

Characteristics

Arm-level characteristics

Characteristic	Botulinum toxin type A (Xeomin) (N = 73)	Placebo (N = 75)
% Female Sample size	n = 38 ; % = 52	n = 33 ; % = 44
Mean age (SD) (years) Mean (SD)	58.1 (10.2)	53.3 (13.3)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Botulinum toxin type A (Xeomin) (N = 73)	Placebo (N = 75)
Severity of spasticity Mean (SD)	NR (NR)	NR (NR)
Time period after stroke (Months) Mean (SD)	60.9 (*empty data*)	49.2 (47.9)
Type of spasticity Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- Baseline
- 12 week (</= 6 months)

Dichotomous outcomes

Outcome	Botulinum toxin type A (Xeomin), Baseline, N = 73	Botulinum toxin type A (Xeomin), 12 week, N = 73	Placebo, Baseline, N = 75	Placebo, 12 week, N = 75
Withdrawal due to adverse events Xeomin: 1 paraparesis. Placebo: 1 death due to intracranial hematoma. No of events	n = NR ; % = NR	n = 1 ; % = 1.3	n = NR ; % = NR	n = 1 ; % = 1.3

Withdrawal due to adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomousoutcomes-Withdrawalduetoadverseevents-NoOfEvents-Botulinum toxin type A (Xeomin)-Placebo-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Kerzoncuf, 2020

Bibliographic Reference	Kerzoncuf, M.; Viton, J. M.; Pellas, F.; Cotinat, M.; Calmels, P.; Milhe de Bovis, V.; Delarque, A.; Bensoussan, L.; Poststroke Postural Sway Improved by Botulinum Toxin: A Multicenter Randomized Double-blind Controlled Trial; Archives of Physical Medicine & Rehabilitation; 2020; vol. 101 (no. 2); 242-248

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information

Trial name / registration number	NCT03405948
Study type	Randomised controlled trial (RCT)
Study location	France
Study setting	Multicenter trial. Outpatient follow up.
Study dates	No additional information.
Sources of funding	Supported by the Protocole Hospitalier de Recherche Clinique (PHRC 2005/21).
Inclusion criteria	People with chronic post-stroke lower limb spasticity; 12 month minimum interval since the occurrence of stroke; lower limb spasticity corresponding to a Modified Ashworth Scale of at least 2 on the triceps surae muscle; a six month minimum interval since any previous botulinum toxin A injection; a minimum age of 18 years.
Exclusion criteria	Any previous treatment of spasticity with phenol or alcohol injection and surgery on the paretic side; inability to walk; any contraindications for botulinum toxin or intramuscular injections; pregnancy; inability or refusal to give prior consent; people with a vestibular or cerebellar syndrome; aphasia; severe cognitive impairments; recent cerebrovascular disease; recent lower limb pathology liable to interfere with the assessment.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	No additional information.
Intervention(s)	Botulinum toxin type A (Botox) N=23 Botulinum toxin type A (Botox) maximum dose 300 U injected by intramuscular injection. The muscle of interest was located by applying electrostimulation. Botulinum toxin was injected into the lower limb muscles. Concomitant therapy: The use of any rehabilitation procedures, antispastic drugs, and orthoses were continued unchanged during botulinum toxin type A treatment.

Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Moderate (or MAS 2)
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb
Population subgroups	No additional information
Comparator	Placebo N=26 Placebo injection (physiologic serum). Otherwise the same procedure. Concomitant therapy: The use of any rehabilitation procedures, antispastic drugs, and orthoses were continued unchanged during botulinum toxin type A treatment.
Number of participants	49

Duration of follow-up	4-6 weeks after the treatment
Indirectness	No additional information
Additional comments	No information on method of analysis, likely based on completers only

Study arms

Onabotulinum toxin type A (Botox) (N = 23)
Botulinum toxin type A (Botox) maximum dose 300 U injected by intramuscular injection. The muscle of interest was located by applying electrostimulation. Botulinum toxin was injected into the lower limb muscles. Concomitant therapy: The use of any rehabilitation procedures, antispastic drugs, and orthoses were continued unchanged during botulinum toxin type A treatment.

Placebo (N = 26)
Placebo injection (physiologic serum). Otherwise the same procedure. Concomitant therapy: The use of any rehabilitation procedures, antispastic drugs, and orthoses were continued unchanged during botulinum toxin type A treatment.

Characteristics

Arm-level characteristics

Characteristic	Onabotulinum toxin type A (Botox) (N = 23)	Placebo (N = 26)
% Female Sample size	n = 12 ; % = 53.3	n = 12 ; % = 46.7
Mean age (SD) (years)	53.43 (14.76)	50.69 (12.94)

Characteristic	Onabotulinum toxin type A (Botox) (N = 23)	Placebo (N = 26)
Mean (SD)		
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Severity of spasticity Combination of modified ashworth scale scores for soleus, gastrocnemius and tibialis posterior Mean (SD)	2.7 (1.3)	2.28 (1.29)
Time period after stroke (Months) Mean (SD)	50.04 (28.67)	71.04 (67.05)
Type of spasticity Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- Baseline
- 6 week (</=6 months)

Continuous outcome

Outcome	Onabotulinum toxin type A (Botox), Baseline, N = 23	Onabotulinum toxin type A (Botox), 6 week, N = 19	Placebo, Baseline, N = 26	Placebo, 6 week, N = 21
Stroke outcome measures (Ashworth Score) Scale range: 0-5. Change scores. Combination of the scores for gastrocnemius, soleus and tibialis posterior. Mean (SD)	2.7 (1.3)	-0.74 (1.01)	2.28 (1.29)	-0.17 (0.89)

Stroke outcome measures (Ashworth Score) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuousoutcome-Strokeoutcomemeasures(AshworthScore)-MeanSD-Botulinum toxin type A (Botox)-Placebo-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Lairamore, 2014

Bibliographic Reference	Lairamore, C. I.; Garrison, M. K.; Bourgeon, L.; Mennemeier, M.; Effects of functional electrical stimulation on gait recovery post-neurological injury during inpatient rehabilitation; Perceptual & Motor Skills; 2014; vol. 119 (no. 2); 591-608

1 **Study details**

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	United States of America
Study setting	Outpatient follow up
Study dates	No additional information
Sources of funding	No additional information.
Inclusion criteria	People with non-progressive forms of brain injury (traumatic brain injury = 3, surgical removal of an aneurysm = 1, stroke = 28); at least 18 years old; were able to walk 10 meters with moderate or less assistance as determined by the participants treating physical therapist using functional independence measure guidelines; had ankle dorsiflexion passive range of motion to 0 degrees or greater.
Exclusion criteria	Receiving other forms of electrical stimulation to the lower extremity; had contra-indications to electrical stimulation; any prior condition that limited the ability to walk.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	No additional information

Intervention(s)	Functional Electrical Stimulation (FES) N=16 A Bioness L300 unit was used to deliver FES. The Bioness L300 is a neuroprosthesis that delivers electrical pulses over the peroneal nerve and the TA muscle causing the ankle to dorsiflex during the swing phase of gait. The unit was fitted and stimulation parameters set by a single, trained researcher. The stimulation was provided with adequate amplitude to provide ankle dorsiflexion during the swing phase of gait. The intensity of the stimulation varied from 15-76 milliamps and was set at the lowest amplitude that produced a muscle contraction that provided foot clearance during the swing phase of gait. Electrical stimulation was delivered using a continuous, biphasic symmetric waveform with a pulse width of 200 microseconds with a pulse rate of 30 Hz. Concomitant therapy: All people were enrolled in an inpatient rehabilitation program and received 1.5 hour of physical therapy 5 days per week.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Not stated/unclear
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb

Population subgroups	No additional information
Comparator	Placebo/sham therapy N=16 The same unit was used but only sensory stimulation was applied. The intensity of stimulation varied from 3-12 milliamps and was set at the lowest amplitude that produced a mild sensory stimulus without producing a palpable muscle contraction. The electrodes were placed over the tibia to ensure that stimulation did not reach the muscles. Concomitant therapy: All people were enrolled in an inpatient rehabilitation program and received 1.5 hour of physical therapy 5 days per week.
Number of participants	32
Duration of follow-up	11 days
Indirectness	12.5% of the population had a condition other than stroke. Therefore, outcomes should be considered to include population indirectness.
Additional comments	Unclear method of analysis. It appears only completers were included in the analysis.

Study arms

Functional Electrical Stimulation (FES) (N = 16)
A Bioness L300 unit was used to deliver FES. The Bioness L300 is a neuroprosthesis that delivers electrical pulses over the peroneal nerve and the TA muscle causing the ankle to dorsiflex during the swing phase of gait. The unit was fitted and stimulation parameters set by a single, trained researcher. The stimulation was provided with adequate amplitude to provide ankle dorsiflexion during the swing phase of gait. The intensity of the stimulation varied from 15-76 milliamps and was set at the lowest amplitude that produced a muscle contraction that provided foot clearance during the swing phase of gait. Electrical stimulation was delivered using a continuous,

biphasic symmetric waveform with a pulse width of 200 microseconds with a pulse rate of 30 Hz. Concomitant therapy: All people were enrolled in an inpatient rehabilitation program and received 1.5 hour of physical therapy 5 days per week.

Placebo/sham therapy (N = 16)

The same unit was used but only sensory stimulation was applied. The intensity of stimulation varied from 3-12 milliamps and was set at the lowest amplitude that produced a mild sensory stimulus without producing a palpable muscle contraction. The electrodes were placed over the tibia to ensure that stimulation did not reach the muscles. Concomitant therapy: All people were enrolled in an inpatient rehabilitation program and received 1.5 hour of physical therapy 5 days per week.

Characteristics

Arm-level characteristics

Characteristic	Functional Electrical Stimulation (FES) (N = 16)	Placebo/sham therapy (N = 16)
% Female Sample size	n = 3 ; % = 18.8	n = 7 ; % = 43.8
Mean age (SD) (years) Mean (SD)	54.8 (13.4)	47.8 (18.6)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Severity of spasticity	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Functional Electrical Stimulation (FES) (N = 16)	Placebo/sham therapy (N = 16)
Sample size		
Time period after stroke (days) Mean (SD)	15.5 (8.2)	12.9 (5.9)
Type of spasticity Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- Baseline
- 11 day (</=6 months)

Continuous outcomes

Outcome	Functional Electrical Stimulation (FES), Baseline, N = 13	Functional Electrical Stimulation (FES), 11 day, N = 13	Placebo/sham therapy, Baseline, N = 13	Placebo/sham therapy, 11 day, N = 13
Activities of daily living (Functional Independence Measure - Locomotion) Scale range: 1-7. Change scores. Mean (SD)	1.5 (0.9)	2.2 (0.9)	1.9 (1.3)	2.1 (1.2)

Outcome	Functional Electrical Stimulation (FES), Baseline, N = 13	Functional Electrical Stimulation (FES), 11 day, N = 13	Placebo/sham therapy, Baseline, N = 13	Placebo/sham therapy, 11 day, N = 13
Physical function - lower limb (walking speed) (m/s) Change scores Mean (SD)	0.15 (0.09)	0.13 (0.13)	0.2 (0.14)	0.11 (0.11)

Activities of daily living (Functional Independence Measure - Locomotion) - Polarity - Higher values are better

Physical function - lower limb (walking speed) - Polarity - Higher values are better

Dichotomous outcome

Outcome	Functional Electrical Stimulation (FES), Baseline, N = 16	Functional Electrical Stimulation (FES), 11 day, N = 16	Placebo/sham therapy, Baseline, N = 16	Placebo/sham therapy, 11 day, N = 16
Withdrawal due to adverse events No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Withdrawal due to adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuousoutcomes-Activitiesofdailyliving(FunctionalIndependenceMeasure-Locomotion)-MeanSD-Functional Electrical Stimulation (FES)-Placebo/sham therapy-t11

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Physicalfunction-lowerlimb(walkingspeed)-MeanSD-Functional Electrical Stimulation (FES)-Placebo/sham therapy-t11

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcome-Withdrawalduetoadverseevents-NoOfEvents-Functional Electrical Stimulation (FES)-Placebo/sham therapy-t11

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Lannin, 2018

Bibliographic Reference	Lannin, N. A.; Ada, L.; Levy, T.; English, C.; Ratcliffe, J.; Sindhusake, D.; Crotty, M.; Intensive therapy after botulinum toxin in adults with spasticity after stroke versus botulinum toxin alone or therapy alone: a pilot, feasibility randomized trial; Pilot & Feasibility Studies; 2018; vol. 4; 82

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Australia
Study setting	Rehabilitation centre
Study dates	September 2010 - September 2011
Sources of funding	No additional information
Inclusion criteria	Referred to a spasticity clinic for management of spasticity of the upper and/or lower limb as indicated by a score of 2 or more on the modified Ashworth scale

	At least 1 month post-neurologically impaired Medically stable Able to understand simple instructions (Mini Mental State Examination score ≥ 21)
Exclusion criteria	Received botulinum toxin-A in the previous 5 months Known allergy or hypersensitivity to botulinum toxin-A Another significant health conditions (such as arthritis) Pregnant or breastfeeding Unable to attend the hospital for clinic appointments
Stratification - Type of spasticity	Focal spasticity study reports that around 70% of pts were affected by UL spasticity however some pts had UL and LL affected and could be classed as multifocal spasticity. Therefore majority seem to fall under focal spasticity.
Recruitment / selection of participants	Participants referred to a spasticity clinic for management of spasticity of the upper and/or lower limb
Intervention(s)	The experimental group received botulinum toxin-A injections by an experienced rehabilitation physician. Muscles injected were determined by the physician based on whether they appeared to contribute to abnormal limb position and impair use of the limb. If indicated, participants received injections into both upper and lower limb muscles during the same injection session; a maximum dose of 500 U was given in one session. Muscle localization was undertaken via the use of Teflon-coated injection needles allowing electrical stimulation for muscle localization. Participants then undertook an intensive 8-week rehabilitation program delivered by physiotherapists and occupational therapists. The intensive rehabilitation program consisted of serial casting for contracture reduction, strengthening, and task specific training. Upper/lower limb casts were applied] with the muscle in its maximum obtainable range over the first 2 weeks. Once the final cast was removed, participants received 6 weeks of intensive therapy. Twelve 1-h clinic-based sessions were provided over 6 weeks, with participants undertaking self-directed practice of three 1-h sessions per weekday (each session consisting of 30 min of electrical stimulation and 30 min of task-specific training), i.e., a total of 90 h of self-directed practice.

Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mixed
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	not applicable
Population subgroups	No additional information
Comparator	Intensive 8-week rehabilitation program delivered by physiotherapists and occupational therapists. The intensive rehabilitation program consisted of serial casting for contracture reduction, strengthening, and task specific training. Upper/lower limb casts were applied with the muscle in its maximum obtainable range over the first 2 weeks. Once the final cast was removed, participants received 6 weeks of intensive therapy. Twelve 1-h clinic-based sessions were provided over 6 weeks, with participants undertaking self-directed practice of three 1-h sessions per weekday (each session consisting of 30 min of electrical stimulation and 30 min of task-specific training), i.e., a total of 90 h of self-directed practice.
Number of participants	23; 11 in BTX group, 12 in Usual care
Duration of follow-up	12 weeks
Indirectness	Population indirectness - 3 participants (14%) with neurological disorders other than stroke (1 MS, 2 TBI)

Additional comments	Intention to treat

Study arms

Onabotulinum toxin A (BOTOX) (N = 12)
Botulinum toxin-A plus 8-week intensive rehabilitation program

Usual care (N = 14)
8-week intensive rehabilitation program

Characteristics

Arm-level characteristics

Characteristic	Onabotulinum toxin A (BOTOX) (N = 12)	Usual care (N = 14)
% Female Sample size	n = 3 ; % = 25	n = 4 ; % = 29
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Severity of spasticity Nominal	NR	NR

Characteristic	Onabotulinum toxin A (BOTOX) (N = 12)	Usual care (N = 14)
Time period after stroke (Months) Mean (SD)	36 (49)	38 (37)
Type of spasticity Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Onabotulinum toxin A (BOTOX), Baseline, N = 12	Onabotulinum toxin A (BOTOX), 12 week, N = 12	Usual care, Baseline, N = 14	Usual care, 12 week, N = 14
Spasticity Tardieu Scale (scale range 0-4, final scores) Mean (SD)	2.5 (0.7)	2.3 (0.7)	2.2 (0.6)	2.2 (0.8)
Physical Function - Lower Limb (metres per second) 6-minute walk test (final scores) Mean (SD)	0.18 (0.16)	0.27 (0.23)	0.46 (0.58)	0.35 (0.6)

Spasticity - Polarity - Lower values are better
Physical Function - Lower Limb - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Physical Function - Lower Limb

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Spasticity

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Lee, 2013

Bibliographic Reference	Lee, H. J.; Cho, K. H.; Lee, W. H.; The effects of body weight support treadmill training with power-assisted functional electrical stimulation on functional movement and gait in stroke patients; American Journal of Physical Medicine & Rehabilitation; 2013; vol. 92 (no. 12); 1051-9

1 **Study details**

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Republic of Korea
Study setting	Rehabilitation centre
Study dates	No additional information
Sources of funding	No additional information
Inclusion criteria	Diagnosis of stroke shown by MRI or CT At least 5 degrees of ankle passive range of motion and at least 1 of 5 in ankle dorsiflexion muscle strength (manual muscle test) Sufficient cognition to understand and follow simple instructions Able to walk 10m independently without the use of an assistive device Absence of a musculoskeletal condition that could affect the ability to walk safely

	Brunnstrom stage between 1 and 4 for the lower extremity Absence of a hearing disorder No skin allergy to electric stimulation
Exclusion criteria	Excessive spasticity in the affected leg (≥3 on the MAS) Any comorbidity or disability other than those that would preclude gait training Participation in any other studies or rehabilitation programs Severe heart disease or uncontrolled hypertension and pain Any neurologic or orthopaedic diseases that may interfere with the study
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	Voluntary recruitment from an inpatient rehabilitation hospital
Intervention(s)	A portable two-channel neurotransmitter was used for delivery of electrical stimulation during body weight supported treadmill training (BWSTT). The device induced greater muscle contraction by electrical stimulation in proportion to the integrated EMG signal i.e. the contracting muscle dictates the intensity of the electrical stimulation to the same muscle. Sensitivity of the EMG signal could be set from 1000-10,000 times with an adjustable voltage between 0-160V. Electrodes were attached to the tibialis anterior muscle. Prior to the start of the intervention, participants underwent an assessment for the detection of threshold intensity which was used to set the device. Stimulation was administered during BWSTT, with 40% body weight initially supported and being progressively reduced by 10% each week. Participants underwent BWSTT for 30 minutes a day, 5 days a week for 4 weeks.
Subgroup 1: Severity of spasticity (as stated by category or as measured by	Not stated/unclear

modified Ashworth scale [MAS])	
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb
Population subgroups	No additional information
Comparator	Same as intervention but with no electrical stimulation during BWSTT
Number of participants	30; 15 per group
Duration of follow-up	4 weeks
Indirectness	No additional information
Additional comments	No additional information

Study arms

Functional electrical stimulation (FES) (N = 15)
Body weight supported treadmill training with power-assisted functional electrical stimulation

Usual care (N = 15)
Body weight supported treadmill training

Characteristics

Arm-level characteristics

Characteristic	Functional electrical stimulation (FES) (N = 15)	Usual care (N = 15)
% Female Sample size	n = 3 ; % = 20	n = 5 ; % = 33
Mean age (SD) (years) Mean (SD)	52.47 (9.41)	56.73 (7.24)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Severity of spasticity MAS Nominal	NR	NR
MAS 1 Nominal	5	*empty data*
MAS 1 plus	9	9

Characteristic	Functional electrical stimulation (FES) (N = 15)	Usual care (N = 15)
Nominal		
MAS 2 Nominal	1	2
Time period after stroke (Months) Mean (SD)	4 (0.41)	4.07 (1.03)
Type of spasticity Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 4 week

Continuous Outcomes

Outcome	Functional electrical stimulation (FES), Baseline, N = 15	Functional electrical stimulation (FES), 4 week, N = 15	Usual care, Baseline, N = 15	Usual care, 4 week, N = 15
Physical Function - Lower Limb Berg Balance Scale (scale range 0-56 ; change scores) Mean (SD)	NA (NA)	10.93 (4.74)	NA (NA)	6 (3.02)

Physical Function - Lower Limb - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Functional electrical stimulation (FES), Baseline, N = 15	Functional electrical stimulation (FES), 4 week, N = 15	Usual care, Baseline, N = 15	Usual care, 4 week, N = 15
Discontinuation No of events	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0

Discontinuation - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Physical Function - Lower Limb

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Discontinuation-NoOfEvents-Body weight supported treadmill training with power-assisted functional electrical stimulation-Treadmill training only-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Lee, 2015

Bibliographic Reference	Lee, Y. Y.; Lin, K. C.; Cheng, H. J.; Wu, C. Y.; Hsieh, Y. W.; Chen, C. K.; Effects of combining robot-assisted therapy with neuromuscular electrical stimulation on motor impairment, motor and daily function, and quality of life in patients with chronic stroke: a double-blinded randomized controlled trial; Journal of Neuroengineering & Rehabilitation; 2015; vol. 12; 96

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Taiwan
Study setting	Hospital
Study dates	2012 - 2014
Sources of funding	This study was supported in part by the National Health Research Institutes (NHRI-EX104-10403PI), the Ministry of Science and Technology (102-2314-B002-154-MY2, 102-2628-B-182-005-MY3, and 103-2314-B-182-004-MY3), Healthy

	Ageing Research Center at Chang Gung University (EMRPD1E1711), and Chang Gung Memorial Hospital (CMRPD1B0332, CMRPD1C0403) in Taiwan.
Inclusion criteria	First unilateral stroke > 6 months Aged between 20 and 80 years UE Fugl-Meyer Assessment (UE-FMA) sub-score between 25 and 50 Mini-Mental State Examination score ≥24 Not participating in other research trials during the study period
Exclusion criteria	Comorbidity with other neurological or psychological disorders Severe visuoperceptual impairment Joint arthritis that might prohibit the participant from performing the tasks Received botulinum toxin injection within 3 months Unstable medical condition
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	Clinical occupational therapists recruited participants with stroke from 5 hospitals in Taiwan
Intervention(s)	The Bi-Manu-Track robotic arm training system was used in this study. The participants sat in front of a height-adjustable table and held the handles of the BMT with the elbow flexed at 90◦ and forearms in the neutral position. The robotic training targeted wrist flexion-extension and forearm pronation-supination movements with 3 different training modes: passive-passive (mode 1), active-passive (mode 2), and active-active (mode 3). These 3 modes were chosen in order to progressively improve the movement capacity of the paretic arm. Under the passive-passive mode, both paretic and non-paretic UEs were guided passively by the robotic handle. During the active-passive mode, the non-paretic UE moved the

	robot handle actively whereas the paretic limb was passively guided by the device. As for the active-active mode, both arms actively move the robot arm against some pre-set resistance. For each movement, the participants practiced 200 repetitions in mode 1, 750 repetitions in mode 2, and 50–200 repetitions in mode 3. Movement repetition of mode 3 was dependent upon each individual's capability and was gradually increased throughout the treatment sessions. In each RT treatment session (60–70 minutes), approximately a total of 2000– 2300 repetitions were generated for forearm pronation-supination and wrist flexion-extension. After the RT, the participants received an additional 20 to 30 minutes of functional task training to facilitate transferring the acquired movements to daily activities. The selected functional tasks involved forearm pronation-supination or wrist flexion-extension movements, such as twisting a towel or bouncing a ball. During mode 2 and 3 of RT, NMES was also applied to the paretic arm. The stimulation parameters were symmetrical biphasic square waveform with a frequency of 30 pulses per second and a pulse duration of 200 μs. The stimulation intensity was targeted at a muscle contraction level. For the participants who were unable to tolerate the stimulation intensity, the stimulation intensity was adjusted to their maximum tolerance level. Magnetic sensing switches were used to control the on and off time of the stimulator. The sensing switches were placed at the end range of the BMT handle, which was set according to each participant's movement capability. The magnetic sensing switch would turn on the stimulator when the participants started a movement, and the stimulator was later turned off when the participants reached the end of the movement. The addition of NMES to RT could facilitate the paretic muscles to contract at the appropriate timing. During mode 3 of RT, the participants were instructed to actively contract the muscle along with the NMES in order to work against the resistance. While active muscle contraction would recruit mainly the slow twitch muscle fibres, NMES could activate the fast twitch muscle fibres. Thus, active muscle contraction along with NMES during mode 3 could induce a larger amount of force output to overcome the resistance. For training the wrist flexion-extension movement, the electrodes were placed on the muscle belly of wrist extensors. For the pronation-supination movements, the electrodes were placed over either the forearm supinator or pronator, depending on which muscle is more impaired. Seventy percent of participants had stimulation applied over their supinator muscles, while 30 % of participants received stimulation over the pronator muscle.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mild (or MAS 1)
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)

Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	No additional information
Comparator	The intervention protocol for the RT + Sham group was exactly the same as the RT + ES group, except that sham NMES was provided during mode 2 and 3 of RT. For the sham stimulation, the stimulator was turned on but the intensity button was adjusted to 0; thus, there was no current output. The participants were notified that the stimulation intensity was below sensory threshold. Functional task practices were also provided after the RT + Sham training.
Number of participants	39; 20 in NMES group, 19 in sham group
Duration of follow-up	4 months
Indirectness	No additional information
Additional comments	No additional information

Study arms

Neuromuscular electrical stimulation (NMES) (N = 20)
Neuromuscular electrical stimulation and robot therapy

Sham NMES (N = 19)
Sham and robot therapy

Characteristics

Arm-level characteristics

Characteristic	Neuromuscular electrical stimulation (NMES) (N = 20)	Sham NMES (N = 19)
% Female Sample size	n = 5 ; % = 25	n = 5 ; % = 26
Mean age (SD) (years) Mean (SD)	54.07 (11.85)	53.75 (9.11)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Severity of spasticity Nominal	NR	NR
Time period after stroke (Months) Mean (SD)	25.4 (17.09)	27.95 (16.2)
Type of spasticity Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 1 month
- 4 month

Continuous Outcomes

Outcome	Neuromuscular electrical stimulation (NMES), Baseline, N = 20	Neuromuscular electrical stimulation (NMES), 1 month, N = 20	Neuromuscular electrical stimulation (NMES), 4 month, N = 20	Sham NMES, Baseline, N = 19	Sham NMES, 1 month, N = 19	Sham NMES, 4 month, N = 19
Physical Function - upper limb Fugl-Meyer Assessment (scale range 0-66; final values) Mean (SD)	30.7 (9.76)	34.6 (9.79)	32.9 (8.75)	26.89 (10.66)	30.68 (10.02)	29.21 (9.25)
Spasticity Modified Ashworth Scale (scale range 0-4; final values) Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Forearm Pronator Mean (SD)	1.1 (0.58)	1.18 (0.63)	NR (NR)	1.37 (0.7)	1.29 (0.75)	NR (NR)

Outcome	Neuromuscular electrical stimulation (NMES), Baseline, N = 20	Neuromuscular electrical stimulation (NMES), 1 month, N = 20	Neuromuscular electrical stimulation (NMES), 4 month, N = 20	Sham NMES, Baseline, N = 19	Sham NMES, 1 month, N = 19	Sham NMES, 4 month, N = 19
Forearm Supinator Mean (SD)	0.05 (0.22)	0.05 (0.22)	NR (NR)	0.05 (0.23)	0.13 (0.4)	NR (NR)
Wrist Flexor Mean (SD)	1.35 (0.59)	1.08 (0.49)	NR (NR)	1.03 (0.66)	1.13 (0.64)	NR (NR)
Wrist Extensor Mean (SD)	0.28 (0.5)	0.18 (0.44)	NR (NR)	0.21 (0.42)	0.21 (0.42)	NR (NR)
Stroke-Specific Patient-Reported Outcome Measures Stroke Impact Scale (scale range 0-100; final values) Mean (SD)	58.87 (9.57)	64.43 (12.34)	57.43 (12.54)	56.57 (11.33)	64.19 (14.12)	54.17 (8.4)

1 Physical Function - upper limb - Polarity - Higher values are better
2 Spasticity - Polarity - Lower values are better
3 Stroke-Specific Patient-Reported Outcome Measures - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Neuromuscular electrical stimulation (NMES), Baseline, N = 20	Neuromuscular electrical stimulation (NMES), 1 month, N = 20	Neuromuscular electrical stimulation (NMES), 4 month, N = 20	Sham NMES, Baseline, N = 19	Sham NMES, 1 month, N = 19	Sham NMES, 4 month, N = 19
Discontinuation No of events	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0

Discontinuation - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Spasticity

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Stroke Specific Patient Reported Outcome Measures

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Physical Function - upper limb

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Discontinuation-NoOfEvents-Neuromuscular electrical stimulation and robot therapy -Sham and robot therapy-t1

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Li, 2014

Bibliographic Reference	Li, H.; Liu, H.; Liu, C.; Shi, G.; Zhou, W.; Zhao, C.; Zhang, T.; Wang, X.; Wang, G.; Zhao, Y.; Sun, J.; Wang, J.; Wang, L.; Effect of "Deqi" during the Study of Needling "Wang's Jiaji" Acupoints Treating Spasticity after Stroke; Evidence-Based Complementary & Alternative Medicine: eCAM; 2014; vol. 2014; 715351

Study details

Secondary publication of another included study- see primary study for details	No additional information

Other publications associated with this study included in review	No additional information
Trial name / registration number	This trial was registered with ISRCTN at Current Controlled Trials (ISRCTN84985339)
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Inpatient centre
Study dates	October 2009 - June 2013
Sources of funding	No additional information
Inclusion criteria	Diagnosis of ischemic stroke Onset within 21 days Aged 40–80 years Scores of NIHSS (National Institute of Health stroke scale) ≥4 and ≤21 points Scores of GCS (Glasgow coma scale) ≥7 points, without disorder of consciousness Without severe disability left behind the first stroke Scores of modified Rankin scale ≤1 point Diagnosed by head CT or MRI Written and informed consent

Exclusion criteria	Patients receiving thrombolytic therapy Limb dystonia caused by other diseases Subjects tested in other trials in the last 3 months Combined serious primary heart, liver, kidney, and hematopoietic system diseases and psychiatric patients Pregnant or lactating women Patients with congenitally handicapped patients
Stratification - Type of spasticity	Generalised spasticity
Recruitment / selection of participants	All patients treated in the stroke wards in Beijing Hospital of Traditional Chinese Medicine were screened at the inpatient clinic 2 weeks after onset of stroke.
Intervention(s)	Acupuncture was conducted using disposable sterile stainless needle (0.32 mm × 40 mm), skin disinfection with 75% alcohol, and needle retention for 30 minutes without moxibustion, or electrical stimulation. Patients received 20 sessions of verum acupuncture in 4 weeks. In addition to acupuncture, the basic therapies for cerebrovascular disease were used in all the enrolled patients, including antiplatelet therapy, management of intracranial pressure and blood pressure, neuroprotective agents, treatment of complications, rehabilitation therapy. “Wang’s Jiaji” points selected from Jiaji (EX-B2) are the necessary points used in acupuncture group, including the points located 0.3 cun lateral to the lower border of the 2nd, 4th, 6th, 8th, 10th, and 12th thoracic vertebra, and the 2nd and 4th lumbar vertebra. Piercing vertically, needles are inserted 10–25 mm in depth and manually manipulated by lifting, thrusting, and rotating methods with uniform reinforcing-reducing techniques to produce the sense known as “deqi.”
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Not stated/unclear

Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	Acupuncture
Subgroup 4: For focal and multifocal spasticity only, area affected	not applicable
Population subgroups	No additional information
Comparator	The points used in the sham acupuncture group located 0.1 cun lateral to the lower border of the 2nd, 4th, 6th, 8th, 10th, and 12th thoracic vertebra and the 2nd and 4th lumber vertebra. Piercing vertically, needles are inserted 5 mm in depth and remained for 30 minutes without moxibustion or electrical stimulation, with no needling sensation. In addition to acupuncture, the basic therapies for cerebrovascular disease were used in all the enrolled patients, including antiplatelet therapy, management of intracranial pressure and blood pressure, neuroprotective agents, treatment of complications, rehabilitation therapy.
Number of participants	238; 121 in verum acupuncture group, 117 in sham group
Duration of follow-up	12 weeks
Indirectness	No additional information
Additional comments	No additional information

1

Study arms

Acupuncture (N = 121)

Sham (N = 117)

Characteristics

Arm-level characteristics

Characteristic	**Acupuncture (N = 121)**	**Sham (N = 117)**
% Female Sample size	n = 43 ; % = 35.5	n = 36 ; % = 30.8
Mean age (SD) (years) Mean (SD)	63.2 (10.49)	64.21 (10.19)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Severity of spasticity MAS Score (all limbs) Mean (SD)	12.47 (7.47)	13.01 (6.14)

Characteristic	Acupuncture (N = 121)	Sham (N = 117)
Time period after stroke (days) Mean (SD)	10.93 (6.97)	12.19 (7.45)
Type of spasticity Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Acupuncture, Baseline, N = 121	Acupuncture, 12 week, N = NR	Sham, Baseline, N = 117	Sham, 12 week, N = NR
Spasticity Modified Ashworth Scale (scale range unclear) change scores) higher is better Mean (SD)	12.47 (7.47)	18.31 (9.07)	13.01 (6.14)	12.91 (9.88)
Physical function Fugl-Meyer Assessment (scale range 0-100; change scores) Mean (SD)	30.32 (21.57)	37.76 (22.38)	31.52 (18.96)	24.9 (19.74)

Outcome	Acupuncture, Baseline, N = 121	Acupuncture, 12 week, N = NR	Sham, Baseline, N = 117	Sham, 12 week, N = NR
Activities of daily living Barthel Index (scale range 0-100; change scores) Mean (SD)	33.72 (15.7)	37.89 (20.52)	36.98 (16.13)	24.64 (18.76)
Stroke Specific PROMS Stroke Specialization Quality of Life Scale (scale range 49-245; change scores) Mean (SD)	102.74 (31.15)	67.22 (39.6)	106.09 (35.76)	40.63 (33.33)

Spasticity - Polarity - Higher values are better
Physical function - Polarity - Higher values are better
Activities of daily living - Polarity - Higher values are better
Stroke Specific PROMS - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Spasticity

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Physical function

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Activities of daily living

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Stroke Specific PROMS

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Liao, 2017

Bibliographic Reference	Liao, H. Y.; Ho, W. C.; Chen, C. C.; Lin, J. G.; Chang, C. C.; Chen, L. Y.; Lee, D. C.; Lee, Y. C.; Clinical Evaluation of Acupuncture as Treatment for Complications of Cerebrovascular Accidents: A Randomized, Sham-Controlled, Subject- and Assessor-Blind Trial; Evidence-based Complementary and Alternative Medicine; 2017; vol. 2017 (no. no pagination)

1 **Study details**

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	Clinicaltrials.gov - NCT02197663
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	No additional information
Study dates	June 2014 - October 2015
Sources of funding	This study was supported by China Medical University under the Aim for Top University Plan of the Ministry of Education, Taiwan, and The Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW105-TDU-B-212-133019).
Inclusion criteria	All patients with first-time incident stroke who were admitted to the Neurological, Neurosurgical, Physical Medicine and Rehabilitation, or Chinese Medicine Departments at the China Medical University Hospital were considered eligible for recruitment.
Exclusion criteria	Unable to follow instructions/cooperate during screening interview History of previous stroke or other serious disease e.g. cancer, dementia, heart failure, COPD, liver cirrhosis, kidney failure
Stratification - Type of spasticity	Generalised spasticity

Recruitment / selection of participants	Interviews were held with all new stroke patients. Of the 171 patients with first-time stroke who presented during the period, 61 met the inclusion criteria and 52 of them provided signed informed consent to participate.
Intervention(s)	A single practitioner of Chinese Medicine with more than 15 years of experience in acupuncture performed all of the interventions. Manual acupuncture was carried out in patients in the supine position and comprised both body and scalp acupuncture for a total of 20 minutes per session 3 times per week for a total of 24 sessions. The following acupoints were needled in all patients: Baihui (GV-20), Sishencong (EX-HN1), temporal threeneedle technique (Jin three-needle therapy, one side for the weakness limbs), Quchi (LI11), Hegu (LI4), Neiguan (PC6), Waiguan (TE5), Yanglingquan (GB34), Zusanli (ST36), Sanyinjiao (SP6), and Taichong (LR3). Other acupoints were needled based on each patient's symptoms, such as Speech II or Speech III areas (Jiao's Scalp Acupuncture) for aphasia, Jinjin (EX-HN 12) and Yuye (EX-HN 13) for dysarthria, and Fenglung (ST40) and Chizexue (LU5) for sputum. Each acupoint was stimulated to elicit a needle sensation (de qi) and needling depth was based on the excitation of de qi. All procedures were carried out with disposable needles measuring 0.25 mm in diameter (32-gauge) and 44 mm in length (Yu Kuang, Taipei, Taiwan). Patients in both groups also received conventional western rehabilitation with the same frequency and received western medications as needed during inpatient admission and outpatient tracking.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Not stated/unclear
Subgroup 2: Time period after stroke when trial starts	Not stated/unclear
Subgroup 3: Acupuncture/dry needling	Acupuncture
Subgroup 4: For focal and multifocal	not applicable

spasticity only, area affected	
Population subgroups	No additional information
Comparator	Participants in the sham group also received 24 sessions of acupuncture treatment; however, needling was performed 1 cm away from the real acupoints. In addition, none of the participants in the sham group received scalp acupuncture. All procedures were carried out to a depth of 0.5 cm with disposable needles measuring 0.16 mm in diameter (40-gauge) and 12.7 mm in length (Yu Kuang, Taipei, Taiwan). No needle sensation (de qi) was elicited. Patients in both groups also received conventional western rehabilitation with the same frequency and received western medications as needed during inpatient admission and outpatient tracking.
Number of participants	48; 28 in acupuncture group, 20 in sham group
Duration of follow-up	8 weeks
Indirectness	No additional information
Additional comments	ITT with last observation carried forward imputation of missing data

Study arms

Acupuncture (N = 28)

Sham (N = 20)

1 **Characteristics**

2 ***Arm-level characteristics***

Characteristic	Acupuncture (N = 28)	Sham (N = 20)
% Female Sample size	n = 9 ; % = 33.33	n = 9 ; % = 45
Mean age (SD) (years) Mean (SD)	62.29 (12.33)	55.45 (15.22)
Ethnicity Nominal	NR	NR
Comorbidities Sample size	n = NR ; % = NR	n = NR ; % = NR
Hypertension Sample size	n = 22 ; % = 78.57	n = 13 ; % = 65
Diabetes Sample size	n = 5 ; % = 17.86	n = 6
Heart disease Sample size	n = 5 ; % = 17.86	n = 4 ; % = 13.3
Hyperlipdaemia Sample size	n = 0 ; % = 0	n = 1 ; % = 5

Characteristic	Acupuncture (N = 28)	Sham (N = 20)
Severity of spasticity Nominal	NR	NR
Time period after stroke Nominal	NR	NR
Type of spasticity Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 8 week

Continuous Outcomes

Outcome	Acupuncture , Baseline, N = 28	Acupuncture , 8 week, N = 28	Sham, Baseline, N = 20	Sham, 8 week, N = 20
Activities of daily living Barthel Index (scale range 0-100; change scores) Mean (SD)	59.64 (41.94)	13.39 (25.57)	65.75 (34.08)	12.25 (19.5)

Outcome	Acupuncture , Baseline, N = 28	Acupuncture , 8 week, N = 28	Sham, Baseline, N = 20	Sham, 8 week, N = 20
Pain VAS (scale range 0-10; change scores) Mean (SD)	1.56 (2.97)	-1.11 (2.54)	1.47 (2.23)	0.27 (2.11)

Activities of daily living - Polarity - Higher values are better

Pain - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	Acupuncture , Baseline, N = 28	Acupuncture , 8 week, N = 28	Sham, Baseline, N = 20	Sham, 8 week, N = 20
Withdrawal due to Adverse Effects Nominal	NA	1	NA	2
Withdrawal due to Adverse Effects No of events	n = NA ; % = NA	n = 1 ; % = 4	*empty data*	n = 2 ; % = 10

Withdrawal due to Adverse Effects - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Activities of daily living

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Pain

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Withdrawal due to Adverse Effects

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Lin, 2011

Bibliographic Reference	Lin, Z.; Yan, T.; Long-term effectiveness of neuromuscular electrical stimulation for promoting motor recovery of the upper extremity after stroke; Journal of Rehabilitation Medicine; 2011; vol. 43 (no. 6); 506-10

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Inpatient
Study dates	January - August 2008
Sources of funding	Financed by projects of GDSTC (No. 2007B031502005, 2010A040302002)
Inclusion criteria	first stroke; within 3 months post-onset Admitted to the Neurology or Rehabilitation Department Diagnosed with either cerebral infarction or cerebral haemorrhage using either computed tomography or magnetic resonance imaging fulfilling the diagnostic and classification criteria for stroke established by the Chinese Neuroscience and Neurosurgery Institute

	Age range 44–80 years, with hemiplegia of one upper limb Shoulder flexor strength before treatment was grade 3 or less (out of 5) No severe cognitive dysfunction (with a score of 7 or better on the abbreviated mental test) Willing to sign an informed consent form
Exclusion criteria	Progressive stroke Subarachnoid haemorrhage Shoulder muscle strength ≥ grade 3 Severe heart, liver, kidney or infectious disease Head injury Tumour Score < 7 on the abbreviated mental test Younger than 44 years or older than 80 years Not willing to sign the consent form
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	Patients admitted to the Neurology or Rehabilitation Department within 3-months of first stroke
Intervention(s)	All patients received the same standard treatment, including physical therapy and occupational therapy, for 30 min on 5 days each week for 3 weeks, respectively. The patients in the intervention group were given neuromuscular electrical stimulation. Protocols were fixed and they were run automatically, not trigged by electromyography (EMG), when the

	stimulator was on, in order to mimic the function of the upper limb, such as the activity of drinking or eating. The surface electrodes were applied over the motor points near the middle of the supraspinatus muscle and the deltoid muscle on the paretic side, as well as over the wrist extensor. The stimulation was at a frequency of 30 Hz, with a pulse width of 300 μs, and ramp up and down times of 1 s each. The stimulus pulse was a symmetrical biphasic waveform. The amplitude of the current was adjusted to the maximal tolerance of the patient, in a range up to 90 mA, and to produce shoulder abduction of approximately 30–50 degrees and full wrist extension with a duty cycle of 5 s on and 5 s off. The total stimuli were 180 cycles during 1 treatment session. Treatment lasted for 30 min, 5 days per week for 3 weeks.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mild (or MAS 1)
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	No additional information
Comparator	All patients received the same standard treatment, including physical therapy and occupational therapy, for 30 min on 5 days each week for 3 weeks, respectively. The control group did not receive any electrical stimulation during the study period.
Number of participants	37; 19 in neuromuscular electrical stimulation group, 18 in usual care

Duration of follow-up	6 months
Indirectness	No additional information
Additional comments	No additional information

Study arms

Neuromuscular Electrical Stimulation (N = 19)
Neuromuscular electrical stimulation plus standard rehabilitation

Usual Care (N = 18)
Standard rehabilitation

Characteristics

Arm-level characteristics

Characteristic	Neuromuscular Electrical Stimulation (N = 19)	Usual Care (N = 18)
% Female Sample size	n = 8 ; % = 42	n = 7 ; % = 39
Mean age (SD) (years) Mean (SD)	62.2 (8.7)	66 (9.6)
Ethnicity	NR	NR

Characteristic	Neuromuscular Electrical Stimulation (N = 19)	Usual Care (N = 18)
Nominal		
Comorbidities Nominal	NR	NR
Severity of spasticity Modified Ashworth Scale Mean (SD)	0.53 (0.5)	0.5 (0.51)
Time period after stroke (days) Mean (SD)	43.5 (25.2)	41.3 (26.5)
Type of spasticity Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 6 month

Continuous Outcomes

Outcome	Neuromuscular Electrical Stimulation , Baseline, N = 23	Neuromuscular Electrical Stimulation , 6 month, N = 19	Usual Care, Baseline, N = 23	Usual Care, 6 month, N = 18
Spasticity Modified Ashworth Scale (scale range 0-4; final values) Mean (SD)	0.53 (0.5)	1.67 (0.52)	0.5 (0.51)	1.86 (0.38)
Activities of daily living Barthel Index (scale range 0-100; final values) Mean (SD)	31 (10.1)	79.2 (5.2)	30.3 (8.7)	66.1 (11.3)

Spasticity - Polarity - Lower values are better

Activities of daily living - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Spasticity

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Activities of daily living

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Lindsay, 2021

Bibliographic Reference	Lindsay, C.; Ispoglou, S.; Helliwell, B.; Hicklin, D.; Sturman, S.; Pandyan, A.; Can the early use of botulinum toxin in post stroke spasticity reduce contracture development? A randomised controlled trial; Clinical Rehabilitation; 2021; vol. 35 (no. 3); 399-409

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	EudraCT (2010-021257-39), ClinicalTrials.gov-Identifier: NCT01882556
Study type	Randomised controlled trial (RCT)

Study location	UK
Study setting	Stroke unit in a tertiary care hospital
Study dates	
Sources of funding	This paper summarises independent research funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit Programme (PB-PG-0808-16319). Allergan provided the drug used and an unrestricted educational grant to support this study.
Inclusion criteria	Aged over 18 Diagnosis of a first stroke within the last 42 days Score of ≤ 2 on the easiest pick and place task on the grasp subsection of the Action Research Arm Test (ARAT) (i.e. lift and place a 2.5 cm3 wooden block)
Exclusion criteria	Significant musculoskeletal conditions prior to stroke Contra-indications to electrical stimulation Known previous spasticity Hypersensitivity to excipients of Botox Infection at the proposed injection sites Pregnant
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	Screening for spasticity was carried out 3-times per week by a physiotherapist for a period of six weeks from stroke onset. If during this screening period, the patient developed spasticity and had a score of less than or equal to two on the grasp subsection of the Action Research Arm Test they were randomised to either the treatment or control group.
Intervention(s)	Intramuscular injections of Onabotulinumtoxin-A were administered to all six muscles of the affected arm in predetermined doses. Localisation of the involved muscles was determined primarily by electrical stimulation techniques and where this

	was not possible by using ultrasound imaging. Electrical stimulation to the wrist extensors was provided to all patients recruited to the trial. Electrical stimulation was used to produce a movement through the full range of wrist extension while optimising participant comfort (pulse width was set to 300μs; frequency was set to 40Hz with an on time of 30 seconds including a five second ramp up and five second ramp down followed by a 30 seconds off time) for a period of ninety days.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Not stated/unclear
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	No additional information
Comparator	0.9% sodium chloride solution placebo
Number of participants	97 randomised; 49 in Botox group, 48 in placebo group
Duration of follow-up	6 months
Indirectness	No additional information

Additional comments	Intention to treat

Study arms

Onaotulinum Toxin A (BOTOX) (N = 49)

Placebo (N = 48)

Characteristics

Arm-level characteristics

Characteristic	Onaotulinum Toxin A (BOTOX) (N = 49)	Placebo (N = 48)
% Female Sample size	n = 21 ; % = 47	n = 24 ; % = 50
Mean age (SD) (years) Mean (SD)	67 (17.1)	68.1 (14.8)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Characteristic	Onaotulinum Toxin A (BOTOX) (N = 49)	Placebo (N = 48)
Severity of spasticity NIHSS (arm) Mean (SD)	3.6 (0.6)	3.6 (0.6)
Time period after stroke (days) Mean (SD)	16.8 (8.9)	19.1 (9.5)
Type of spasticity Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 6 month

Continuous Outcomes

Outcome	Onaotulinum Toxin A (BOTOX), Baseline, N = 49	Onaotulinum Toxin A (BOTOX), 6 month, N = 40	Placebo, Baseline, N = 48	Placebo, 6 month, N = 43
Physical Function - upper limb Action Research Arm Test (scale range 0-57; final values) Mean (SD)	1 (2.6)	15.3 (21.6)	0.4 (1.7)	12.4 (20.7)

Outcome	Onaotulinum Toxin A (BOTOX), Baseline, N = 49	Onaotulinum Toxin A (BOTOX), 6 month, N = 40	Placebo, Baseline, N = 48	Placebo, 6 month, N = 43
Discontinuation Nominal	0	9	0	5
Discontinuation No of events	n = 0 ; % = 0	n = 9 ; % = 23	n = 0 ; % = 0	n = 5 ; % = 12

Physical Function - upper limb - Polarity - Higher values are better
Discontinuation - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Physical Function - upper limb

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Discontinuation-Nominal-Botulinum Toxin A-Placebo-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Malhotra, 2013

Bibliographic Reference	Malhotra, S.; Rosewilliam, S.; Hermens, H.; Roffe, C.; Jones, P.; Pandyan, A. D.; A randomized controlled trial of surface neuromuscular electrical stimulation applied early after acute stroke: effects on wrist pain, spasticity and contractures; Clinical Rehabilitation; 2013; vol. 27 (no. 7); 579-90

Study details

Secondary publication of another included study- see primary study for details	Secondary analysis of Rosewilliam et al., (2012) 'Can surface neuromuscular electrical stimulation of the wrist and hand combined with routine therapy facilitate recovery of arm function in patients with stroke?'
Other publications associated with this study included in review	No additional information
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	UK
Study setting	Hospital / home-based mix
Study dates	No additional information
Sources of funding	This work was supported by Action Medical Research and Barnwood House Trust (grant number: AP0993). The surface neuromuscular stimulators were supplied by department of medical physics and biomedical engineering at Salisbury District Hospital. The equipment maintenance support was provided by Biometrics Ltd.

Inclusion criteria	No useful hand function, defined as a score of 0 in the grasp subsection of the Action Research Arm Test No contraindication to surface neuromuscular electrical stimulation
Exclusion criteria	Medically unstable Previous medical history of osteoarthritis, rheumatoid arthritis or soft tissue injuries that resulted in contractures Reduced range of movement in the wrist and fingers Unwilling to take part in the study
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	Stroke patients admitted to North Staffordshire University Hospital
Intervention(s)	Patients in the treatment arm received 30-minute sessions of surface neuromuscular electrical stimulation to the wrist and finger extensors at least twice a day (a maximum of three times a day) for five days a week. Surface neuromuscular electrical stimulation was delivered by surface electrodes (inactive electrode placed just below the common extensor origin and active electrode placed such that the stimulation produced balanced extension of the wrist, that is, extension without ulnar and radial deviation) positioned on the dorsal surface of the forearm. The stimulation parameters were set to produce slow movement through the full range at maximum participant comfort (pulse width = 300 μs; ON time = 15 s; OFF time = 15 s). The ON time included a ramp up time of 6 s and a ramp down time of 6 s and the frequency of stimulation was set to 40 Hz. The intensity of stimulation was adjusted to obtain maximum range of wrist and finger extension without inducing pain or fatigue. After completing the initial treatment session, the patient or their carer (relative) was trained to apply the surface neuromuscular electrical stimulation system and deliver the treatment independently. Patients were given a defined module of routine physiotherapy, with interventions which reflected local clinical practice for a period of six weeks in addition to the usual clinical treatment on the stroke unit. The protocol classified therapies based on therapy input as passive, active assisted, active/strengthening and functional. Usual care was also provided.
Subgroup 1: Severity of spasticity (as stated by category	Not stated/unclear

or as measured by modified Ashworth scale [MAS])	
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	No additional information
Comparator	Patients in the control group were not given electrical stimulation. Their care was otherwise the same as that of patients in the intervention group. Patients in both the control and treatment arms were given a defined module of routine physiotherapy, with interventions which reflected local clinical practice, for a period of six weeks in addition to the usual clinical treatment on the stroke unit. The protocol classified therapies based on therapy input as passive, active assisted, active/strengthening and functional. Treatment compliance in both arms was monitored using a patient record. Both groups also had usual care.
Number of participants	90; 45 in NMES group, 45 in usual care group
Duration of follow-up	36 weeks
Indirectness	No additional information
Additional comments	ITT (for patients surviving up to the analysed time point - gradual decline as follow-up duration increased)

	Missing values were imputed in two ways: A) the mean of two adjacent values was used when an intermediate assessment was missed B) the last value was carried forward when someone dropped out of the study

Study arms

Neuromuscular Electrical Stimulation (N = 45)

Usual Care (N = 45)

Characteristics

Arm-level characteristics

Characteristic	**Neuromuscular Electrical Stimulation (N = 45)**	**Usual Care (N = 45)**
% Female Sample size	n = 22 ; % = 49	n = 21 ; % = 53
Mean age (SD) (years) Median (range) Median (IQR)	74 (32 to 98)	74 (52 to 90)
Ethnicity Nominal	NR	NR

Characteristic	Neuromuscular Electrical Stimulation (N = 45)	Usual Care (N = 45)
Comorbidities Nominal	NR	NR
Severity of spasticity Nominal	NR	NR
Time period after stroke (Months) Median (range) Median (IQR)	3 (1 to 6)	3 (1 to 6)
Type of spasticity Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 24 week
- 36 week

Continuous Outcomes

Outcome	Neuromuscular Electrical Stimulation , Baseline, N = 45	Neuromuscular Electrical Stimulation , 24 week, N = 33	Neuromuscular Electrical Stimulation , 36 week, N = 31	Usual Care, Baseline, N = 45	Usual Care, 24 week, N = 37	Usual Care, 36 week, N = 36
Pain Verbal Rating Scale (scale range 0-5; final values) Mean (SD)	0.5 (1.14)	0.4 (1.03)	0.4 (1)	0.4 (1.01)	1.1 (1.46)	1 (1.62)

Pain - Polarity - Lower values are better

discontinuation

Outcome	Neuromuscular Electrical Stimulation , Baseline, N = 45	Neuromuscular Electrical Stimulation , 24 week, N = 45	Neuromuscular Electrical Stimulation , 36 week, N = 45	Usual Care, Baseline, N = 45	Usual Care, 24 week, N = 45	Usual Care, 36 week, N = 45
Discontinuation No of events	n = 0 ; % = 0	n = 19	n = 20	n = 0 ; % = 0	n = 16	n = 20

Discontinuation - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Pain

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to allocation concealment)*
Overall bias and Directness	Overall Directness	Directly applicable

discontinuation-Discontinuation-NoOfEvents-Neuromuscular Electrical Stimulation -Usual Care-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

discontinuation-Discontinuation-NoOfEvents-Neuromuscular Electrical Stimulation -Usual Care-t36

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Pain-MeanSD-Neuromuscular Electrical Stimulation -Usual Care-t36

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to allocation concealment)*
Overall bias and Directness	Overall Directness	Directly applicable

Marciniak, 2012

Bibliographic Reference	Marciniak, C. M.; Harvey, R. L.; Gagnon, C. M.; Duraski, S. A.; Denby, F. A.; McCarty, S.; Bravi, L. A.; Polo, K. M.; Fierstein, K. M.; Does botulinum toxin type A decrease pain and lessen disability in hemiplegic survivors of stroke with shoulder pain and spasticity?: a randomized, double-blind, placebo-controlled trial; American Journal of Physical Medicine & Rehabilitation; 2012; vol. 91 (no. 12); 1007-19

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	Clinicaltrials.gov (NCT00661089)

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Rehabilitation centre
Study dates	No additional information
Sources of funding	Funded by an unrestricted educational grant from Allergan Inc, for whom the main author has been a consultant
Inclusion criteria	≥18 years of age Weight of >88 lbs Diagnosis of stroke with resultant hemiplegia or hemiparesis Stable medical illnesses Willingness to remain on a stable dose of anti-spasticity medication for the duration of the study and the preceding 3 weeks Received physical therapy or occupational therapy for shoulder pain for at least 2 weeks with no change in pain or function Shoulder pain ≥4 on the VAS at the time of screening Ashworth Scale rating ≥3 for shoulder tone for adductors and internal rotators at the time of screening No history of Botox injections before 1998 Ability to to appropriately rank pain on a cognitive function screening tool where the subjects were asked to rank pain associated with 3 painful scenarios Negative serum pregnancy test drawn on the day of injection for women with childbearing potential Participants on warfarin were required to have an international normalised ratio in the therapeutic range or subtherapeutic range within the week before injection

Exclusion criteria	Known allergy to study medication or sensitivity to the study medication or it's components Pregnancy / planning pregnancy Breast feeding Women of childbearing potential not using a reliable means of contraception Concurrent use of aminoglycoside antibiotics, curare-like agents, or other agents that might interfere with neuromuscular function Any medical condition such as myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis or other disorders that would put the participant at increased risk with exposure to Botox Infection of dermatologic condition at the injection site Presence of significant fixed contracture of the study limb shoulder Significant inflammation or oedema of the study limb Obesity to the degree that shoulder landmarks were obscured such that the medication could not be safely injected Planned initiation of new anti-spasticity medication during the study period Concurrent medical condition that may be the more likely cause of shoulder pain or that may put the participant at significant increased risk Significant aphasia to the degree that the assessment tools would not be completely reliable
Stratification - Type of spasticity	Focal spasticity

Recruitment / selection of participants	Post-stroke patients reporting pain associated with tightness of the shoulder muscles were recruited from the outpatient physical medicine and rehabilitation clinics, outpatient occupational therapy and physical therapy clinics, affiliated sites, a local stroke support group, an institutional Website, and inpatient services.
Intervention(s)	Study coordinators prepared injection solutions by drawing up 2ml of saline. Two syringes were used for two vials of Botox at a concentration of 100units/ml. Participants had a total of 100-150 units injected into the pectoralis major muscle. A total of 40-60 units were injected into the teres major muscle if the shoulder extensors exhibited spasticity of an Ashworth grade of 3 or 4. Dosage was adjusted on the basis of the MAS score and muscle size, as determined by the injectors. Three sites were injected in the pectoralis major muscle at the anterior aspect of the shoulder and one site was injected in the teres major muscle at the posterior aspect of the shoulder, lateral and superior to the scapular tip. Electromyographic guidance was used for the injections.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Severe (or MAS 3)
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	No additional information
Comparator	2ml saline with no additional drug

Number of participants	21 randomised; 10 to Botox group, 11 to placebo group
Duration of follow-up	12 weeks
Indirectness	No additional information
Additional comments	Intention to treat

Study arms

Onabotulinum Toxin A (BOTOX) (N = 10)

Placebo (N = 11)

Characteristics

Arm-level characteristics

Characteristic	**Onabotulinum Toxin A (BOTOX) (N = 10)**	**Placebo (N = 11)**
% Female Sample size	n = 4 ; % = 40	n = 4 ; % = 36.4
Mean age (SD) (years) Mean (SD)	60.2 (7.8)	59.8 (10.3)
Ethnicity	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Onabotulinum Toxin A (BOTOX) (N = 10)	Placebo (N = 11)
Sample size		
White Sample size	% = 70	n = NR ; % = 33.3
African-American Sample size	n = 2 ; % = 20	n = NR ; % = 66.7
Hispanic / Latino Sample size	n = 1 ; % = 10	n = NR ; % = 0
Comorbidities Nominal	NR	NR
Severity of spasticity MAS (shoulder flexors) Median (IQR)	3 (3 to 4)	2 (1 to 3)
Time period after stroke Nominal	NR	NR
Type of spasticity Nominal	NR	NR

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Outcomes

Study timepoints

- Baseline
- 16 week

discontinuation

Outcome	Onabotulinum Toxin A (BOTOX), Baseline, N = 10	Onabotulinum Toxin A (BOTOX), 16 week, N = 10	Placebo, Baseline, N = 11	Placebo, 16 week, N = 11
Discontinuation No of events	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 2 ; % = 18.8

Discontinuation - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

discontinuation-Discontinuation-NoOfEvents-Onabotulinum Toxin A-Placebo-t16

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Marco, 2007

Bibliographic Reference	Marco, E.; Duarte, E.; Vila, J.; Tejero, M.; Guillen, A.; Boza, R.; Escalada, F.; Espadaler, J. M.; Is botulinum toxin type A effective in the treatment of spastic shoulder pain in patients after stroke? A double-blind randomized clinical trial; Journal of Rehabilitation Medicine; 2007; vol. 39 (no. 6); 440-7

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	Spanish Agency of Medicines (registration code: RHBESPE/TOXIN/1).
Study type	Randomised controlled trial (RCT)
Study location	Spain
Study setting	Rehabilitation unit in an acute-care general hospital
Study dates	August 2001 - July 2003
Sources of funding	Institut Municipal d'Investigacio Mèdica provided a grant
Inclusion criteria	Aged > 18 years Spastic hemiparesis due to CVA of 3 or more months of evolution

	Moderate-severe spastic shoulder pain Visual Analogue Scale for pain ≥40 mm Spasticity of ≥3 determined by the Modified Ashworth Scale Ability to understand and accept the trial procedures and to sign an informed consent form
Exclusion criteria	Mild hemiparesis (defined as Brunnstrom stage 6) Previous concomitant shoulder pathology Fitted with pacemakers Peripheral nervous system diseases Hypersensitivity to botulinum toxin Pregnant
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	No additional information
Intervention(s)	After having been allocated randomly to 1 of the 2 groups, the patients were treated by means of intramuscular injection, at 4 sites, of 500 units of BTA in the pectoralis major muscle of the paretic side, under electromyographic monitoring. The injection site was located at the upper front of the chest next to the shoulder where the muscle fibres converge towards their insertion on a line arising from the coracoid apophysis and passing downward. Subsequently, all the patients were treated with conventional TENS, consisting of short pulses (250 µsec) of high frequency (75 megahertz) and low intensity for a 6-week period. Although all participants were still undergoing training in daily living activities and different aspects of mobility, none of them followed any specific treatment for alleviating pain or improving shoulder mobility
Subgroup 1: Severity of	Severe (or MAS 3)

spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	No additional information
Comparator	Placebo in place of Botox injection
Number of participants	31 randomised; 16 in Botox group, 15 in placebo group
Duration of follow-up	6 months
Indirectness	No additional information
Additional comments	No additional information

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Study arms

Abotulinum Toxin A (Dysport) and TENS (N = 14)

Placebo and TENS (N = 15)

Characteristics

Arm-level characteristics

Characteristic	Abotulinum Toxin A (Dysport) and TENS (N = 14)	Placebo and TENS (N = 15)
% Female Sample size	n = 4 ; % = 28.6	n = 4 ; % = 26.7
Mean age (SD) (years) Mean (SD)	63.9 (10.6)	67.2 (7.4)
Ethnicity Nominal	NR	NR
Comorbidities Sample size	n = NA ; % = NA	n = NA ; % = NA
Hypertension Sample size	n = 9 ; % = 64.3	n = 11 ; % = 73.3
Diabetes mellitus	n = 3 ; % = 21.4	n = 5 ; % = 33.3

Characteristic	Abotulinum Toxin A (Dysport) and TENS (N = 14)	Placebo and TENS (N = 15)
Sample size		
Prior Cerebrovascular Accident Sample size	n = 2 ; % = 14.3	n = 3 ; % = 20
Heart disease Sample size	n = 3 ; % = 21.4	n = 3 ; % = 20
Respiritory Disease Sample size	n = 2 ; % = 14.3	n = 0 ; % = 0
Neoplasias Sample size	n = 0 ; % = 0	n = 4 ; % = 26.7
Severity of spasticity Modified Ashworth Scale Mean (SD)	3.1 (0.7)	3.13 (0.6)
Time period after stroke Median (IQR)	174 (89 to 263)	133 (112 to 210)
Type of spasticity Nominal	NR	NR

1

Outcomes

Study timepoints

- Baseline
- 6 month

Continuous Outcomes

Outcome	Abotulinum Toxin A (Dysport) and TENS, Baseline, N = 14	Abotulinum Toxin A (Dysport) and TENS, 6 month, N = 14	Placebo and TENS, Baseline, N = 15	Placebo and TENS, 6 month, N = 15
Spasticity Modified Ashworth Scale (scale range 0-5; final values) Mean (SD)	3.1 (0.7)	2.9 (1.2)	3.13 (0.6)	3.2 (0.9)
Pain VAS (scale range 0-100; final values) Mean (SD)	76.4 (15.6)	30.1 (26.9)	70.1 (15.3)	48.3 (29.4)

Spasticity - Polarity - Lower values are better

Pain - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	Abotulinum Toxin A (Dysport) and TENS, Baseline, N = 14	Abotulinum Toxin A (Dysport) and TENS, 6 month, N = 14	Placebo and TENS, Baseline, N = 15	Placebo and TENS, 6 month, N = 15
Withdrawal due to Adverse Effects Nominal	NA	0	NA	0

Outcome	Abotulinum Toxin A (Dysport) and TENS, Baseline, N = 14	Abotulinum Toxin A (Dysport) and TENS, 6 month, N = 14	Placebo and TENS, Baseline, N = 15	Placebo and TENS, 6 month, N = 15
Withdrawal due to Adverse Effects No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Withdrawal due to Adverse Effects - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Spasticity

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Pain

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Withdrawal due to Adverse Effects

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Masakado, 2020

Bibliographic Reference	Masakado, Y.; Abo, M.; Kondo, K.; Saeki, S.; Saitoh, E.; Dekundy, A.; Hanschmann, A.; Kaji, R.; Group, J. Pure Study; Efficacy and safety of incobotulinumtoxinA in post-stroke upper-limb spasticity in Japanese subjects: results from a randomized, double-blind, placebo-controlled study (J-PURE); Journal of Neurology; 2020; vol. 267 (no. 7); 2029-2041

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	(J-PURE; JapicCTI Number: CTI-153029)
Study type	Randomised controlled trial (RCT)

Study location	Japan
Study setting	No additional information
Study dates	November 2015 - April 2018
Sources of funding	Financial support for the study was provided by Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany
Inclusion criteria	20–80 years of age Unilateral post-stroke upper-limb spasticity Botulinum toxin-naïve or pre-treated with onabotulinumtoxinA ≥ 16 weeks prior to the respective screening visit Modified Ashworth Scale ratings of≥3 and≥2 for wrist flexor and finger flexor muscle tone, respectively, at screening and baseline visits Disability Assessment Scale rating≥2 for at least one functional disability domain at screening and baseline Clinical need for a total dose of incobotulinumtoxinA 400 U
Exclusion criteria	Fixed contracture or muscle hypertonia of another type (e.g., rigidity) in the affected joint(s) to be treated Bilateral upper-limb paresis, paralysis or tetraparesis
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	No additional information
Intervention(s)	One injection cycle of incobotulinumtoxinA 400 U or incobotulinumtoxinA 250 U
Subgroup 1: Severity of spasticity (as stated by category or as measured by	Mixed

modified Ashworth scale [MAS])	
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	No additional information
Comparator	One injection cycle of a matching placebo (either high or low dose placebo)
Number of participants	100; 44 in 400U group, 23 in 250U group, 22 in high dose placebo group, 11 in low dose placebo group
Duration of follow-up	52 weeks
Indirectness	No additional information
Additional comments	Isolated missing values were calculated using non-missing values and any remaining missing values were imputed from baseline wrist MAS

Study arms

Incobotulinum Toxin A (Xeomin) (N = 67)

Placebo (N = 33)

Characteristics

Arm-level characteristics

Characteristic	Incobotulinum Toxin A (Xeomin) (N = 67)	Placebo (N = 33)
% Female Sample size	n = 15 ; % = 22.3	n = 10 ; % = 30.3
Mean age (SD) (years) Mean (SD)	60.83 (10.9)	57.33 (13.36)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 67 ; % = 100	n = 33 ; % = 100
Comorbidities Nominal	NR	NR
Severity of spasticity Nominal	NR	NR
Time period after stroke Nominal	NR	NR

Characteristic	Incobotulinum Toxin A (Xeomin) (N = 67)	Placebo (N = 33)
Type of spasticity Nominal	NR	NR

Outcomes

Study timepoints

- 12 week

Dichotomous Outcomes

Outcome	Incobotulinum Toxin A (Xeomin), 12 week, N = 67	Placebo, 12 week, N = 33
Withdrawal due to Adverse Effects Nominal	2	4
Withdrawal due to Adverse Effects No of events	n = 2 ; % = 3	n = 4 ; % = 12

Withdrawal due to Adverse Effects - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Withdrawal due to Adverse Effects

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Masakado, 2022

Bibliographic Reference	Masakado, Yoshihisa; Kagaya, Hitoshi; Kondo, Kunitsugu; Otaka, Yohei; Dekundy, Andrzej; Hanschmann, Angelika; Geister, Thorin L; Kaji, Ryuji; Efficacy and Safety of IncobotulinumtoxinA in the Treatment of Lower Limb Spasticity in Japanese Subjects.; Frontiers in neurology; 2022; vol. 13; 832937

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	Masakado Y, Abo M, Kondo K, Sakei S, Saitoh E, Dekunday A, et al. Efficacy and safety of incobotulinum toxin A in post-stroke upper limb spasticity in Japanese subjects: results from a randomized, double blind, placebo-controlled study (J-PURE). J Neurol. (2020) 267:2029– 41. doi: 10.1007/s00415-020-09777-5
Trial name / registration number	(Japic clinical study database No. CTI-153030, 7 October 2015)

Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	Multicentre outpatient
Study dates	NR
Sources of funding	This study was funded by Merz Pharmaceuticals GmbH in accordance with Good Publication Practice (GPP3) guidelines.
Inclusion criteria	Male and female subjects, 20–80 years of age, and of East Asian race (recruited in Japan) were eligible for the study if they had unilateral LL spasticity with equinus foot deformity caused by a stroke at least 6 months prior to the screening visit, a bodyweight of at least 50 kg, clinical need for a total dose of incobotulinumtoxinA 400 U, a Modified Ashworth Scale (MAS) spasticity sum score for the plantar flexors (MASPF) of ≥3 at screening and the baseline injection visit, and were botulinum toxin-naïve or pretreated. The clinical need for incobotulinumtoxinA 400 U was decided according to the experience-based opinion of the investigator. This need was derived from the patient's spasticity status and the expected improvement incobotulinumtoxinA could provide. A washout period of at least 16 weeks was required between pretreatment with any BoNT for any indication and the screening visit for this study.
Exclusion criteria	Subjects were not eligible if they had: fixed contracture (defined as severe restriction of the range of joint movement on passive stretch) or other types of muscle hypertonia (e.g., rigidity) in the affected joint(s) intended to be treated; nonstrokerelated spasticity; bilateral LL paresis, paralysis, or tetraparesis; any previous and planned surgical treatment for spasticity in the target muscles; or planned concomitant treatment with BoNT-A for any other body region during the study period.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	This multicenter study enrolled subjects at Japanese sites only and consisted of three periods.
Intervention(s)	Incobotulinum Toxin A (Xeomin) N=104 A single injection cycle of incobotulinum toxin A 400 U compared with placebo in the pes equinus muscles during an observation period of 12 weeks. Guided injection using electromyography, nerve stimulation, or ultrasound imaging was

	performed at all injection sessions to identify the target muscles and facilitate injection. The injection dilution used was 50 U/mL. The total dose of incobotulinum toxin A was fixed at 400 U. Concomitant therapy: Concomitant therapies allowed during the study included oral centrally acting muscle relaxants, antidepressants, anticoagulants, physiotherapy, occupational therapy, and other rehabilitation measures to treat spasticity. Physiotherapy, occupational therapy, or any other rehabilitation measures to treat spasticity of the target limb were required to remain stable during the MP. Prohibited concomitant therapies included botulinum toxins other than incobotulinum toxin A, antibiotics, or parenterally administered drugs interfering with neuromuscular transmission, phenol or alcohol injections, antispasticity medications with peripheral muscle relaxants, and surgery in the target limb within 8 weeks prior to screening.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Severe (or MAS 3)
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb
Population subgroups	NR

Comparator	Placebo/sham N=104 Placebo vials that had the same appearance as incobotulinum toxin A vials to allow double blinding of the subject and investigator. Concomitant therapy: Concomitant therapies allowed during the study included oral centrally acting muscle relaxants, antidepressants, anticoagulants, physiotherapy, occupational therapy, and other rehabilitation measures to treat spasticity. Physiotherapy, occupational therapy, or any other rehabilitation measures to treat spasticity of the target limb were required to remain stable during the MP. Prohibited concomitant therapies included botulinum toxins other than incobotulinum toxin A, antibiotics, or parenterally administered drugs interfering with neuromuscular transmission, phenol or alcohol injections, antispastic medications with peripheral muscle relaxants, and surgery in the target limb within 8 weeks prior to screening.
Number of participants	208
Duration of follow-up	12 weeks
Indirectness	NR
Additional comments	NR

Study arms

Incobotulinum Toxin A (Xeomin) (N = 104)

A single injection cycle of incobotulinum toxin A 400 U compared with placebo in the pes equinus muscles during an observation period of 12 weeks. Guided injection using electromyography, nerve stimulation, or ultrasound imaging was performed at all injection sessions to identify the target muscles and facilitate injection. The injection dilution used was 50 U/mL. The total dose of incobotulinum toxin A was fixed at 400 U. Concomitant therapy: Concomitant therapies allowed during the study included oral centrally acting muscle relaxants, antidepressants, anticoagulants, physiotherapy, occupational therapy, and other rehabilitation measures to treat spasticity. Physiotherapy, occupational therapy, or any other rehabilitation measures to treat spasticity of the target limb were required to remain stable during the MP. Prohibited concomitant therapies included botulinum toxins other than incobotulinum toxin A, antibiotics, or

parenterally administered drugs interfering with neuromuscular transmission, phenol or alcohol injections, antispasticity medications with peripheral muscle relaxants, and surgery in the target limb within 8 weeks prior to screening.

Placebo/sham (N = 104)

Placebo vials that had the same appearance as incobotulinum toxin A vials to allow double blinding of the subject and investigator. Concomitant therapy: Concomitant therapies allowed during the study included oral centrally acting muscle relaxants, antidepressants, anticoagulants, physiotherapy, occupational therapy, and other rehabilitation measures to treat spasticity. Physiotherapy, occupational therapy, or any other rehabilitation measures to treat spasticity of the target limb were required to remain stable during the MP. Prohibited concomitant therapies included botulinum toxins other than incobotulinum toxin A, antibiotics, or parenterally administered drugs interfering with neuromuscular transmission, phenol or alcohol injections, antispastic medications with peripheral muscle relaxants, and surgery in the target limb within 8 weeks prior to screening.

Characteristics

Arm-level characteristics

Characteristic	**Incobotulinum Toxin A (Xeomin) (N = 104)**	**Placebo/sham (N = 104)**
% Female Sample size	n = 26 ; % = 25	n = 20 ; % = 19.2
Mean age (SD) Mean (SD)	59.5 (11.2)	58.8 (11)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Characteristic	Incobotulinum Toxin A (Xeomin) (N = 104)	Placebo/sham (N = 104)
Severity of spasticity Mean (SD)	3 (0)	3 (0)
Time period after stroke months Mean (SD)	79.8 (65)	86 (69.5)
Type of spasticity Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 week
- 8 week (For spasticity only)

Continuous outcomes (1)

Outcome	Incobotulinum Toxin A (Xeomin), Baseline, N = 104	Incobotulinum Toxin A (Xeomin), 12 week, N = 56	Incobotulinum Toxin A (Xeomin), 8 week, N = 104	Placebo/sham, Baseline, N = 104	Placebo/sham, 12 week, N = 60	Placebo/sham, 8 week, N = 104
Physical function - lower limb (10 meter walk test) (seconds)	NR (NR)	-1.2 (1.4)	NA (NA)	NR (NR)	0.7 (1.4)	NA (NA)

Outcome	Incobotulinum Toxin A (Xeomin), Baseline, N = 104	Incobotulinum Toxin A (Xeomin), 12 week, N = 56	Incobotulinum Toxin A (Xeomin), 8 week, N = 104	Placebo/sham, Baseline, N = 104	Placebo/sham, 12 week, N = 60	Placebo/sham, 8 week, N = 104
Least square mean difference and SE. Change score. Mean (SE)						

1 Physical function - lower limb (10 meter walk test) - Polarity - Lower values are better

2 ***Dichotomous outcomes***

Outcome	Incobotulinum Toxin A (Xeomin), Baseline, N = 104	Incobotulinum Toxin A (Xeomin), 12 week, N = 104	Incobotulinum Toxin A (Xeomin), 8 week, N = 104	Placebo/sham, Baseline, N = 104	Placebo/sham, 12 week, N = 104	Placebo/sham, 8 week, N = 104
Withdrawal due to adverse events No of events	n = 0 ; % = 0	n = 1 ; % = 1	n = NA ; % = NA	n = 0 ; % = 0	n = 2 ; % = 1.9	n = NA ; % = NA

3 Withdrawal due to adverse events - Polarity - Lower values are better

4 ***Continuous outcomes (2)***

Outcome	Incobotulinum Toxin A (Xeomin), Baseline, N = 104	Incobotulinum Toxin A (Xeomin), 12 week, N = 104	Incobotulinum Toxin A (Xeomin), 8 week, N = 104	Placebo/sham, Baseline, N = 104	Placebo/sham, 12 week, N = 104	Placebo/sham, 8 week, N = 104
Pain (Ankle pain score - Item 2 of the Patient's Assessment of Spasticity, Pain and	NR (NR)	-0.6 (0.2)	NA (NA)	NR (NR)	-0.5 (0.2)	NA (NA)

Outcome	Incobotulinum Toxin A (Xeomin), Baseline, N = 104	Incobotulinum Toxin A (Xeomin), 12 week, N = 104	Incobotulinum Toxin A (Xeomin), 8 week, N = 104	Placebo/sham, Baseline, N = 104	Placebo/sham, 12 week, N = 104	Placebo/sham, 8 week, N = 104
Spasms scale) Scale range unclear. Least square mean difference. Change score. Mean (SE)						
Spasticity outcome measure (Modified Ashworth Scale - Ankle Inversion/Foot Supination Score) Reported at 4 weeks, 6 weeks and 8 weeks only. Scale range: 0-4. Change scores. Mean (SD)	NR (NR)	NR (NR)	-0.6 (0.1)	NR (NR)	NR (NR)	-0.4 (0.1)

1 Pain (Ankle pain score - Item 2 of the Patient's Assessment of Spasticity, Pain and Spasms scale) - Polarity - Lower values are better
2 Spasticity outcome measure (Modified Ashworth Scale - Ankle Inversion/Foot Supination Score) - Polarity - Lower values are better

3

4

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuousoutcomes-PhysicalfunctionLowerlimb(10meterwalktest)changescore-MeanSE-Incobotulinum Toxin A (Xeomin) total dose 400 U-Placebo-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Withdrawalduetoadverseevents-NoOfEvents-Incobotulinum Toxin A (Xeomin) total dose 400 U-Placebo-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes(2)-Pain(Anklepainscore-Item2ofthePatient'sAssessmentofSpasticity,PainandSpasmsscale)-MeanSE-Incobotulinum Toxin A (Xeomin)-Placebo/sham-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes(2)-Spasticityoutcomemeasure(ModifiedAshworthScale-AnkleInversion/FootSupinationScore)-MeanSD-Incobotulinum Toxin A (Xeomin)-Placebo/sham-t8

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

McCrory, 2009

Bibliographic Reference	McCrory, P.; Turner-Stokes, L.; Baguley, I. J.; De Graaff, S.; Katrak, P.; Sandanam, J.; Davies, L.; Munns, M.; Hughes, A.; Botulinum toxin A for treatment of upper limb spasticity following stroke: a multi-centre randomized placebo-controlled study of the effects on quality of life and other person-centred outcomes; Journal of Rehabilitation Medicine; 2009; vol. 41 (no. 7); 536-44

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	Turner-Stokes 2010
Trial name / registration number	No additional information

Study type	Randomised controlled trial (RCT)
Study location	Australia
Study setting	6 outpatient spasticity clinics
Study dates	November 2004 - January 2006
Sources of funding	Fully funded by Ipsen Pty Ltd, Australia
Inclusion criteria	>18 years Had a stroke at least 6 months previously Had moderate to severe spasticity of the arm as defined by a minimum score of 2 on the Modified Ashworth Scale in at least 2 out of 3 of wrist, elbow and finger flexor muscles and a minimum of 1+ for the third area Had sufficient cognitive and communication ability to be able to give written informed consent
Exclusion criteria	Established severe contracture or other neurological impairments Receiving concurrent aminoglycoside antibiotics Received botulinum toxin treatment within the past 120 days or had been previously treated with phenol or intrathecal baclofen for arm spasticity
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	Adults with hemiplegic stroke and severe or moderately severe spasticity following stroke were recruited from spasticity clinics in 6 centres in Australia, through referral from hospital stroke/neurology units, rehabilitation centres, community physiotherapists and newspaper advertisements.
Intervention(s)	Treatment comprised injections of BoNT-A (total dose range 750–1000 units) into the principal spastic muscles of the distal upper limb (restricted to muscles acting at elbow, wrist and finger joints) at week 0. The selection of muscles, use of single or multiple injection sites within a given muscle, and electromyography or nerve/muscle stimulation to assist accurate

	placement were all at the clinicians' discretion. Patients received re-treatment with the same agent as their first cycle at week 12 with a total dose range of 500–1000 units according to the response in the initial cycle.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Moderate (or MAS 2)
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	No additional information
Comparator	Placebo injection in place of Botox
Number of participants	96 randomised; 54 in Botox group, 42 in placebo group
Duration of follow-up	24 weeks
Indirectness	No additional information
Additional comments	Efficacy data for primary and secondary end-points were analysed using an intention-to-treat population, defined as all patients who were randomly assigned and who received at least one dose of study medication (54 BoNT-A, 42 placebo).

	Six patients did not complete as allocated leaving 90 for analysis per protocol (52 BoNT-A, 38 placebo). Missing data were imputed using a Last Observation Carried Forward (LOCF) method.

Study arms

Abootulinum Toxin A (Dysport) (N = 54)

Placebo (N = 42)

Characteristics

Arm-level characteristics

Characteristic	Abootulinum Toxin A (Dysport) (N = 54)	Placebo (N = 42)
% Female Sample size	n = 22 ; % = 40	n = 16 ; % = 38
Mean age (SD) (years) Mean (SD)	59.7 (12.2)	58.4 (14.6)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 49 ; % = 90.7	n = 40 ; % = 95.2

Characteristic	Abootulinum Toxin A (Dysport) (N = 54)	Placebo (N = 42)
Asian Sample size	n = 5 ; % = 9.3	n = 2 ; % = 4.8
Comorbidities Nominal	NR	NR
Severity of spasticity MAS (across all joints) Mean (SD)	7.1 (1.2)	6.9 (1.1)
Time period after stroke (years) Mean (SD)	5.3 (8.7)	6.6 (12.6)
Type of spasticity Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 20 week

Continuous Outcomes

Outcome	Abootulinum Toxin A (Dysport), Baseline, N = 54	Abootulinum Toxin A (Dysport), 20 week, N = 54	Placebo, Baseline, N = 42	Placebo, 20 week, N = 42
Quality of life AQoL (scale range 0.00-1.00; change scores) Mean (SD)	NA (NA)	0.03 (0.15)	NA (NA)	0.06 (0.13)
Pain VAS (scale range 0-100; change scores) Mean (SD)	NA (NA)	-10.8 (42)	NA (NA)	-0.7 (39.1)
Spasticity 3-Joint Combined MAS (scale range 0-12; change scores) Mean (SD)	NA (NA)	-1.8 (1.6)	NA (NA)	-0.2 (1.2)
Discontinuation No of events	n = 0 ; % = 0	n = 1 ; % = 0.54	n = 0 ; % = 0	n = 4 ; % = 1.92

Quality of life - Polarity - Higher values are better
Pain - Polarity - Lower values are better
Spasticity - Polarity - Lower values are better
Discontinuation - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Pain

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Quality of life

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Spasticity

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Discontinuation-NoOfEvents-Botulinum Toxin A-Placebo-t20

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Medici, 1989

Bibliographic Reference	Medici, M.; Pebet, M.; Ciblis, D.; A double-blind, long-term study of tizanidine ('Sirdalud') in spasticity due to cerebrovascular lesions; Current Medical Research and Opinion; 1989; vol. 11 (no. 6); 398-407

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Uruguay
Study setting	No additional information
Study dates	No additional information

Sources of funding	No additional information
Inclusion criteria	Aged 18-70 years Spasticity due to cerebrovascular disease
Exclusion criteria	Heart disease Severe arterial hypertension Orthostatic hypotension Chronic alcoholism Insulin-dependent diabetes mellitus Impaired liver or renal function Pathological blood chemistry values Overt psychopathology
Stratification - Type of spasticity	Generalised spasticity
Recruitment / selection of participants	No additional information
Intervention(s)	After a washout period of 4-5 days, during which all anti-spastic medication was withdrawn, a 2-week titration phase was initiated. Patients received 2 capsules tizanidine (8mg)per day, which increased by 1 capsule every 3 days to a maximum of 5 capsules per day (20mg tizanidine) administered in three daily doses. The investigator was free to stop the titration at any level if sufficient control of spasticity was achieved or if intolerable side effects occurred. The optimal dose achieved at the

	end of the titration phase was then continued during a 30-week maintenance phase. Concomitant medication, other than drugs exhibiting muscle relaxing properties, were allowed and registered.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mixed
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	not applicable
Population subgroups	No additional information
Comparator	After a washout period of 4-5 days, during which all anti-spastic medication was withdrawn, a 2-week titration phase was initiated. Patients received 2 capsules baclofen (20mg)per day, which increased by 1 capsule every 3 days to a maximum of 5 capsules per day (50mg baclofen) administered in three daily doses. The investigator was free to stop the titration at any level if sufficient control of spasticity was achieved or if intolerable side effects occurred. The optimal dose achieved at the end of the titration phase was then continued during a 30-week maintenance phase. Concomitant medication, other than drugs exhibiting muscle relaxing properties, were allowed and registered.
Number of participants	30; 15 in tizanidine group, 15 in baclofen group

Duration of follow-up	52 weeks
Indirectness	No additional information
Additional comments	Valid patients analysis included patients who fulfilled entry criteria and completed the study End-point analysis included all patients who entered the study, but did not necessarily complete it

Study arms

Tizanidine (N = 15)

Baclofen (N = 15)

Characteristics

Arm-level characteristics

Characteristic	**Tizanidine (N = 15)**	**Baclofen (N = 15)**
% Female Sample size	n = 4 ; % = 26.6	n = 2 ; % = 13.3
Mean age (SD) Mean (range) Mean (95% CI)	50 (22 to 73)	49 (24 to 68)
Ethnicity	NR	NR

Characteristic	Tizanidine (N = 15)	Baclofen (N = 15)
Nominal		
Comorbidities Nominal	NR	NR
Severity of spasticity Nominal	NR	NR
Moderate Nominal	8	10
Severe Nominal	7	4
Time period after stroke (years) Mean (range) Mean (95% CI)	2.47 (0.1 to 10)	4.5 (0.5 to 14)
Type of spasticity Nominal	NR	NR

Outcomes

Study timepoints

- 0 month (baseline)
- 12 month

Dichotomous Outcomes

Outcome	Tizanidine , 0 month, N = 15	Tizanidine , 12 month, N = 15	Baclofen , 0 month, N = 15	Baclofen , 12 month, N = 15
Withdrawal due to Adverse Effects Nominal	0	1	0	4
Withdrawal due to Adverse Effects No of events	n = 0 ; % = 0	n = 1 ; % = 7	n = 0 ; % = 0	n = 4 ; % = 27

Withdrawal due to Adverse Effects - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Withdrawal due to Adverse Effects

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Mesci, 2009

Bibliographic Reference	Mesci, N.; Ozdemir, F.; Kabayel, D. D.; Tokuc, B.; The effects of neuromuscular electrical stimulation on clinical improvement in hemiplegic lower extremity rehabilitation in chronic stroke: a single-blind, randomised, controlled trial; Disability & Rehabilitation; 2009; vol. 31 (no. 24); 2047-54

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Turkey
Study setting	Inpatient treatment centre
Study dates	No additional information
Sources of funding	No additional information
Inclusion criteria	Clinical picture of hemiplegia or hemiparesis due to a stroke experienced for the first time ≥3 months since stroke Psychosocial suitability Aged between 45 and 80 years Mobility of the ankle to permit at least a neutral position

	Spasticity <4 on the MAS Normal deep sensation
Exclusion criteria	Disorders of central nervous system Any additional medical or psychological condition that would affect the ability to comply with study protocol Previous treatment with NMES or FES Fixed ankle/foot contracture Ataxia, disthonia, dyskinesia and accompanying lower motor neuron or peripheral neural lesions Serious cardiac disease Skin and peripheral circulation disorders
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	Patients receiving an inpatient treatment
Intervention(s)	All patients received a 4-week inpatient treatment with a conventional exercise program. The program aimed to enhance patients motor, sensational and functional improvement, using methods including appropriate positioning of the extremities, range of motion exercises, active assistive exercises, progressive resistive exercises, endurance training, standing up and balance training. Additionally, self-care skills, mobility proficiency and basic/advanced daily life activities were targeted for achieving improvement. The NMES group received NMES treatment for hemiplegic foot dorsiflexor muscles for 4 weeks, 5 days a week for a total of 20 sessions. The device used was an EMG-triggered electrical stimulation device with pre-loaded durations and modulations specific to hemiplegic spasticity. During NMES, patients remained seated with the soles of their feet in contact with the floor. Electrodes were placed right above the fibular head and at the midpoint of the tibialis anterior muscle on the front side of the leg using velcro tissue bandages. The characteristic of the NMES program was a symmetrical biphasic wave of 50Hz frequency, 400usn width for a total of 20 minutes. Current density and electrode

	positions were set separately for each session so that first the toes, then the ankle dorsiflexors would be fully contracted with no discomfort or pain.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mixed
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb
Population subgroups	No additional information
Comparator	All patients received a 4-week inpatient treatment with a conventional exercise program. The program aimed to enhance patients motor, sensational and functional improvement, using methods including appropriate positioning of the extremities, range of motion exercises, active assistive exercises, progressive resistive exercises, endurance training, standing up and balance training. Additionally, self-care skills, mobility proficiency and basic/advanced daily life activities were targeted for achieving improvement.
Number of participants	40; 20 in NMES group, 20 in control group
Duration of follow-up	4 weeks

Indirectness	No additional information
Additional comments	No additional information

Study arms

Neuromuscular Electrical Stimulation (NMES) (N = 20)
Neuromuscular Electrical Stimulation plus Rehabilitation Program

Usual care (N = 20)
Rehabilitation Program Only

Characteristics

Arm-level characteristics

Characteristic	Neuromuscular Electrical Stimulation (NMES) (N = 20)	Usual care (N = 20)
% Female Sample size	n = 8 ; % = 40	n = 9 ; % = 45
Mean age (SD) (years) Mean (SD)	62.65 (7.52)	59.1 (8.58)
Ethnicity Nominal	NR	NR

Characteristic	Neuromuscular Electrical Stimulation (NMES) (N = 20)	Usual care (N = 20)
Comorbidities Nominal	NR	NR
Severity of spasticity MAS Mean (SD)	2.1 (0.7)	1.3 (1)
Time period after stroke (Months) Mean (SD)	9.45 (4.8)	7.3 (4.42)
Type of spasticity Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 4 week

Continuous Outcomes

Outcome	Neuromuscular Electrical Stimulation (NMES), Baseline, N = 20	Neuromuscular Electrical Stimulation (NMES), 4 week, N = 20	Usual care, Baseline, N = 20	Usual care, 4 week, N = 20
Spasticity MAS (scale range 0-4; change scores) Mean (SD)	NA (NA)	-1.2 (0.5)	NA (NA)	-0.15 (0.6)
Physical Function - Lower Limb Rivermead Motor Assessment (scale range 0-23; change scores) Mean (SD)	NA (NA)	2.95 (2.7)	NA (NA)	2.05 (2.1)
Discontinuation Nominal	0	0	0	0
Discontinuation No of events	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0

Spasticity - Polarity - Lower values are better

Physical Function - Lower Limb - Polarity - Higher values are better

Discontinuation - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Spasticity

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to concerns with randomisation process)*
Overall bias and Directness	Overall Directness	Directly applicable

Physical Function - Lower Limb

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to concerns over randomisation process)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Discontinuation-Nominal-Neuromuscular Electrical Stimulation plus Rehabilitation Program -Rehabilitation Program Only-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to concerns with randomisation process)*
Overall bias and Directness	Overall Directness	Directly applicable

1 Moon, 2021

Bibliographic Reference	Moon, J. H.; Cho, H. Y.; Hahm, S. C.; Influence of Electrotherapy with Task-Oriented Training on Spasticity, Hand Function, Upper Limb Function, and Activities of Daily Living in Patients with Subacute Stroke: A Double-Blinded, Randomized, Controlled Trial; Healthcare; 2021; vol. 9 (no. 8); 03

2

3 **Study details**

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	WHO International Clinical Trials Registry Platform, KCT0006318
Study type	Randomised controlled trial (RCT)
Study location	Korea
Study setting	No additional information
Study dates	No additional information
Sources of funding	No external funding
Inclusion criteria	First stroke diagnosed by a neurologist Middle cerebral artery lesions

	Stroke onset between 1 and 3 months Fair upper limb manual muscle test findings
Exclusion criteria	Other neurological diseases, such as degenerative diseases Severe sensory deficit Severe aphasia and severe neglect Severe spasticity (contracture)
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	No additional information
Intervention(s)	TENS was applied for 30 min before occupational therapy. Electrical stimulation (100 Hz, 200 μs) below the motor threshold was applied to the triceps muscle and wrist extensor muscle belly using a 2-channel TENS unit. Stimulation was applied to the level at which muscle contraction was observed. TENS was applied by a physical therapist not involved in this study. Occupational therapy with task-oriented training using stacking cones, rings, putty, ROM arcs, pegboards, coins, and towels was conducted. The task-oriented training was repeated for three categories: gross movement, grip, and pinch. The subjects were trained for 10 min per category and allowed to rest if they experienced fatigue. The training intensity of the tasks gradually increased after setting goals according to each subject's athletic performance. Physical therapy—such as walking, stretching, and lower limb muscle-strengthening exercises—was also performed. Occupational and physical therapy were each performed for 30 min a day, 5 times a week, for 4 weeks.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mild (or MAS 1)

Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	No additional information
Comparator	In the placebo-TENS group, electrodes were attached to the same locations as the TENS group, and a transient current was delivered for 30s, then ramped down to zero over 15s. Patients in the placebo-TENS group also received the same occupational therapy as the TENS group for 30 mins a day, 5 times a week for 4 weeks.
Number of participants	48 randomised; 24 in TENS group, 24 in placebo TENS group
Duration of follow-up	4 weeks
Indirectness	No additional information
Additional comments	No additional information

Study arms

Transcutaneous Electrical Nerve Stimulation (TENS) (N = 22)

Placebo (N = 21)

Characteristics

Arm-level characteristics

Characteristic	Transcutaneous Electrical Nerve Stimulation (TENS) (N = 22)	Placebo (N = 21)
% Female Sample size	n = 13 ; % = 59	n = 10 ; % = 48
Mean age (SD) (years) Mean (SD)	61.23 (7.24)	61.62 (8.32)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Severity of spasticity MAS Mean (SD)	1.23 (0.53)	1.29 (0.46)
Time period after stroke (days) Mean (SD)	59.41 (16.77)	57.95 (15.33)
Type of spasticity Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 4 week

Continuous Outcomes

Outcome	Transcutaneous Electrical Nerve Stimulation (TENS), Baseline, N = 22	Transcutaneous Electrical Nerve Stimulation (TENS), 4 week, N = 22	Placebo, Baseline, N = 21	Placebo, 4 week, N = 21
Spasticity MAS (scale range 0-4; change scores) Mean (SD)	NA (NA)	-0.55 (0.67)	NA (NA)	-0.24 (0.54)
Activities of daily living Barthel Index (scale range 0-100; change scores) Mean (SD)	NA (NA)	18.96 (11.8)	NA (NA)	13.86 (8.57)

Spasticity - Polarity - Lower values are better

Activities of daily living - Polarity - Higher values are better

discontinuation

Outcome	Transcutaneous Electrical Nerve Stimulation (TENS), Baseline, N = 22	Transcutaneous Electrical Nerve Stimulation (TENS), 4 week, N = 22	Placebo, Baseline, N = 21	Placebo, 4 week, N = 21
Discontinuation - due to adverse events Nominal	0	2	0	3
Discontinuation - due to adverse events No of events	n = 0 ; % = 0	n = 2 ; % = 9	n = 0 ; % = 0	n = 3 ; % = 14

Discontinuation - due to adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Spasticity

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Activities of daily living

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

discontinuation-Discontinuation-Nominal-Transcutaneous Electrical Nerve Stimulation (TENS)-Placebo-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Moon, 2003

Bibliographic Reference	Moon, S. K.; Whang, Y. K.; Park, S. U.; Ko, C. N.; Kim, Y. S.; Bae, H. S.; Cho, K. H.; Antispastic effect of electroacupuncture and moxibustion in stroke patients; American Journal of Chinese Medicine; 2003; vol. 31 (no. 3); 467-74

Study details

Secondary publication of another included study- see primary study for details	No additional information

Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Korea
Study setting	Inpatient
Study dates	No additional information
Sources of funding	No additional information
Inclusion criteria	No additional information
Exclusion criteria	No additional information
Stratification - Type of spasticity	Generalised spasticity
Recruitment / selection of participants	Patients were recruited in a consecutive manner among those who were admitted to Kyung Hee University Medical Center for rehabilitation therapy for stroke
Intervention(s)	All patients received the same routine acupuncture therapy for stroke and ROM exercises once per day. Acupuncture was given at acupoint: Pai-Hui, Shuei-Ko, Cheng-Chiang, Ch'u-Ch'ih, San-Li, Wai-Kuan, Ho-Ku, Tsu-San-Li, Hsuan-Chung and T'ai-Ch'ung on both paretic and non-paretic sides. Steel needles were used and were kept in place for 30 minutes at a time. Electrical stimulation was applied every other day for 15 days (8 sessions) with a frequency of 50Hz administered to the four needles on the Ch'u-Ch'ih-San-Li and Wai-Huan-Ho-Ku points of the paretic side for 30 minutes at a time. The amplitude was adjusted to be strong enough for patients to feel stimulation but not to elicit visible muscle contractions.
Subgroup 1: Severity of spasticity (as stated by category	Severe (or MAS 3)

or as measured by modified Ashworth scale [MAS])	
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	Acupuncture
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	No additional information
Comparator	All patients received the same routine acupuncture therapy for stroke and ROM exercises once per day. Acupuncture was given at acupoint: Pai-Hui, Shuei-Ko, Cheng-Chiang, Ch'u-Ch'ih, San-Li, Wai-Kuan, Ho-Ku, Tsu-San-Li, Hsuan-Chung and T'ai-Ch'ung on both paretic and non-paretic sides. Steel needles were used and were kept in place for 30 minutes at a time.
Number of participants	45 in study; 15 in EA group, 10 in Mox group (excluded from comparison), 10 in control group
Duration of follow-up	15 days
Indirectness	No additional information
Additional comments	No additional information

1

Study arms

Electroacupuncture (N = 15)

Acupuncture (N = 10)

Characteristics

Arm-level characteristics

Characteristic	Electroacupuncture (N = 15)	Acupuncture (N = 10)
% Female Sample size	n = 8 ; % = 53	n = 6 ; % = 60
Mean age (SD) (years) Mean (SD)	58.2 (10.8)	65.1 (7.9)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Severity of spasticity MAS Mean (SD)	3.3 (1.04)	3.5 (0.71)

Characteristic	Electroacupuncture (N = 15)	Acupuncture (N = 10)
Time period after stroke (Months) Mean (SD)	3.7 (3.7)	2.7 (1.4)
Type of spasticity Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 15 day

Continuous Outcomes

Outcome	Electroacupuncture , Baseline, N = 15	Electroacupuncture , 15 day, N = 15	Acupuncture , Baseline, N = 10	Acupuncture , 15 day, N = 10
Spasticity MAS (scale range 0-5; final values) Mean (SD)	3.3 (1.04)	2.1 (0.8)	3.5 (0.71)	3.2 (0.79)

Spasticity - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Spasticity

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Morone, 2012

Bibliographic Reference	Morone, G.; Fusco, A.; Di Capua, P.; Coiro, P.; Pratesi, L.; Walking training with foot drop stimulator controlled by a tilt sensor to improve walking outcomes: a randomized controlled pilot study in patients with stroke in subacute phase; Stroke Research and Treatment; 2012; vol. 2012; 523564

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information

Study type	Randomised controlled trial (RCT)
Study location	Italy
Study setting	No additional information
Study dates	No additional information
Sources of funding	No funding declared
Inclusion criteria	First stroke, in subacute phase Aged between 18 and 80 years Inadequate ankle dorsiflexion during the swing phase of gait, resulting in inadequate limb clearance Adequate cognitive and communication function to give informed consent and understand the training instructions (MMSE > 24) Able to ambulate with or without aid of one person with assistive device if needed (FAC 2, 3, or 4), at least 10 meters
Exclusion criteria	Severe cardiac disease If present, an ankle contracture of at least 5 degrees of plantar flexion when knee is extended Orthopaedics or other neurological conditions different from stroke affecting ambulation
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	No additional information
Intervention(s)	20 sessions of 40 minutes, 5 times per week of walking training with Walkaide. For Walkaide, a set-up phase was necessary in which a manual controller and a heel sensor pressure data were collected and connected to the other electronic components. Data obtained in the set-up phase and matching them with the rehabilitative purpose, was necessary to choose tilt parameters to correct foot drop. Both groups undertook 40 minutes with a physiotherapist dedicated to improve activity of daily living and/or exercise for hand recovery.

Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mixed
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb
Population subgroups	No additional information
Comparator	20 sessions of 40 minutes, 5 times per week of walking training with an ankle-foot orthosis. Both groups undertook 40 minutes with a physiotherapist dedicated to improve activity of daily living and/or exercise for hand recovery.
Number of participants	20; 10 in NMES group, 10 in control group
Duration of follow-up	1-month
Indirectness	No additional information
Additional comments	No additional information

1

Study arms

Neuromuscular Electrical Stimulation (NMES) (N = 10)

Usual care (N = 10)
Conventional Neuromotor Rehabilitation

Characteristics

Arm-level characteristics

Characteristic	**Neuromuscular Electrical Stimulation (NMES) (N = 10)**	**Usual care (N = 10)**
% Female Nominal	NR	NR
Mean age (SD) (years) Mean (SD)	61.2 (16.2)	53.3 (14.6)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Severity of spasticity Nominal	NR	NR

Characteristic	Neuromuscular Electrical Stimulation (NMES) (N = 10)	Usual care (N = 10)
Time period after stroke (days) Mean (SD)	27 (27)	13 (7)
Type of spasticity Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 1 month

Continuous Outcomes

Outcome	Neuromuscular Electrical Stimulation (NMES), Baseline, N = 10	Neuromuscular Electrical Stimulation (NMES), 1 month, N = 10	Usual care, Baseline, N = 10	Usual care, 1 month, N = 10
Physical Function - Lower Limb (metres per second) Walking Speed (final values) Mean (SD)	0.31 (0.15)	0.5 (0.2)	0.38 (0.2)	0.49 (0.24)

Physical Function - Lower Limb - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Physical Function - Lower Limb

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Nakipoglu Yuzer, 2017

Bibliographic Reference	Nakipoglu Yuzer, G. F.; Kose Donmez, B.; Ozgirgin, N.; A Randomized Controlled Study: Effectiveness of Functional Electrical Stimulation on Wrist and Finger Flexor Spasticity in Hemiplegia; Journal of Stroke & Cerebrovascular Diseases; 2017; vol. 26 (no. 7); 1467-1471

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NR

Study type	Randomised controlled trial (RCT)
Study location	Turkey
Study setting	Rehabilitation hospital inpatients
Study dates	NR
Sources of funding	NR
Inclusion criteria	Inpatients with a 3-month history of CVA with at least a stage 2 wrist spasticity MAS score and who were able to cooperate were included in the study.
Exclusion criteria	Patients with a previous motor deficit in the upper extremity, or motor neuron disease active infection, other neurological disorders, uncompensated cardiac disease, tumour, cardiac pacemaker and convulsion history were excluded.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	Inpatients who had at least 3 months history of CVA and MAS 2 wrist spasticity were included
Intervention(s)	FES was applied to the motor points of the wrist extensor muscles in the study group. A FES device with 2 channels and 2 surface electrodes producing low-frequency currents was used. the intensity of the stimulation was set to produce full wrist and finger extension with a duty cycle of 10 seconds on and off. the stimulus pulse was a biphasic rectangular waveform with a pulse width of 300 micro seconds, a frequency of 30 hz and a ramp up and down time of 2 seconds. stimulus intensity was increased to the level that could be tolerated by the patients. FED was applied 30 minutes per day for 5 days a week for a total of 20 sessions per patient. Surface electrodes were positioned to allow active movement throughout the ROM and the stimulus intensity was individualised for the patient. Conventional treated consisting of passive ROM exercises, stretching exercises, and a wrist-hand static splint was also used and provided to both study groups.
Subgroup 1: Severity of spasticity (as stated by category	Moderate (or MAS 2)

or as measured by modified Ashworth scale [MAS])	
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	NA
Comparator	Conventional treated consisting of passive ROM exercises, stretching exercises, and a wrist-hand static splint were given to the control group.
Number of participants	30
Duration of follow-up	Follow up at discharge
Indirectness	Follow up at discharge only
Additional comments	NR

1

Study arms

Functional electrical stimulation (N = 15)

conventional care (N = 15)

Characteristics

Study-level characteristics

Characteristic	Study (N = 30)
Ethnicity Nominal	NR
Comorbidities Nominal	NR
Type of spasticity Nominal	NR

Arm-level characteristics

Characteristic	Functional electrical stimulation (N = 15)	conventional care (N = 15)
% Female Nominal	23.3	20

Characteristic	Functional electrical stimulation (N = 15)	conventional care (N = 15)
Mean age (SD) Mean (SD)	60.2 (12.2)	57.66 (10.63)
Severity of spasticity Nominal	NR	NR
MAS 2 % Nominal	20	53.3
MAS 3 % Nominal	80	46.7
Time period after stroke months Mean (SD)	4.6 (1.33)	4.86 (1.49)

Outcomes

Study timepoints

- Baseline
- 4 week (Study reports FU at discharge only - no time point provided but intervention lasted 4 weeks)

FES vs usual care

Outcome	Functional electrical stimulation, Baseline, N = 15	Functional electrical stimulation, 4 week, N = 15	conventional care, Baseline, N = 15	conventional care, 4 week, N = 15
Activities of daily living - Barthel Index (final values) 0-100 Mean (SD)	54.66 (7.43)	61 (8.49)	49.66 (7.18)	52.66 (8.2)
physical function - upper extremity - Rivermead Motor assessment hand? final values Mean (SD)	2.2 (0.86)	2.86 (1.06)	1.86 (0.3)	2.2 (0.94)

Activities of daily living - Barthel Index - Polarity - Higher values are better
physical function - upper extremity - Rivermead Motor assessment hand? - Polarity - Higher values are better
Final values

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

FESvsusualcare-Activitiesofdailyliving-BarthelIndex-MeanSD-Functional electrical stimulation-conventional care-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Due to missing data and issues arising with the randomisation process)*
Overall bias and Directness	Overall Directness	Directly applicable

FESvsusualcare-physicalfunction-upperextremity-RivermeadMotorassessmenthand?-MeanSD-Functional electrical stimulation-conventional care-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Due to missing data, issues arising with the randomisation process and bias in the selection of reported result)*
Overall bias and Directness	Overall Directness	Directly applicable

Ng, 2007

Bibliographic Reference	Ng, S. S.; Hui-Chan, C. W.; Transcutaneous electrical nerve stimulation combined with task-related training improves lower limb functions in subjects with chronic stroke; Stroke; 2007; vol. 38 (no. 11); 2953-9

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	

Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	community rehabilitation network
Study dates	NR
Sources of funding	This study was supported by the Health Service Research Fund (K-ZK34) from the Hong Kong Government (SAR) and a scholarship from The Hong Kong Polytechnic University to S.S.M.N.
Inclusion criteria	Subjects were included if they had a single stroke at least 1 year ago, were able to walk 10 m unassisted with or without walking aids, and had a Composite Spasticity Score21 of ≥10 in their ankle plantarflexors.
Exclusion criteria	Exclusion criteria were medical comorbidity, receptive dysphasia, or cognitive impairment denoted by scoring <7 of 10 on the Abbreviated Mental Test.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	NR
Intervention(s)	The TENS group received 60 minutes of TENS (100 Hz, 0.2-ms square pulses, 2 to 3 times sensory threshold) from a TENS stimulator (CEFAR Dumo 2.4 K; Cefar Medical Products AB, Lund, Sweden). Electrodes were placed over 4 acupuncture points of the affected leg, namely ST 36 (Zusanli), LV 3 (Taichong), GB 34 (Yanglinquan), and UB 60 (Kunlun). These acupoints were selected according to traditional Chinese medicine23 and a previous stroke study. The TENS+TRT group received 60 minutes of TENS followed by 60 minutes of TRT modified from Carr and Shepherd.9 TRT included 4 weightbearing and stepping exercises using wooden blocks of 2.5 or 5 cm in height: (1) loading exercise on the affected leg; (2) stepping up exercise with the affected leg; (3) stepping down exercise with the unaffected leg; (4) heel lifts from a dorsiflexed position in standing and 2 functional training; (5) standing up from a chair, walking a short distance, and returning to the chair; and (6) walking with rhythmic auditory cues generated by a metronome. Standardized progression was made by the physiotherapist by using higher wooden blocks when subjects could perform the

	weightbearing exercises 20 times without compensatory movement and by increasing the number of repetitions completed within 10 minutes. Walking was progressed by increasing its speed. Subjects were required to perform the home program daily 5 days a week for 4 weeks. During this period, they attended 8 instruction sessions in our laboratory to ensure that they could follow the home program properly and for the physiotherapist to progress the exercise level as needed. Daily log books were entered by all subjects. To ensure treatment compliance, the physiotherapist made regular telephone reminders and checked clients' daily log books in every instruction session.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Moderate (or MAS 2)
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb
Population subgroups	NR
Comparator	The control group received no treatment.

	The PLBO+TRT group received 60 minutes of PLBO-TENS from identical-looking TENS devices with the electrical circuit disconnected inside followed by 60 minutes of TRT as described subsequently. TRT included 4 weightbearing and stepping exercises using wooden blocks of 2.5 or 5 cm in height: (1) loading exercise on the affected leg; (2) stepping up exercise with the affected leg; (3) stepping down exercise with the unaffected leg; (4) heel lifts from a dorsiflexed position in standing and 2 functional training; (5) standing up from a chair, walking a short distance, and returning to the chair; and (6) walking with rhythmic auditory cues generated by a metronome. Subjects were required to perform the home program daily 5 days a week for 4 weeks. During this period, they attended 8 instruction sessions in our laboratory to ensure that they could follow the home program properly and for the physiotherapist to progress the exercise level as needed. Daily log books were entered by all subjects. To ensure treatment compliance, the physiotherapist made regular telephone reminders and checked clients' daily log books in every instruction session.
Number of participants	88
Duration of follow-up	8 weeks
Indirectness	NA
Additional comments	NR

Study arms

Transcutaneous electrical nerve stimulation (TENS) (N = 44)

TENS and TENS + task related training. The 2 intervention groups have been combined for the purposes of this review

Usual care (N = 22)

Sham therapy (N = 22)
Placebo TENS + task related training

Characteristics

Study-level characteristics

Characteristic	Study (N = 88)
Ethnicity Nominal	NR
Comorbidities Nominal	NR
Type of spasticity Nominal	NR

Arm-level characteristics

Characteristic	Transcutaneous electrical nerve stimulation (TENS) (N = 44)	Usual care (N = 22)	Sham therapy (N = 22)
% Female Nominal	17.5	15	15
Mean age (SD)	57.5 (8.2)	57.3 (8.6)	57.1 (7.8)

Characteristic	Transcutaneous electrical nerve stimulation (TENS) (N = 44)	Usual care (N = 22)	Sham therapy (N = 22)
Mean (SD)			
Severity of spasticity Nominal	NR	NR	NR
Severity of spasticity Mean (SD)	12.1 (1.7)	11.8 (1.6)	12.2 (1.5)
Time period after stroke Mean (SD)	5.6 (3.6)	5.2 (2.9)	4.7 (4.1)

Outcomes

Study timepoints

- Baseline
- 8 week

TENS vs placebo vs control

Outcome	Transcutaneous electrical nerve stimulation (TENS), Baseline, N = 44	Transcutaneous electrical nerve stimulation (TENS), 8 week, N = 40	Usual care, Baseline, N = 22	Usual care, 8 week, N = 20	Sham therapy, Baseline, N = 22	Sham therapy, 8 week, N = 20
Spasticity outcome - Composite Spasticity Scale (final values)	12.1 (1.7)	11.3 (1.6)	11.8 (1.6)	11.7 (1.6)	12.2 (1.5)	11.4 (1.5)

Outcome	Transcutaneous electrical nerve stimulation (TENS), Baseline, N = 44	Transcutaneous electrical nerve stimulation (TENS), 8 week, N = 40	Usual care, Baseline, N = 22	Usual care, 8 week, N = 20	Sham therapy, Baseline, N = 22	Sham therapy, 8 week, N = 20
Mean (SD)						

Spasticity outcome - Composite Spasticity Scale - Polarity - Lower values are better
Final values

discontinuation

Outcome	Transcutaneous electrical nerve stimulation (TENS), Baseline, N = 44	Transcutaneous electrical nerve stimulation (TENS), 8 week, N = 44	Usual care, Baseline, N = 22	Usual care, 8 week, N = 22	Sham therapy, Baseline, N = 22	Sham therapy, 8 week, N = 22
Discontinuation No of events	n = 0 ; % = 0	n = 4 ; % = 9.09	n = 0 ; % = 0	n = 2 ; % = 9.09	n = 0	n = 2 ; % = 9.09

Discontinuation - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

discontinuation-Discontinuation-NoOfEvents-TENS and TENS + task related training-control -Placebo TENS + task related training-t8

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

TENSvsplacebovscontrol-Spasticityoutcome-CompositeSpasticityScale-MeanSD-TENS and TENS + task related training-control - Placebo TENS + task related training-t8

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Ng, 2009

Bibliographic Reference	Ng, S. S.; Hui-Chan, C. W.; Does the use of TENS increase the effectiveness of exercise for improving walking after stroke? A randomized controlled clinical trial; Clinical Rehabilitation; 2009; vol. 23 (no. 12); 1093-103

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)

Study location	China
Study setting	Outpatient setting
Study dates	NR
Sources of funding	This study was supported by the Health Service Research Fund (# K-ZK34) from the Hong Kong Government (SAR), and a scholarship from The Hong Kong Polytechnic University to S. Ng.
Inclusion criteria	Subjects with spastic plantarflexors were recruited through a local rehabilitation network in Hong Kong. They were required to fulfil the following inclusion criteria: (1) between 50 and 75 years of age; (2) having experienced only a single stroke; (3) at least one year post stroke; (4) manifesting moderate to severe spasticity in the affected ankle plantarflexors with composite spasticity score12 410 (NB TENS was found to be effective in decreasing plantarflexor spasticity in our previous study11,13); (5) at least 10 of passive ankle dorsiflexion so that they could perform the heel lift exercise.
Exclusion criteria	Subjects were excluded if they had any pre-existing neurological disorder other than the stroke, medical comorbidity that precluded them from undergoing the exercise training and assessment protocol, or cognitive impairment (scoring 57 on the Abbreviated Mental Test).1
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	Subjects with spastic plantarflexors were recruited through a local rehabilitation network in Hong Kong.
Intervention(s)	The subjects in the three intervention groups received 20 sessions of their assigned treatment for five days a week for four weeks. The TENS group received 60 minutes of TENS, delivered through two pairs of self-adhesive electrodes placed on four selected acupuncture points of the affected lower extremity, namely ST 36 (Zusanli), LV 3 (Taichong), GB 34 (Yanglinquan) and UB 60 (Kunlun), with the cathodes placed proximally. The acupuncture points chosen are recommended in the Chinese medicine literature,16 and their stimulation has been shown in previous studies17,18 to improve motor recovery in stroke patients. Trains of electrical stimulation pulses were delivered at 100 Hz using a square pulse stimulator (pulse width 0.2 ms). The stimulus intensity was adjusted to about twice each patient's sensory threshold, defined as the minimal tingling sensation felt by the patients. The TENS + exercise group received 60 minutes of the same TENS protocol followed by 60 minutes of task-related exercises recommended for stroke rehabilitation.19 The exercises aimed to improve the muscle strength in the affected lower limb and walking capacity. The subjects were given photographs of the electrode positions for the TENS and sham treatment, and photographs of each exercise with detailed written instructions. Daily logbooks and regular telephone contacts were incorporated to increase subjects' treatment compliance.

Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb
Population subgroups	NR
Comparator	Placebo = The placebo stimulation + exercise group performed 60 minutes of the same exercise after receiving 60 minutes of placebo stimulation from identical looking stimulation devices, but with the electrical circuit disconnected inside. Subjects in the three intervention groups were asked to carry out the programme at home, but all of them were required to attend eight instruction sessions first in order to ensure that they performed the exercises safely and progressed the exercises as necessary. The subjects were given photographs of the electrode positions for the TENS and sham treatment, and photographs of each exercise with detailed written instructions. Daily logbooks and regular telephone contacts were incorporated to increase subjects' treatment compliance. Control = The control group received no treatment, and they just attended four assessment sessions.
Number of participants	109
Duration of follow-up	8 weeks (4 weeks post intervention)

Indirectness	NA
Additional comments	NR

Study arms

Transcutaneous electrical nerve stimulation (TENS) (N = 55)
TENS group + TENS and exercise group. Combined the 2 treatment groups for the purposes of this review

Usual care (N = 29)

Sham therapy (N = 25)
Placebo stimulation + exercise group

Characteristics

Study-level characteristics

Characteristic	**Study (N = 109)**
Ethnicity Nominal	NR
Comorbidities Nominal	NR

Characteristic	Study (N = 109)
Type of spasticity Nominal	NR

Arm-level characteristics

Characteristic	Transcutaneous electrical nerve stimulation (TENS) (N = 55)	Usual care (N = 29)	Sham therapy (N = 25)
% Female Nominal	18.8	31	20
Mean age (SD) Mean (SD)	57.14 (7.8)	55.5 (8)	56.9 (8.6)
Severity of spasticity Mean (SD)	9.18 (1.14)	9.5 (0.7)	9.1 (0.9)
Time period after stroke years Mean (SD)	4.8 (3.4)	5 (3)	4.3 (3.8)

Outcomes

Study timepoints

- Baseline
- 8 week

TENS vs Placebo Vs Control

Outcome	Transcutaneous electrical nerve stimulation (TENS), Baseline, N = 55	Transcutaneous electrical nerve stimulation (TENS), 8 week, N = 51	Usual care, Baseline, N = 29	Usual care, 8 week, N = 27	Sham therapy, Baseline, N = 25	Sham therapy, 8 week, N = 23
physical function - lower limb - timed up and go final values Mean (SD)	24.08 (14.5)	21.4 (10.6)	22.9 (13.5)	23.2 (14.9)	29.4 (22.1)	27.8 (22.8)

physical function - lower limb - timed up and go - Polarity - Lower values are better
Final values

discontinuation

Outcome	Transcutaneous electrical nerve stimulation (TENS), Baseline, N = 55	Transcutaneous electrical nerve stimulation (TENS), 8 week, N = 55	Usual care, Baseline, N = 29	Usual care, 8 week, N = 29	Sham therapy, Baseline, N = 25	Sham therapy, 8 week, N = 25
Discontinuation No of events	n = 0 ; % = 0	n = 4 ; % = 7.27	n = 0 ; % = 0	n = 2 ; % = 6.9	n = 0 ; % = 0	n = 2 ; % = 8

Discontinuation - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

discontinuation-Discontinuation-NoOfEvents-TENS group + TENS and exercise group-Control group-Placebo stimulation + exercise group-t8

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

TENSvsPlaceboVsControl-physicalfunction-lowerlimb-timedupandgo-MeanSD-TENS group + TENS and exercise group-Control group-Placebo stimulation + exercise group-t8

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Park, 2014

Bibliographic Reference	Park, J.; Seo, D.; Choi, W.; Lee, S.; The effects of exercise with TENS on spasticity, balance, and gait in patients with chronic stroke: a randomized controlled trial; Medical Science Monitor; 2014; vol. 20; 1890-6

Study details

Secondary publication of another included	NA

study- see primary study for details	
Other publications associated with this study included in review	NA
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	South Korea
Study setting	4 rehabilitation hospitals in Seoul, South Korea
Study dates	NR
Sources of funding	This research was supported by a Sahmyook University Research Grant
Inclusion criteria	Participants were included if they had been diagnosed with hemiplegic stroke more than 6 months previously (to exclude natural recovery) and were able to walk 10 m independently.
Exclusion criteria	Exclusion criteria included cognitive impairment indicated by scoring higher than 24 on the Mini-Mental State Examination [15], other orthopedic disease, and visual or auditory disorders
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	One hundred participants were initially recruited from 4 rehabilitation hospitals in Seoul, South Korea. Thirty quadriplegic patients, 29 patients who could not walk 10 m independently, 4 patients with orthopedic disorder, and 3 patients with cerebellar disease were excluded from the study
Intervention(s)	TENS plus therapeutic exercise group (TENS group) Two-channel TENS (TENS-7000, Koalaty Products Inc., USA) was used. TENS electrodes (5 cm2) were placed on the affected lower extremity on the lateral and medial quadriceps and gastrocnemius. A frequency of 100 Hz and a pulse width 200 μs were used. Participant pre-stimulation threshold was measured from 0.01 mA and stimulated by 90% amplitude using the sub-sensory threshold [4]. Stimulation was 30 min, and the patient perceived no sensation. TENS was used with the general exercise program.

	Participants in the 2 groups engaged in the same 30-min therapeutic exercise 5 days per week for 6 weeks. Participants engaged in a 30-min exercise with a physical therapist. The exercise comprised a one-to-one ROM exercise (10 min), a functional mat exercise (10 min), and a gait exercise (10 min), which were each performed at a difficulty level appropriate for the patient. In order to minimize differences between the present and previous interventions, the exercise program was performed according to the pre-set principles, once 1 week before the experiment, and 6 times during the experiment; thus, there were 7 education and practice sessions in total. Education was provided to resolve problems occurring during the exercise program, and to teach performance of exercise program according to the established principles. Participants in both groups performed exercises in the same manner.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Moderate (or MAS 2)
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb
Population subgroups	NR

Comparator	Placebo TENS plus therapeutic exercise group (Placebo TENS group) Two-channel TENS was used in the same manner as in the TENS group. However, stimulation was not applied and patients were informed that the treatment would be imperceptible. Participants in the 2 groups engaged in the same 30-min therapeutic exercise 5 days per week for 6 weeks. Participants engaged in a 30-min exercise with a physical therapist. The exercise comprised a one-to-one ROM exercise (10 min), a functional mat exercise (10 min), and a gait exercise (10 min), which were each performed at a difficulty level appropriate for the patient. In order to minimize differences between the present and previous interventions, the exercise program was performed according to the pre-set principles, once 1 week before the experiment, and 6 times during the experiment; thus, there were 7 education and practice sessions in total. Education was provided to resolve problems occurring during the exercise program, and to teach performance of exercise program according to the established principles. Participants in both groups performed exercises in the same manner.
Number of participants	29
Duration of follow-up	post intervention 6 weeks
Indirectness	NA
Additional comments	NR

Study arms

Transcutaneous electrical nerve stimulation (TENS) (N = 17)
TENS plus therapeutic exercise

Sham therapy (N = 17)
Placebo TENS plus therapeutic exercise

1

2 **Characteristics**

3 ***Study-level characteristics***

Characteristic	Study (N = 29)
Ethnicity Nominal	NR
Comorbidities Nominal	NR
Type of spasticity Nominal	NR

4

5 ***Arm-level characteristics***

Characteristic	Transcutaneous electrical nerve stimulation (TENS) (N = 17)	Sham therapy (N = 17)
% Female Nominal	20	42.86
Mean age (SD) Mean (SD)	71.2 (3.46)	71.14 (3.82)
Severity of spasticity Mean (SD)	2.6 (0.63)	2.5 (0.76)

Characteristic	Transcutaneous electrical nerve stimulation (TENS) (N = 17)	Sham therapy (N = 17)
Time period after stroke Mean (SD)	18.66 (2.46)	18.57 (1.74)

Outcomes

Study timepoints

- Baseline
- 6 week

TENS versus placebo

Outcome	Transcutaneous electrical nerve stimulation (TENS), Baseline, N = 17	Transcutaneous electrical nerve stimulation (TENS), 6 week, N = 15	Sham therapy, Baseline, N = 17	Sham therapy, 6 week, N = 14
spasticity outcome - MAS (final values) 0-4 Mean (SD)	2.6 (0.63)	1.8 (0.41)	2.5 (0.76)	2.36 (0.74)
physical function - lower limb - timed up and go (final values) Mean (SD)	26.16 (11.71)	21.84 (9.28)	25.7 (12.41)	24.61 (11.61)

spasticity outcome - MAS - Polarity - Lower values are better
physical function - lower limb - timed up and go - Polarity - Lower values are better

Final values

discontinuation

Outcome	Transcutaneous electrical nerve stimulation (TENS), Baseline, N = 17	Transcutaneous electrical nerve stimulation (TENS), 6 week, N = 17	Sham therapy, Baseline, N = 17	Sham therapy, 6 week, N = 17
Discontinuation TENS= 1 discharge, 1 = absent from training. Placebo = 3 = discharge No of events	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0

Discontinuation - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

discontinuation-Discontinuation-NoOfEvents-TENS plus therapeutic exercise-Placebo TENS plus therapeutic exercise-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to missing data)*
Overall bias and Directness	Overall Directness	Directly applicable

TENSversusplacebo-spasticityoutcome-MAS-MeanSD-TENS plus therapeutic exercise-Placebo TENS plus therapeutic exercise-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to missing data)*
Overall bias and Directness	Overall Directness	Directly applicable

TENSversusplacebo-physicalfunction-lowerlimb-timedupandgo-MeanSD-TENS plus therapeutic exercise-Placebo TENS plus therapeutic exercise-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to missing data)*
Overall bias and Directness	Overall Directness	Directly applicable

Patel, 2020

Bibliographic Reference	Patel, A. T.; Ward, A. B.; Geis, C.; Jost, W. H.; Liu, C.; Dimitrova, R.; Impact of early intervention with onabotulinumtoxinA treatment in adult patients with post-stroke lower limb spasticity: results from the double-blind, placebo-controlled, phase 3 REFLEX study; Journal of Neural Transmission; 2020; vol. 127 (no. 12); 1619-1629

Study details

Secondary publication of another included	NR

study- see primary study for details	
Other publications associated with this study included in review	Wein T, Esquenazi A, Jost WH, Ward AB, Pan G, Dimitrova R (2018) OnabotulinumtoxinA for the treatment of post-stroke distal lowerlimb spasticity: a randomized trial. PM R 10:693–703
Trial name / registration number	The REFLEX study (ClinicalTrials.gov Identifier NCT01575054)
Study type	Randomised controlled trial (RCT)
Study location	Conducted at 60 sites throughout Canada, the United States, Czech Republic, Germany, Hungary, Poland, Russia, the United Kingdom, and South Korea
Study setting	multicentre in a number of countries worldwide
Study dates	NR
Sources of funding	This study was sponsored by Allergan plc (Dublin, Ireland). Writing and editorial assistance was provided to the authors by Dana Franznick, PharmD, of Complete Healthcare Communications, LLC, and was funded by Allergan plc; and by Karen Pemberton, PhD, of Evidence Scientifc Solutions, Inc, Philadelphia, PA, and funded by Allergan plc. All authors met the ICMJE authorship criteria. Neither honoraria nor payments were made for authorship.
Inclusion criteria	The study enrolled men and women aged 18–85 years with a diagnosis of PSLLS (determined by a MAS score≥3 in the ankle plantar fexors), with the most recent stroke occurring≥3 months before screening. Enrolled patients were either naive to onabotulinumtoxinA or, if previously treated, had undergone no treatment with onabotulinumtoxinA for≥20 weeks (spasticity indication) or≥12 weeks (any other indication) before the screening visit.
Exclusion criteria	Patients were excluded from study participation if there was an etiology other than stroke contributing to spasticity or if they had spasticity in the contralateral leg requiring treatment, if there was any medical or neurologic condition that might put the patient at increased risk with exposure to onabotulinumtoxinA, or if the patient had an intrathecal baclofen pump. Women of childbearing potential who were not using a reliable method of contraception or women who were pregnant, nursing, or planning a pregnancy during the study period were also excluded.
Stratification - Type of spasticity	Multifocal spasticity

Recruitment / selection of participants	NR
Intervention(s)	OnabotulinumtoxinA was reconstituted with sterile saline (4 mL of preservativefree 0.9% normal saline to each 100 U). Patients received intramuscular injections of onabotulinumtoxinA 300 U into three sites each of the gastrocnemius (medial and lateral heads), soleus, and tibialis posterior muscles (i.e., mandatory ankle muscles. An optional dose of up to 100 U onabotulinumtoxinA was injected into the fexor digitorum longus, fexor digitorum brevis, fexor hallucis longus, extensor hallucis, or rectus femoris if clinically indicated. The need to inject the rectus femoris was determined by a clinical evaluation and a MAS knee score of≥1. The need to inject the remaining optional muscles was based on the investigator's clinical judgment. The injector and patient were blinded to whether active drug or placebo was given. Study treatments were provided in identical vials and cartons to maintain masking of the study treatment. To ensure that the injector remained blinded in the double-blind treatment phase, an independent drug reconstitutor was responsible for preparing the study medication according to the specific dilution requirements. During the double-blind phase, the initiation of any medications for spasticity, muscle relaxants, or antiepileptic medications was prohibited. Only those on a stable dose and regimen before the frst day of the study were permitted. The initiation of physical therapy or the use of static or dynamic splints within 14 days of the frst study visit was also prohibited. Patients who entered the study receiving any of the aforementioned treatments were to remain on a stable dose or regimen throughout the double-blind phase.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Severe (or MAS 3)
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and	Lower limb

multifocal spasticity only, area affected	
Population subgroups	analysis split into <24 months post stroke and >24 months post stroke
Comparator	Placebo (0.9 mg sodium chloride) was reconstituted with sterile saline (4 mL of preservativefree 0.9% normal saline to each 100 U). Patients received intramuscular injections of placebo into three sites each of the gastrocnemius (medial and lateral heads), soleus, and tibialis posterior muscles (i.e., mandatory ankle muscles; Table 1). An optional dose of up to 100 U onabotulinumtoxinA or placebo was injected into the fexor digitorum longus, fexor digitorum brevis, fexor hallucis longus, extensor hallucis, or rectus femoris if clinically indicated. The need to inject the rectus femoris was determined by a clinical evaluation and a MAS knee score of≥1. The need to inject the remaining optional muscles was based on the investigator's clinical judgment. The injector and patient were blinded to whether active drug or placebo was given. Study treatments were provided in identical vials and cartons to maintain masking of the study treatment. To ensure that the injector remained blinded in the double-blind treatment phase, an independent drug reconstitutor was responsible for preparing the study medication according to the specific dilution requirements. During the double-blind phase, the initiation of any medications for spasticity, muscle relaxants, or antiepileptic medications was prohibited. Only those on a stable dose and regimen before the frst day of the study were permitted. The initiation of physical therapy or the use of static or dynamic splints within 14 days of the frst study visit was also prohibited. Patients who entered the study receiving any of the aforementioned treatments were to remain on a stable dose or regimen throughout the double-blind phase.
Number of participants	468
Duration of follow-up	12 weeks
Indirectness	na
Additional comments	

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Study arms

Onabotulinum toxin A ((BOTOX) 300–400 U (N = 233)

placebo (N = 235)

Characteristics

Study-level characteristics

Characteristic	Study (N = 465)
Ethnicity Nominal	NR
Comorbidities Nominal	NR
Severity of spasticity Nominal	NR
Type of spasticity Nominal	NR

Arm-level characteristics

Characteristic	Onabotulinum toxin A ((BOTOX) 300–400 U (N = 233)	placebo (N = 235)
% Female Nominal	36.48	34.04
Mean age (SD) Mean (SD)	56 (12.63)	56.94 (11.82)
Time period after stroke years Mean (SD)	5.6 (6.21)	5.09 (6.17)

Outcomes

Study timepoints

- Baseline
- 12 week

discontinuation

Outcome	Onabotulinum toxin A ((BOTOX) 300–400 U, Baseline, N = 233	Onabotulinum toxin A ((BOTOX) 300–400 U, 12 week, N = 233	placebo, Baseline, N = 235	placebo, 12 week, N = 235
Discontinuation reasons not provided No of events	n = 0 ; % = 0	n = 10 ; % = 23.3	n = 0 ; % = 0	n = 8 ; % = 3.4

Discontinuation - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

discontinuation-Discontinuation-NoOfEvents-onabotulinumtoxinA 300–400 U-placebo-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Pittock, 2003

Bibliographic Reference	Pittock, S. J.; Moore, A. P.; Hardiman, O.; Ehler, E.; Kovac, M.; Bojakowski, J.; Al Khawaja, I.; Brozman, M.; Kanovsky, P.; Skorometz, A.; Slawek, J.; Reichel, G.; Stenner, A.; Timerbaeva, S.; Stelmasiak, Z.; Zifko, U. A.; Bhakta, B.; Coxon, E.; A double-blind randomised placebo-controlled evaluation of three doses of botulinum toxin type A (Dysport) in the treatment of spastic equinovarus deformity after stroke; Cerebrovascular Diseases; 2003; vol. 15 (no. 4); 289-300

Study details

Secondary publication of another included study- see primary study for details	NA

Other publications associated with this study included in review	NA
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	a number of countries worldwide. unclear
Study setting	Multicentre design
Study dates	NR
Sources of funding	Ipsen UK sponsored the study and designed the study in consultation with senior authors. Ipsen were responsible for the recruitment of the researchers and monitoring of data collection. The station analysis was performed by Harrington statistics and Data management, with a small number if additional tests being performed inhouse at Ipsen.
Inclusion criteria	patients who had suffered a stroke at least 3 months before the start of the study. All has hemiparesis with spastic equinovarus deformity of the ankle preventing full active dorsiflexion. They were all ambulatory and able to walk more than 5m but had a walking speed of <90% normal over 10m.
Exclusion criteria	Patients with fixed contractures, previous treatment with alcohol phenol or surgery, BoNT-A treatment for leg spasticity in the past 6 months, known sensitivity to BoNT-A or underlying non-stroke related neurological impairment were excluded. Patients with fixed contractures of the knee and hip as defined by inability to reach a neutral ankle when prone were excluded.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	NR
Intervention(s)	Dysport (Ipsen ltd) was supplied in clear vials as a freeze-dried white pellet containing a C botulinum type A - haemoglutin complex. The contents of 4 vials were reconstituted with 1.0ml sodium chloride injection B.P. (0.9% w/v) giving a total of 4ml. One millilitre was injected at each of four sites. EMG guidance was not used. At each site medial and lateral injections were made.

Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Not stated/unclear
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb
Population subgroups	NR
Comparator	The placebo was supplied in identical vials to the Botulimun toxin and contained excipients alone giving a total of 4ml. One millilitre was injected at each of four sites. EMG guidance was not used. At each site medial and lateral injections were made.
Number of participants	234
Duration of follow-up	12 weeks
Indirectness	NR

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Study arms

Abootulinum Toxin A (Dysport) at 500, 1,000 or 1,500 units (N = 179)

Placebo (N = 55)

Characteristics

Study-level characteristics

Characteristic	Study (N = 234)
Ethnicity Nominal	NR
Comorbidities Nominal	NR
Severity of spasticity Nominal	NR
Type of spasticity Nominal	NR

Arm-level characteristics

Characteristic	Abootulinum Toxin A (Dysport) at 500, 1,000 or 1,500 units (N = 179)	Placebo (N = 55)
% Female Nominal	38.5	32.7
Mean age (SD) Mean (SD)	59.29 (12.31)	55.9 (11.4)
Time period after stroke months Mean (SD)	3.27 (3.48)	3.6 (5)

Outcomes

Study timepoints

- Baseline
- 12 week

Botulinum toxin A Vs Placebo

Outcome	Abootulinum Toxin A (Dysport) at 500, 1,000 or 1,500 units, Baseline, N = 164	Abootulinum Toxin A (Dysport) at 500, 1,000 or 1,500 units, 12 week, N = 164	Placebo, Baseline, N = 54	Placebo, 12 week, N = 54
Physical function - lower limb - 2-min walking test?	41.6 (21.46)	49.66 (30.02)	41.1 (23.1)	50.5 (27.8)

Outcome	Abootulinum Toxin A (Dysport) at 500, 1,000 or 1,500 units, Baseline, N = 164	Abootulinum Toxin A (Dysport) at 500, 1,000 or 1,500 units, 12 week, N = 164	Placebo, Baseline, N = 54	Placebo, 12 week, N = 54
(metres) final values Mean (SD)				

Physical function - lower limb - 2-min walking test? - Polarity - Higher values are better
Final Values

Discontinuation

Outcome	Abootulinum Toxin A (Dysport) at 500, 1,000 or 1,500 units, Baseline, N = 179	Abootulinum Toxin A (Dysport) at 500, 1,000 or 1,500 units, 12 week, N = 179	Placebo, Baseline, N = 55	Placebo, 12 week, N = 55
Discontinuation No of events	n = 0 ; % = 0	n = 24 ; % = 13.41	n = 0 ; % = 0	n = 1 ; % = 1.82

Discontinuation - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

BotoxVsPlacebo-Physicalfunction-lowerlimb-2-minwalkingtest?-MeanSD-Botulinum Toxin dysport at 500, 1,000 or 1,500 units-Placebo-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to missing data)*
Overall bias and Directness	Overall Directness	Directly applicable

Discontinuation-Discontinuation-NoOfEvents-Botulinum Toxin dysport at 500, 1,000 or 1,500 units-Placebo-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Prazeres, 2018

Bibliographic Reference	Prazeres, A.; Lira, M.; Aguiar, P.; Monteiro, L.; Vilasboas, I.; Melo, A.; Efficacy of physical therapy associated with botulinum toxin type A on functional performance in post-stroke spasticity: A randomized, double-blinded, placebo-controlled trial; Neurology International; 2018; vol. 10 (no. 2); 7385

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NA
Trial name / registration number	NA

Study type	Randomised controlled trial (RCT)
Study location	Brazil
Study setting	Neurorehabilitation unit at an University Hospital in Northeastern, Brazil
Study dates	August 2009 and September 2012.
Sources of funding	This work was funded by Brazilian National Institutes of Science (CITECS/INNT/CNPq), CAPES, and UFBA.
Inclusion criteria	Inclusion criteria were defined diagnosis of post-stroke spasticity, age between 50-70 years-old, being in a regular program of physical therapy, at least one-year and no more than five-year history between the vascular event and study inclusion.
Exclusion criteria	Subjects who presented with conditions that impaired research procedures such as uncontrolled hypertension, structured joint contractions, prior BTx-A treatment in the last six months, regular use of medications to spasticity, renal or hepatic chronic diseases, hematological disorders, and pregnant or breast-feeding women were excluded
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	NR
Intervention(s)	BTx-A injections were applied by a specialized neurologist on predetermined muscles. A nurse prepared injections with their respective codes, derived from randomization. Patients allocated to intervention group received BTx-A injections (Dysport ®-Ipsen). Patients and injectors remained blinded regarding the intervention. Since the baseline evaluation all patients were included in a pre-determined protocol of physical exercises including muscle strength, flexibility, endurance and functional training. Sessions were scheduled twice a week, with an interval between sessions of 24h. Each session lasted 30 minutes with one-minute break between each activity involving physical effort. The first five minutes of each session consisted of flexibility activities with sustained stretching (15 seconds) and joint mobilization on the affected limb, followed by muscle strength training with concentric and eccentric movements with progressive loads depending on the patient performance in the following 10 minutes. The final movements consisted of gait and upper limb functional training combined with endurance exercises. These activities were performed in two different days: trunk, upper limb and arm functional training in the first day and pelvis, lower limb and gait training in the second day. The same instructor previously trained all physical therapists before performing study procedures.

Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Moderate (or MAS 2)
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	NA
Comparator	BTx-A injections were applied by a specialized neurologist on predetermined muscles. A nurse prepared injections with their respective codes, derived from randomization. Patients allocated to the control group received injections prepared with saline solution. Since the baseline evaluation all patients were included in a pre-determined protocol of physical exercises including muscle strength, flexibility, endurance and functional training. Sessions were scheduled twice a week, with an interval between sessions of 24h. Each session lasted 30 minutes with one-minute break between each activity involving physical effort. The first five minutes of each session consisted of flexibility activities with sustained stretching (15 seconds) and joint mobilization on the affected limb, followed by muscle strength training with concentric and eccentric movements with progressive loads depending on the patient performance in the following 10 minutes. The final movements consisted of gait

	and upper limb functional training combined with endurance exercises. These activities were performed in two different days: trunk, upper limb and arm functional training in the first day and pelvis, lower limb and gait training in the second day. The same instructor previously trained all physical therapists before performing study procedures.
Number of participants	40
Duration of follow-up	3, 6 and 9 months
Indirectness	NA

Study arms

Abobotulinum toxin type A (Dysport) (N = 20)
Abobotulinum toxin type A (Dysport) and physiotherapy

Placebo (N = 20)
Placebo and Physiotherapy

Characteristics

Study-level characteristics

Characteristic	**Study (N = 40)**
Ethnicity Nominal	NR
Type of spasticity Nominal	NR

Arm-level characteristics

Characteristic	Abobotulinum toxin type A (Dysport) (N = 20)	Placebo (N = 20)
% Female Nominal	40	40
Mean age (SD) Mean (SD)	52.5 (11.01)	52.05 (12.51)
Comorbidities other Nominal	10	5
Hypertension % Nominal	90	85
Diabetes mellitus % Nominal	20	20
Severity of spasticity Mean (SD)	2.2 (0.42)	2.2 (0.42)
Time period after stroke Mean (SD)	34.15 (21.43)	32.05 (14.89)

Outcomes

Study timepoints

- Baseline
- 3 month
- 9 month

Botulinum Toxin A vs Placebo

Outcome	Abobotulinum toxin type A (Dysport), Baseline, N = 20	Abobotulinum toxin type A (Dysport), 3 month, N = 20	Abobotulinum toxin type A (Dysport), 9 month, N = 20	Placebo, Baseline, N = 20	Placebo, 3 month, N = 20	Placebo, 9 month, N = 20
spasticity outcome - MAS (final values) Mean (SD)	2.2 (0.42)	1.3 (1.22)	1.4 (1.04)	2.2 (0.42)	1.5 (0.92)	1.9 (0.67)

Final values

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

BotoxAvsPlacebo-spasticityoutcome-MAS-MeanSD-botulinum toxin type A (BTx-A) and physiotherapy-Placebo and Physiotherapy-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Study reports 3 pts had missing data but did not report which treatment group they were from or reasons)*
Overall bias and Directness	Overall Directness	Directly applicable

BotulinumToxinAvsPlacebo-spasticityoutcome-MAS-MeanSD-botulinum toxin type A (BTx-A) and physiotherapy-Placebo and Physiotherapy-t9

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Study reports 3 pts had missing data but did not report which treatment group they were from or reasons)*
Overall bias and Directness	Overall Directness	Directly applicable

Rosales, 2018

Bibliographic Reference	Rosales, R. L.; Balcaitiene, J.; Berard, H.; Maisonobe, P.; Goh, K. J.; Kumthornthip, W.; Mazlan, M.; Latif, L. A.; Delos Santos, M. M. D.; Chotiyarnwong, C.; Tanvijit, P.; Nuez, O.; Kong, K. H.; Early AbobotulinumtoxinA (Dysport R) in Post-Stroke Adult Upper Limb Spasticity: ONTIME Pilot Study; Toxins; 2018; vol. 10 (no. 7); 21

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	Keng He Kong, Jovita Balcaitiene, Hugues Berard, Pascal Maisonobe, Khean Jin Goh, Witsanu Kumthornthip, Raymond L. Rosales,

	Effect of early use of AbobotulinumtoxinA after stroke on spasticity progression: Protocol for a randomised controlled pilot study in adult subjects with moderate to severe upper limb spasticity (ONTIME pilot), Contemporary Clinical Trials Communications, Volume 6, 2017, Pages 9-16, ISSN 2451-8654,
Trial name / registration number	ONTIME study (NCT02321436)
Study type	Randomised controlled trial (RCT)
Study location	Conducted at four centers in Malaysia, Thailand, Singapore, and the Philippines
Study setting	Conducted at four centers in Malaysia, Thailand, Singapore, and the Philippines
Study dates	Initiated in December 2014 and completed in March 2016
Sources of funding	This study was funded by Ipsen Pharma.
Inclusion criteria	18 (or age of consent according to national law) to 80 years of age; Presenting 2–12 weeks after first ever stroke according to World Health Organisation criteria. Ischemic/hemorrhagic stroke as confirmed by computerised tomography (CT) or magnetic resonance imaging (MRI). Previous transient ischemic attack or clinically silent infarct detected by CT/MRI are not to be considered as previous stroke; Presence of spasticity, either symptomatic or asymptomatic, in the relevant upper limb. Symptomatic spasticity is defined as having at least one of the following items: impaired passive or active function score ≥1 on a 4-point Likert scale; presence of involuntary movements score ≥1 on a 4-point Likert scale; pain score ≥4 on a numeric pain rating scale (NPRS) on top of increased muscle tone (MAS score ≥2). Asymptomatic spasticity is defined as having increased muscle tone (MAS score ≥2) and a score of 0 on Likert scales for active function, passive function and involuntary movement, and pain score <4 on NPRS, in the relevant upper limb. A MAS score of 2 or more in at least one of the following muscle groups: elbow flexors or pronators, wrist flexors, or finger flexors.

Exclusion criteria	Concurrent neuromuscular junction (NMJ) diseases or any other neurological disorders that could interfere with the assessment of spasticity in the primary targeted muscle group; these include prior neuropathies as well as local joint, tendon, and intrinsic muscle disorders; Current treatment with drugs that affect NMJ transmission, including aminoglycosides, aminoquinolines, cyclosporine and d-penicillamine; Previous surgery of the affected muscles, ligaments and tendons; Previous BoNT-A injection within 6 months prior to study entry for any condition, or at any time in the relevant upper limb; Subjects likely to be treated with BoNT-A in the lower limb and other body regions during the double-blind period of the trial; Known hypersensitivity to BoNT-A or to any of the test materials or related compounds; Any medical condition (including severe dysphagia or airway disease) that may increase the likelihood of adverse events related to BoNT-A treatment. Presence of severe comorbidities such as congestive heart failure, myocardial infarction, multiple organ failure, hepatic or renal failure, or severe infection; Pregnant or lactating woman or premenopausal women not willing to use contraceptive measures throughout the duration of the study. Anti-spasticity medications (e.g. baclofen) may be continued during study treatment, but only if on a stable dose.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	Male and female adult Asian subjects who meet the following inclusion criteria will be eligible to be enrolled onto the study; recruitment will stop once 42 evaluable subjects have been randomised. It is planned that 40–60% of subjects in each treatment group will present with symptomatic spasticity and 40–60% with asymptomatic spasticity. 2.4. Inclusion criteria
Intervention(s)	Patients received intramuscular injections, administered using a 25-gauge needle, of abobotulinumtoxinA 500U or equal volume placebo into selected muscles. AbobotulinumtoxinA and placebo were provided as white lyophilized powders for reconstitution (Dysport®, Ipsen Pharma SAS, Paris, France), packed in vials containing 500U BoNT-A hemagglutinin complex or excipients of the investigational product, respectively. Vials were reconstituted with 2.5 mL of preservative-free sodium chloride for injection (0.9%; 200 mL). Doses were administered per muscle according to investigators' judgements. Recommended dosing regimens were previously published. Most patients participated in occupational and physiotherapy practices.
Subgroup 1: Severity of spasticity (as	Moderate (or MAS 2)

stated by category or as measured by modified Ashworth scale [MAS])	
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	NR
Comparator	Patients received intramuscular injections, administered using a 25-gauge needle, of abobotulinumtoxinA 500U or equal volume placebo into selected muscles. AbobotulinumtoxinA and placebo were provided as white lyophilized powders for reconstitution (Dysport®, Ipsen Pharma SAS, Paris, France), packed in vials containing 500U BoNT-A hemagglutinin complex or excipients of the investigational product, respectively.
Number of participants	42
Duration of follow-up	12 weeks
Indirectness	NR
Additional comments	NR

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Study arms

Abobotulinum toxin A (Dysport) 500U (N = 28)

Placebo (N = 14)

Characteristics

Study-level characteristics

Characteristic	Study (N = 42)
Ethnicity Nominal	NR
Comorbidities Nominal	NR
Type of spasticity Nominal	NR

Arm-level characteristics

Characteristic	Abobotulinum toxin A (Dysport) 500U (N = 28)	Placebo (N = 14)
% Female Nominal	17.9	28.6

Characteristic	Abobotulinum toxin A (Dysport) 500U (N = 28)	Placebo (N = 14)
Mean age (SD) Mean (SD)	61.5 (13.2)	56.5 (9.7)
Severity of spasticity Mean (SD)	2.11 (0.31)	2.14 (0.36)
Time period after stroke weeks Mean (SD)	6.18 (2.87)	6.52 (2.53)

Outcomes

Study timepoints

- Baseline
- 12 week

Botulinum Toxin A vs placebo

Outcome	Abobotulinum toxin A (Dysport) 500U, Baseline, N = 28	Abobotulinum toxin A (Dysport) 500U, 12 week, N = 27	Placebo, Baseline, N = 14	Placebo, 12 week, N = 27

Final values

discontinuation

Outcome	Abobotulinum toxin A (Dysport) 500U, Baseline, N = 28	Abobotulinum toxin A (Dysport) 500U, 12 week, N = 28	Placebo, Baseline, N = 14	Placebo, 12 week, N = 14
Discontinuation - due to adverse events intervention = 1 due to withdrew consent, placebo = 1 lost to FU No of events	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0

Discontinuation - due to adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

discontinuation-Discontinuation-duetoadverseevents-NoOfEvents-abobotulinumtoxinA 500U-Placebo-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Rosales, 2012

Bibliographic Reference	Rosales, R. L.; Kong, K. H.; Goh, K. J.; Kumthornthip, W.; Mok, V. C.; Delgado-De Los Santos, M. M.; Chua, K. S.; Abdullah, S. J.; Zakine, B.; Maisonobe, P.; Magis, A.; Wong, K. S.; Botulinum toxin injection for hypertonicity of the upper extremity within 12 weeks after stroke: a randomized controlled trial; Neurorehabilitation & Neural Repair; 2012; vol. 26 (no. 7); 812-21

1 **Study details**

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	This study is registered at ClinicalTrials.gov (registration number NCT00234546).
Study type	Randomised controlled trial (RCT)
Study location	Hong Kong, Malaysia, the Philippines, Singapore, and Thailand.
Study setting	Participating centers were 5 neurological and rehabilitation units in Hong Kong, Malaysia, the Philippines, Singapore, and Thailand.
Study dates	February 2003 - April 2007
Sources of funding	The author(s) received financial support for the research from Ipsen Pharma, as detailed in the Declaration of Conflicting Interests. The authors received no financial support for authorship, and/or publication of this article. Medical writing support as described in the Acknowledgements was funded by Ipsen Pharma.
Inclusion criteria	Patients were recruited within 2 to 12 weeks after their first-ever stroke with impairment according to World Health Organization criteria.15 Ischemic or haemorrhagic stroke was confirmed by CT/MRI. Patients were required to have a MAS score of 1+ (slight increase in muscle tone manifested by a catch, followed by minimal resistance throughout the remainder [less than half] of the range of motion) or higher in the elbow or wrist joint. They also had to have weakness of at least grade 2 according to Medical Research Council16 criteria in the relevant joint to be eligible.
Exclusion criteria	Exclusion criteria included pregnancy/lactation, pre-stroke Rankin score greater than 1, known hypersensitivity to test materials or related compounds, pre-existing neuromuscular junction disease or neurogenic disorder that could induce muscle hypertonus, and previous treatment with botulinum toxin. Patients who were unable (eg, those with dysphasia or cognitive deficit) or unwilling to comply with the protocol were also excluded.

Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	Men and women aged 18 to 80 years and of Asian ethnicity were eligible. Participants were required to give written informed consent. Patients were recruited within 2 to 12 weeks after their first-ever stroke with impairment according to World Health Organization criteria
Intervention(s)	BoNT-A (Dysport 500 U toxin–hemagglutinin complex, human albumin and lactose, freeze-dried powder for injection, Tredegar, UK) and placebo (same constituents except toxin–hemagglutanin complex) were reconstituted locally with 2.5 mL normal saline. Because of the relatively small body size of Asian patients, a dose of Dysport 500 U was selected. Also, because of the muscle weakness present in early stroke, administering a low dose of 500 U was thought to be an appropriate approach. The recommended dose distribution was 2 injections of 200 U in a 1-mL volume for the biceps brachii, 1 injection of 100 U in a 0.5-mL volume in the brachioradialis, 1 injection of 100 U in a 0.5-mL volume in the flexor carpi ulnaris, and 1 injection of 100 U in a 0.5-mL volume in the flexor carpi radialis. Optional muscles were the flexor digitorum superficialis, the flexor digitorum profundus, and the flexor pollicis longus. Investigators were permitted to adjust the dose per targeted muscle, depending on the level of hypertonicity, as long as the total dosage per patient was 500 U. Such adjustments were recorded on the case report form. No additional anti spasticity medication was permitted after entry. Patients were permitted to continue any anti spasticity medication already in place, although dose adjustment was not permitted. All patients continued with their standard rehabilitation programs throughout the study, as deemed suitable by the attending physician. These generally consisted of a 30- to 60-minute program of range of motion plus stretching exercises, strengthening and endurance exercises, and electrical stimulation in some cases.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Moderate (or MAS 2)

Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	NA
Comparator	BoNT-A (Dysport 500 U toxin–hemagglutinin complex, human albumin and lactose, freeze-dried powder for injection, Tredegar, UK) and placebo (same constituents except toxin–hemagglutanin complex) were reconstituted locally with 2.5 mL normal saline. No further details provided on how the injections were delivered for the placebo group. No additional anti spasticity medication was permitted after entry. Patients were permitted to continue any anti spasticity medication already in place, although dose adjustment was not permitted. All patients continued with their standard rehabilitation programs throughout the study, as deemed suitable by the attending physician. These generally consisted of a 30- to 60-minute program of range of motion plus stretching exercises, strengthening and endurance exercises, and electrical stimulation in some cases.
Number of participants	163
Duration of follow-up	4 weeks, 24 weeks
Indirectness	NR

Additional comments	NR

Study arms

Abobotulinum Toxin A (Dysport) 500 U (N = 80)

Placebo (N = 83)

Characteristics

Study-level characteristics

Characteristic	**Study (N = 163)**
Ethnicity Nominal	NR
Comorbidities Nominal	NR
Type of spasticity Nominal	NR

Arm-level characteristics

Characteristic	Abobotulinum Toxin A (Dysport) 500 U (N = 80)	Placebo (N = 83)
% Female Nominal	33	34
Mean age (SD) Mean (range) Custom value	55.7 (23-79)	54.5 (17-79)
Mean age (SD) Mean (range) Mean (SD)	NR (NR)	NR (NR)
Severity of spasticity most affected joint Mean (SD)	1.89 (0.42)	2.03 (0.61)
Time period after stroke Mean (SD)	7 (2.9)	7.7 (3.1)

Outcomes

Study timepoints

- Baseline
- 4 week
- 24 week

Botulinum Toxin A vs placebo

Outcome	Abobotulinum Toxin A (Dysport) 500 U, Baseline, N = 80	Abobotulinum Toxin A (Dysport) 500 U, 4 week, N = 79	Abobotulinum Toxin A (Dysport) 500 U, 24 week, N = NR	Placebo, Baseline, N = 83	Placebo, 4 week, N = 81	Placebo, 24 week, N = NR
spasticity outcome - MAS- most affected joint (final values) 0-4 Mean (SD)	1.89 (0.42)	0.96 (0.77)	NR (NR)	2.03 (0.61)	1.73 (0.77)	NR (NR)

spasticity outcome - MAS- most affected joint - Polarity - Lower values are better

Final values

Discontinuation

Outcome	Abobotulinum Toxin A (Dysport) 500 U, Baseline, N = 80	Abobotulinum Toxin A (Dysport) 500 U, 4 week, N = 80	Abobotulinum Toxin A (Dysport) 500 U, 24 week, N = 80	Placebo, Baseline, N = 83	Placebo, 4 week, N = 83	Placebo, 24 week, N = 83
Discontinuation - due to adverse events intervention = 2 lost to FU, 2 died, Placebo group = 2 lost to FU, 1 died No of events	n = 0 ; % = 0	n = NR ; % = NR	n = 2	n = 0 ; % = 0	n = NR ; % = NR	n = 1

Discontinuation - due to adverse events - Polarity - Lower values are better

change from baseline ANCOVA

Outcome	Abobotulinum Toxin A (Dysport) 500 U vs Placebo, Baseline, N2 = 83, N1 = 80	Abobotulinum Toxin A (Dysport) 500 U vs Placebo, 4 week, N2 = 83, N1 = 80	Abobotulinum Toxin A (Dysport) 500 U vs Placebo, 24 week, N2 = 83, N1 = 80
acitivites of daily living - barthel index Mean (95% CI)	NR (NR to NR)	0.29 (-0.44 to 1.01)	0 (-0.86 to 0.87)
global pain scale Mean (95% CI)	NR (NR to NR)	-7.87 (-13.28 to -2.46)	-7.15 (-13.76 to -0.56)
Stroke outcome - modified Rankin scale Mean (95% CI)	NR (NR to NR)	0.06 (-0.14 to 0.27)	0.09 (-0.14 to 0.32)

acitivites of daily living - barthel index - Polarity - Higher values are better
global pain scale - Polarity - Lower values are better
Stroke outcome - modified Rankin scale - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Botoxvsplacebo-spasticityoutcome-MAS-mostaffectedjoint-MeanSD-BoNT-A (Dysport) 500 U-Placebo-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to bias in selection of reported result)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Discontinuation-Discontinuation-duetoadverseevents-NoOfEvents-BoNT-A (Dysport) 500 U-Placebo-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

changefrombaselineANCOVA-Strokeoutcome-modifiedRankinscale-MeanNineFivePercentCI-BoNT-A (Dysport) 500 U-Placebo-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to bias in selection of reported result)*
Overall bias and Directness	Overall Directness	Directly applicable

changefrombaselineANCOVA-globalpainscale-MeanNineFivePercentCI-BoNT-A (Dysport) 500 U-Placebo-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

changefrombaselineANCOVA-globalpainscale-MeanNineFivePercentCI-BoNT-A (Dysport) 500 U-Placebo-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to bias in selection of reported result)*
Overall bias and Directness	Overall Directness	Directly applicable

changefrombaselineANCOVA-acitivitesofdailyliving-barthelindex-MeanNineFivePercentCI-BoNT-A (Dysport) 500 U-Placebo-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

changefrombaselineANCOVA-acitivitesofdailyliving-barthelindex-MeanNineFivePercentCI-BoNT-A (Dysport) 500 U-Placebo-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Sabut, 2010

Bibliographic Reference	Sabut, S. K.; Sikdar, C.; Mondal, R.; Kumar, R.; Mahadevappa, M.; Restoration of gait and motor recovery by functional electrical stimulation therapy in persons with stroke; Disability & Rehabilitation; 2010; vol. 32 (no. 19); 1594-603

1 **Study details**

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	India
Study setting	Inpatient/outpatient department of National Institute for the orthopedically handicapped, Kolata.
Study dates	NR
Sources of funding	NR
Inclusion criteria	Inclusion criteria: unilateral drop foot due to stroke; first episode of hemiplegia at least 3 months in duration as a result of a stroke with a stable neurology; free from electrical life support device (e.g. pacemaker); ability to understand and follow simple verbal instructions; no medical contraindication to electric stimulation and ability to walk at least 10 meters without assistance.
Exclusion criteria	Exclusion criteria: evidence of a fixed plantarflexion contracture, knee deformity, pregnancy and psychological disorders
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	51 consecutive stroke patients with spastic foot drop recruited from the Inpatient/outpatient department of National Institute for the orthopedically handicapped, Kolata.

Intervention(s)	In the FES group electrical stimulation was given for 20-30 minutes to the tibialias anterior muscle of the paretic limb. Transcutaneous FED was applied with the EMS stimulator. the stimulation current applied with 0.28 ms pulses, at 35 hz in the constant mode within the subjects tolerance level via surface electrodes. the amplitude was adjusted to produce muscle contracting without affecting the patients comfort. the electrodes were place over the common peroneal nerve to elicit dorsiflexion and eversion of the foot during the swing phase of walking. The stimulation timed to the gait cycle by using a heel switch in the shoes, caused ankle dorsiflexion in the the swing phase of the gait cycle. the components of the movement may be varied by adjusting the electrode position and stimulation amplitude. All subjects received the same conventional rehabilitation programme including neurodevelopmental techniques, physiotherapy and occupational therapy, 1h per day, 5 days per week, for 12 weeks.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Moderate (or MAS 2)
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb
Population subgroups	Nr

Comparator	All subjects received the same conventional rehabilitation programme including neurodevelopmental techniques, physiotherapy and occupational therapy, 1h per day, 5 days per week, for 12 weeks.
Number of participants	51
Duration of follow-up	12 week
Indirectness	NR
Additional comments	NR

Study arms

Functional electrical stimulation (FES) (N = 27)
Functional electrical stimulation (FES) + conventional rehabilitation

Usual care (N = 24)
Control group (conventional rehabilitation)

Characteristics

Study-level characteristics

Characteristic	**Study (N = 51)**
Ethnicity Nominal	NR

Characteristic	Study (N = 51)
Comorbidities Nominal	NR
Type of spasticity Nominal	NR

Arm-level characteristics

Characteristic	Functional electrical stimulation (FES) (N = 27)	Usual care (N = 24)
% Female Nominal	NR	NR
Mean age (SD) Mean (SD)	49.1 (8.8)	50.1 (10.4)
Severity of spasticity Mean (SD)	2.9 (0.67)	2.6 (0.57)
Time period after stroke Mean (SD)	17.3 (18.8)	18.2 (11.8)

Outcomes

Study timepoints

- Baseline

- 12 week

FES vs control

Outcome	Functional electrical stimulation (FES), Baseline, N = 27	Functional electrical stimulation (FES), 12 week, N = 27	Usual care, Baseline, N = 24	Usual care, 12 week, N = 24
Spasticity outome - MAS (final values) 0-4 Mean (SD)	2.9 (0.67)	1.8 (0.64)	2.6 (0.57)	2.1 (0.64)
Physical function - lower limb - FMA lower extremity (final values) 0-34 Mean (SD)	18.4 (4.5)	23.7 (4.2)	19.3 (4.7)	21.6 (5.5)
Discontinuation No of events	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0

Spasticity outome - MAS - Polarity - Lower values are better
Physical function - lower limb - FMA lower extremity - Polarity - Higher values are better
Discontinuation - Polarity - Lower values are better
final values

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

FESvscontrol-Discontinuation-NoOfEvents-functional electrical stimulation (FES) + conventional rehabilitation-control group (conventional rehabilitation)-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(prospective interventional study design - pts were assigned alternatively to either intervention or control group)*
Overall bias and Directness	Overall Directness	Directly applicable

FESvscontrol-Physicalfunction-lowerlimb-FMAlowerextremity-MeanSD-functional electrical stimulation (FES) + conventional rehabilitation-control group (conventional rehabilitation)-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(prospective interventional study design - pts were assigned alternatively to either intervention or control group)*
Overall bias and Directness	Overall Directness	Directly applicable

FESvscontrol-Spasticityoutome-MAS-MeanSD-functional electrical stimulation (FES) + conventional rehabilitation-control group (conventional rehabilitation)-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(prospective interventional study design - pts were assigned alternatively to either intervention or control group)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Sahin, 2012

Bibliographic Reference	Sahin, N.; Ugurlu, H.; Albayrak, I.; The efficacy of electrical stimulation in reducing the post-stroke spasticity: a randomized controlled trial; Disability and rehabilitation; 2012; vol. 34 (no. 2); 151-156

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	Turkey
Study setting	Outpatients
Study dates	NR

Sources of funding	NR
Inclusion criteria	Patients between 45-65 years of age, who had developed forearm flexor spasticity following a stroke. Inclusion criteria were hemiplegia for longer than 1 year, score 2 or 3 spasticity according to MAS and a stable neurological state.
Exclusion criteria	Exclusion criteria were the presence of unstable comorbid diseases, sensory deficit, anti-spastic medication usage, treatment with botulinum toxin in the last 6 months, history of epileptic seizures, cardiac pacemaker, severe depression (>18 on the Beck depression index), presence of frequent urinary infections and shoulder pain (over 5 VAS).
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	NR
Intervention(s)	NMES was applied to the wrist extensors, in the form of pulsed current 100 Hx, with a pulse duration of 0.1 msec, in cycles of 3msec, and a resting duration of 9 seconds, for 15 minutes to provide maximum muscular contraction. Cathode was placed on the most excitable region of the muscle and anode was placed on a region close to the lateral epicondyle. This groups received the NMES treatment for 5 days a week, 20 sessions in total. All patients received stretching with PNF applied to the upper extremity after 15 minutes of hot treatment with infrared on the extensor muscles, 5 days a week for 20 sessions. Movement components of this technique include shoulder, scapular, forearm, wrist and finger flexion-extension, abduction-adduction and internal external rotation.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Severe (or MAS 3)
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)

Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	NR
Comparator	Patients received stretching with PNF applied to the upper extremity after 15 minutes of hot treatment with infrared on the extensor muscles, 5 days a week for 20 sessions. Movement components of this technique include shoulder, scapular, forearm, wrist and finger flexion-extension, abduction-adduction and internal external rotation.
Number of participants	44
Duration of follow-up	4 weeks
Indirectness	NA
Additional comments	NR

Study arms

Neuromuscular electrical stimulation (NMES) (N = 22)
NMES + stretching (PNF) + infrared

Usual care (N = 22)
Stretching (PNF) + infrared

1

2 **Characteristics**

3 ***Study-level characteristics***

Characteristic	Study (N = 42)
Ethnicity Nominal	NR
Comorbidities Nominal	NR
Type of spasticity Nominal	NR

4

5 ***Arm-level characteristics***

Characteristic	Neuromuscular electrical stimulation (NMES) (N = 22)	Usual care (N = 22)
% Female Nominal	47.62	42.86
Mean age (SD) Mean (SD)	60.2 (6.2)	59.3 (9.3)
Severity of spasticity Nominal	3	2.8

Characteristic	Neuromuscular electrical stimulation (NMES) (N = 22)	Usual care (N = 22)
Time period after stroke months Mean (SD)	25 (14.6)	35.1 (24.4)

Outcomes

Study timepoints

- Baseline
- 4 week

NMES + stretching vs stretching

Outcome	Neuromuscular electrical stimulation (NMES), Baseline, N = 22	Neuromuscular electrical stimulation (NMES), 4 week, N = 21	Usual care, Baseline, N = 22	Usual care, 4 week, N = 21
spasticity outcome - MAS (median) 0-5, final values Nominal	3.2	1.8	3	2
Physical function - upper limb - functional ndependance measure final values Mean (SD)	107.7 (18.9)	109.8 (18.8)	101.7 (19.6)	102.7 (19.6)

spasticity outcome - MAS - Polarity - Lower values are better

Physical function - upper limb - functional ndependance measure - Polarity - Higher values are better
Final values

discontinuation

Outcome	Neuromuscular electrical stimulation (NMES), Baseline, N = 22	Neuromuscular electrical stimulation (NMES), 4 week, N = 22	Usual care, Baseline, N = 22	Usual care, 4 week, N = 22
Discontinuation treatment = 1 due to trauma, control = 1 due to personal issues No of events	n = 0 ; % = 0	n = 1 ; % = 2.2	n = 0 ; % = 0	n = 1 ; % = 2.2

Discontinuation - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

discontinuation-Discontinuation-NoOfEvents-NMES + stretching (PNF) + infrared-Stretching (PNF) + infrared-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

NMES+stretchingvsstretching-spasticityoutcome-MAS-Nominal-NMES + stretching (PNF) + infrared-Stretching (PNF) + infrared-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

NMES+stretchingvsstretching-Physicalfunction-upperlimb-functionalndependancemeasure-MeanSD-NMES + stretching (PNF) + infrared-Stretching (PNF) + infrared-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Sentandreu-Mano, 2021

Bibliographic Reference	Sentandreu-Mano, T.; Tomas, J. M.; Ricardo Salom Terradez, J.; A randomised clinical trial comparing 35 Hz versus 50 Hz frequency stimulation effects on hand motor recovery in older adults after stroke; Scientific Reports; 2021; vol. 11 (no. 1); 9131

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with	NR

this study included in review	
Trial name / registration number	NCT03913624; 12/04/2019
Study type	Randomised controlled trial (RCT)
Study location	Spain
Study setting	University Hospital of Valencia, Spain. Outpatients
Study dates	July 2009 and September 2014
Sources of funding	Tis research was supported by a Grant from the Regional Ministry of Education (ACIF/2012/017) and from Regional Ministry of Health (004/2010).
Inclusion criteria	The inclusion criteria were presence of spastic hemiparesis caused by stroke (diagnosed by neuroimaging tests), a score ≤ 3 on the MAS for wrist and finger flexors, residual voluntary movement of wrist (active wrist extension ≥ 5° from the resting position) , wrist extension response to stimulation, age ≥ 60 years, post-stroke period < 18 months, clinical stability, and MMSE score ≥ 23 with the absence of significant cognitive impairment, being able to follow basic instructions and to collaborate in the treatment. Te spasticity assessment included the Tardieu Scale and hyperreflexia of the deep tendon reflexes. Exclusion criteria comprised those situations that could alter the results or posed a risk for the patient.
Exclusion criteria	Dermatological reactions with the application of stimulation Significant sensory deficits in the affected arm Previous musculoskeletal problems of the hand Treatment with the botulin toxin Anti-spastic medication usage Cardiac pacemaker, implanted electronic device, or metal implants in the affected arm

	Complex regional pain syndrome Severe aphasia, history of epileptic seizures, psychiatric disorder, or important alterations of behaviour Severe visual impairment Any comorbid neurological disease Important deformity or obesity that affects the application of the NMES Potentially fatal cardiac arrhythmia or other decompensated heart disease Systemic infectious process, cancer, or other terminal disease
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	Participants were recruited from the aforementioned hospital, who attended for physical therapy intervention as outpatients between July 2009 and September 2014.
Intervention(s)	During an 8-week intervention period, training was conducted for 3 days per week (a total of 24 sessions). The two experimental groups received the conventional treatment (the same as the control group) for the same amount of time, plus NMES. The NMES application time was 20 min for the first 2 sessions and 30 min for subsequent sessions. Each NMES session took place under the supervision of an experienced physical therapist.50 Hz NMES group: NMES was applied on wrist and finger extensors. The main electrostimulation parameters consisted of low-frequency current, a stimulation frequency of 50 Hz, symmetrical rectangular biphasic wave, and pulse duration of 300 μs. 35 Hz NMES group: NMES was applied on wrist and finger extensors. The main electrostimulation parameters consisted of low-frequency current, a stimulation frequency of 35 Hz, symmetrical rectangular biphasic wave, and pulse duration of 300 μs. The electrostimulation programmes were only differentiated in the parameter of the stimulation frequency, 35 Hz or 50 Hz, depending on the experimental group to which the patient belonged. The rest of the parameters were the same. The intensity was adjusted in order to allow a maximum extension of wrist and fingers ensuring the patient's comfort. Ramping up/down periods were established at a time of 2 s during the first week, and 1 s for the rest of the study. The contraction-relaxation times were adjusted during the treatment period (5–25 s in the first 2 weeks, 5–20 s in the third week, 5–15 s in the fourth week, 5–10 s during fifth to sixth weeks, and 5–5 s in final weeks). These parameters were modified during the treatment in order to adapt the training progressively and avoid muscle fatigue60,61. Te application time was 20 min for the first two sessions

	and 30 min for subsequent sessions. Tree sessions per week were conducted for a period of 8 weeks. Additionally, the patient was asked to actively participate by means of a voluntary contraction on feeling the stimulus and visualizing the movement. Te electrodes were placed over the extensor muscles of the wrist and fingers, stimulating mainly the extensor carpi radialis longus and brevis, and the extensor digitorum communis. A line of the humeral epicondyle was drawn on the posterior part of the forearm to the midpoint of the wrist joint, and this was divided into three parts, placing one electrode approximately in the proximal third of this described line, and the other electrode in the distal third towards the posterolateral side of the forearm. For the application of the NMES, a portable apparatus (Beac Medical IntelliSTIM® BE 28-E) and disposable self-adhesive surface electrodes (En-Trode® 50 × 50 mm) were used. During an 8-week intervention period, training was conducted for 3 days per week (a total of 24 sessions). The two experimental groups received the conventional treatment (the same as the control group) for the same amount of time,
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mild (or MAS 1)
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)

Population subgroups	NR
Comparator	The control group received standard physical therapy intervention in the reference rehabilitation centre. Two physical therapists with extensive expertise applied the conventional treatment. Each session lasted approximately 60 min with the following structure: (1) Warm-up with cycle ergometer,10 min; (2) Stretching (20 s/2–3 repetitions) and passive/active-assisted upper and lower limb kinesiotherapy (3 series/10–15 repetitions), 10 min; (3) Bimanual exercises (e.g., task-specific exercises such as gripping and releasing objects, shoulder pulley, and elastic band training), 10 min; (4) Mobility and strengthening lower limb exercises (2–3 series, 10–15 repetitions), 10 min; (5) Coordination, balance and gait training, 20 min. The exercises were progressively adapted depending on the degree of motor function of the patient.
Number of participants	69
Duration of follow-up	3 months
Indirectness	NA
Additional comments	NR

Study arms

Neuromuscular electrical stimulation (NMES) (N = 46)

Usual care (N = 23)

1 **Characteristics**

2 ***Study-level characteristics***

Characteristic	Study (N = 69)
Ethnicity Nominal	NR
Type of spasticity Nominal	NR

3

4 ***Arm-level characteristics***

Characteristic	Neuromuscular electrical stimulation (NMES) (N = 46)	Usual care (N = 23)
% Female Nominal	41.46	40
Mean age (SD) Mean (SD)	70.68 (7.15)	71.5 (7.56)
Comorbidities hypertension Nominal	43.9	45
Diabetes Nominal	29.27	35
Time period after stroke	5.76 (3.2)	5.8 (3.24)

Characteristic	Neuromuscular electrical stimulation (NMES) (N = 46)	Usual care (N = 23)
Mean (SD)		

Outcomes

Study timepoints

- Baseline
- 3 month

NMES vs usual care

Outcome	Neuromuscular electrical stimulation (NMES), Baseline, N = 46	Neuromuscular electrical stimulation (NMES), 3 month, N = 41	Usual care, Baseline, N = 23	Usual care, 3 month, N = 20
Spasticity outcome - modified Ashworth scale (final values) 0-4 Mean (SD)	1.94 (1.03)	1.01 (0.79)	1.6 (0.94)	1.28 (0.76)
Activities of daily living - Barthel Index (final values) 0-100 Mean (SD)	60.12 (14.07)	71.83 (15.88)	58.25 (17.11)	64.5 (19.66)

Spasticity outcome - modified Ashworth scale - Polarity - Lower values are better
Activities of daily living - Barthel Index - Polarity - Higher values are better
Final values

Discontinuation

Outcome	Neuromuscular electrical stimulation (NMES), Baseline, N = 46	Neuromuscular electrical stimulation (NMES), 3 month, N = 46	Usual care, Baseline, N = 23	Usual care, 3 month, N = 23
Discontinuation No of events	n = 0 ; % = 0	n = 5 ; % = 10.87	n = 0 ; % = 0	n = 3 ; % = 13.04

Discontinuation - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Discontinuation-Discontinuation-NoOfEvents-NMES with 50 Hz or 35 Hz-Control group-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Due to missing data)*
Overall bias and Directness	Overall Directness	Directly applicable

NMESvsusualcare-Activitiesofdailyliving-BarthelIndex-MeanSD-NMES with 50 Hz or 35 Hz-Control group-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Due to missing data)*
Overall bias and Directness	Overall Directness	Directly applicable

NMESvsusualcare-Spasticityoutcome-modifiedAshworthscale-MeanSD-NMES with 50 Hz or 35 Hz-Control group-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Due to missing data)*
Overall bias and Directness	Overall Directness	Directly applicable

Shaw, 2010

Bibliographic Reference	Shaw, L.; Rodgers, H.; Price, C.; van Wijck, F.; Shackley, P.; Steen, N.; Barnes, M.; Ford, G.; Graham, L.; Bo, Tuls investigators; BoTULS: a multicentre randomised controlled trial to evaluate the clinical effectiveness and cost-effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A; Health Technology Assessment (Winchester, England); 2010; vol. 14 (no. 26); 1-113, iii

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	Shaw 2011 #2889 Shackley 2012 #2882

	Shaw LC, Price CIM, van Wijck FMJ, Shackley P, Steen N, Barnes MP, et al. Botulinum Toxin for the Upper Limb after Stroke (BoTULS) Trial: effect upon impairment, activity limitation and pain. Stroke, in press. Shackley P, Shaw LC, Price CIM, van Wijck FMJ, Barnes MP, Graham LA, et al. Cost-effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A: results from the Botulinum Toxin for the Upper Limb after Stroke (BoTULS) trial. Submitted for publication.
Trial name / registration number	Trial registration: ISRCTN78533119; EudraCT 2004–002427–40; CTA 17136/0230/001. BoTULS
Study type	Randomised controlled trial (RCT)
Study location	UK
Study setting	Twelve stroke services in the north of England. Referrals were received from stroke units, outpatient clinics, day hospitals, community rehabilitation teams, stroke clubs and day centres.
Study dates	July 2005 and March 2008.
Sources of funding	The BoTULS trial research costs were funded by the NIHR Health Technology Assessment programme. Additional treatment costs to provide the upper limb therapy programme were available from an NHS subvention. Ipsen Ltd provided the botulinum toxin type A (Dysport) free of charge.
Inclusion criteria	Adults with a stroke more than 1 month previously who had moderate/severe spasticity and reduced upper limb function who fulfilled all of following criteria were eligible: • age over 18 years • at least 1 month since stroke • upper limb spasticity [Modified Ashworth Scale19 >2 at the elbow and/or spasticity at the hand, wrist or shoulder (there is no validated measure of spasticity at these sites)] • reduced upper limb function (ARAT66 score 0–56) • able to comply with the requirements of the protocol and upper limb therapy programme • informed consent given by participant or legal representative.
Exclusion criteria	Significant speech or cognitive impairment which impeded ability to perform the ARAT66 assessment. • Other significant upper limb impairment, e.g. fracture or frozen shoulder within 6 months, severe arthritis, amputation. • Evidence of fixed contracture. • Pregnancy or lactating. • Female at risk of pregnancy and not willing to take adequate precautions against pregnancy for the duration of the study. • Other diagnosis likely to interfere with rehabilitation or outcome assessments, e.g. registered blind, malignancy. Other diagnosis which may contribute to upper limb spasticity, e.g. multiple sclerosis, cerebral palsy. • Contraindications to intramuscular injection. • Religious objections to blood products [botulinum toxin type A (Dysport) contains human albumin]. • Contraindications to botulinum toxin type A, which include bleeding disorders,

	myasthenia gravis and concurrent use of aminoglycosides. • Use of botulinum toxin to the upper limb in the previous 3 months. • Known allergy or hypersensitivity to any of the test compounds. • Previous enrolment in this study.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	Between July 2005 and March 2008, 333 participants were recruited to the BoTULS trial. One hundred and seventy were randomised to the intervention group and 163 to the control group. Two hundred and eight (62%) participants were randomised before July 2007 and entered the trial for 12 month follow-up. The remaining 125 (38%) participants were followed for 3 months.
Intervention(s)	Participants in the intervention group received botulinum toxin type A (Dysport). Dysport is available as a white lyophilised powder for reconstitution containing 500 units of C. botulinum type A toxin–haemagglutinin complex together with 125µg of a 20% albumin solution and 2.5mg lactose in a clear glass vial. The range of muscles and dosages injected were as described in 'The management of adults with spasticity using botulinum toxin: a guide to clinical practice'.9 The maximum dose of botulinum toxin type A (Dysport) that could be administered at any one time point was 1000 units. All injectors were clinicians trained in the assessment and injection of botulinum toxin in the context of upper limb spasticity. The use of aminoglycosides was prohibited during the study because they enhance the effects of botulinum toxin, thereby increasing the risk of toxicity. Clinicians were advised to use muscle relaxants with caution because the effects of botulinum toxin are enhanced by non-depolarising muscle relaxants. The international normalised ratio of participants taking warfarin was checked before injection. Information about concomitant drug use was given in the patient information sheet and in letters to consultants and general practitioners. If further treatment was necessary at 3, 6 or 9 months, further injections were provided to those in the intervention group. At each visit a letter was sent to the participant's stroke physician, general practitioner and physiotherapist. participants in both groups received the upper limb therapy programme for 4 weeks

Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Moderate (or MAS 2)
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	NR
Comparator	Guidelines highlight that it is important that botulinum toxin is not used in isolation but as part of a comprehensive rehabilitation programme. The upper limb therapy programme was based upon available research evidence from the stroke rehabilitation and skill acquisition literature as well as clinical practice and consisted of two menus. Participants with ARAT 0–3 received menu 1, which was designed specifically for participants with no active upper limb function. Menu 1 aimed at improving and maintaining range of movement, encouraging active assisted upper limb movement in the context of functional activities, along with hand hygiene and positioning. Menu 2 was for participants with some retained active upper limb movement (ARAT 4–56) and was piloted in a previous study. Following stretching of soft tissues affected by spasticity, this menu specifically concentrated on task-orientated practise aimed at patient-centred goals. Upper limb goals were measured by the COPM. Each menu standardised the category of tasks, the number and order of repetitions as well as the amount of feedback for each session, but within these parameters the therapist was able to tailor the specifics of each activity to the ability of the patient. Manuals and training programmes were developed for both upper limb therapy menus

	and all therapists were trained in the delivery of the programme. The upper limb therapy programme was provided by study therapists and each participant received.
Number of participants	333
Duration of follow-up	1 month, 3 months, 12 months
Indirectness	NA
Additional comments	Analyses were undertaken on an 'intention-to-treat' basis; participants were analysed in the group to which they were randomised. Data were exported from the study microsoft access database to spss for analysis. All available data were analysed, missing data were not imputed.

Study arms

Abobotulinum toxin type A (Dysport) (N = 170)
Abobotulinum toxin type A (Dysport) and 4-week upper limb therapy programme. (1 hour twice per week provided by study therapist)

Usual care (N = 163)
4-week upper limb therapy programme (1 hour twice per week provided by study therapist)

Characteristics

Study-level characteristics

Characteristic	**Study (N = 333)**
Ethnicity Nominal	NR

Characteristic	Study (N = 333)
Type of spasticity Nominal	NR

Arm-level characteristics

Characteristic	Abobotulinum toxin type A (Dysport) (N = 170)	Usual care (N = 163)
% Female Nominal	29	35.3
Mean age (SD) Median (IQR)	67 (58.8 to 72.3)	66 (59.8 to 72.3)
Comorbidities Previous stroke/transient ischaemic attack Nominal	28.8	29.6
Ischaemic heart disease Nominal	22.4	23.1
Peripheral arterial occlusive disease Nominal	3.6	5
Diabetes mellitus Nominal	13.1	13.6

Characteristic	Abobotulinum toxin type A (Dysport) (N = 170)	Usual care (N = 163)
Hypertension Nominal	74.3	73.3
Hyperlipidaemia Nominal	65.7	64.4
Atrial fibrillation Nominal	14.5	13.3
Severity of spasticity Nominal	NR	NR
Severity of spasticity Median (IQR)	2 (1 to 2)	2 (1 to 2)
Time period after stroke days Median (IQR)	324 (128.5 to 1387.5)	280 (148.8 to 1145.8)

Outcomes

Study timepoints

- Baseline
- 3 month
- 12 month

1 ***Botox vs usual care***

Outcome	Abobotulinum toxin type A (Dysport), Baseline, N = 170	Abobotulinum toxin type A (Dysport), 3 month, N = 163	Abobotulinum toxin type A (Dysport), 12 month, N = 92	Usual care, Baseline, N = 163	Usual care, 3 month, N = 151	Usual care, 12 month, N = 97
Spasticity outcome - Modified Ashworth Scale at elbow mean change (95% CI) Mean (95% CI)	NR (NR to NR)	-0.3 (-0.4 to -0.1)	-0.3 (-0.5 to 0.1)	NR (NR to NR)	-0.1 (-0.3 to 0.1)	-0.2 (-0.5 to 0.1)
Physical function - upper limb - ARAT - mean change (95% CI) (0-57) study reports -3.1 mean at 12 mo FU in the intervention group? Also final to value for the control group at 12 mo should be 0.1 Mean (95% CI)	NR (NR to NR)	3 (2 to 4.2)	3.1 (1.7 to 4.5)	NR (NR to NR)	1.3 (0.4 to 2.1)	2 (-0.5 to *empty data*)
Person/participant generic health-related quality of life - EQ5D- mean change (final value) 0-1 Mean (95% CI)	NR (NR to NR)	NR (NR to NR)	NR (NR to NR)	NR (NR to NR)	NR (NR to NR)	NR (NR to NR)
Person/participant generic health-related quality of life - EQ5D- mean change (final value) 0-1 Mean (SD)	0.32 (0.3)	0.35 (0.29)	0.32 (0.29)	0.33 (0.3)	0.32 (0.3)	0.27 (0.31)

Outcome	Abobotulinum toxin type A (Dysport), Baseline, N = 170	Abobotulinum toxin type A (Dysport), 3 month, N = 163	Abobotulinum toxin type A (Dysport), 12 month, N = 92	Usual care, Baseline, N = 163	Usual care, 3 month, N = 151	Usual care, 12 month, N = 97
Pain - VAS score mean change 0-10 Mean (95% CI)	NR (NR to NR)	-1.6 (-2.2 to 1.1)	-2.2 (-2.9 to -1.4)	NR (NR to NR)	-1.2 (-1.8 to -0.6)	-0.8 (-1.5 to 0.1)
Stroke-specific Patient-Reported Outcome Measures Stroke Impact Scale domains - mean change Mean (95% CI)	NR (NR to NR)	NR (NR to NR)	NR (NR to NR)	NR (NR to NR)	NR (NR to NR)	NR (NR to NR)
Strength Mean (95% CI)	NR (NR to NR)	-0.2 (-3.4 to 3)	-2.2 (-6.5 to 2.2)	NR (NR to NR)	-1.6 (-5.1 to 1.8)	0.2 (-4.2 to 4.5)
Memory Mean (95% CI)	NR (NR to NR)	-0.8 (-2.3 to 4)	-1.8 (-5.6 to 1.8)	NR (NR to NR)	-2 (-5 to 1)	-5.6 (-9.6 to -1.5)
Emotion Mean (95% CI)	NR (NR to NR)	-1 (-3.4 to 1.5)	-1 (-4 to 1.9)	NR (NR to NR)	-0.1 (-2.8 to 2.6)	-3.5 (-6.9 to -0.1)
Communication Mean (95% CI)	NR (NR to NR)	0.3 (-2.2 to 2.7)	1.2 (-2.4 to 4.7)	NR (NR to NR)	-2.4 (-5.3 to 0.3)	-4.2 (-8.1 to -0.5)
ADL Mean (95% CI)	NR (NR to NR)	2.5 (0 to 5)	0.8 (-2.3 to 3.8)	NR (NR to NR)	-1 (-3.7 to 1.4)	-2.4 (-5.5 to 0.7)
Mobility	NR (NR to NR)	2.9 (-0.5 to 6.2)	-0.8 (-3.9 to 2.2)	NR (NR to *empty data*)	1.7 (-1.3 to 4.7)	-2 (-5.4 to 1.4)

Outcome	Abobotulinum toxin type A (Dysport), Baseline, N = 170	Abobotulinum toxin type A (Dysport), 3 month, N = 163	Abobotulinum toxin type A (Dysport), 12 month, N = 92	Usual care, Baseline, N = 163	Usual care, 3 month, N = 151	Usual care, 12 month, N = 97
Mean (95% CI)						
Hand function Mean (95% CI)	NR (NR to NR)	5 (-0.5 to 10.4)	4.6 (1 to 8.5)	NR (NR to NR)	3.2 (-0.5 to 6.8)	-0.9 (-5.7 to 3.6)
Participation/Handicap Mean (95% CI)	NR (NR to NR)	1.4 (-0.6 to 3.4)	4.2 (-2.4 to 10.7)	NR (NR to NR)	-2 (-6.5 to 2.6)	-1.7 (-7.6 to 4.2)
Physical domain Mean (95% CI)	NR (NR to NR)	1.4 (-0.6 to 3.4)	0.5 (-1.9 to 2.9)	NR (NR to NR)	0.9 (-1.2 to 3.1)	-1.2 (-3.8 to 1.2)
Stroke recovery Mean (95% CI)	NR (NR to NR)	2 (-1.3 to 5.5)	0.5 (-4.5 to 5.7)	NR (NR to NR)	-0.8 (-3.7 to 2.1)	-2.1 (-6.8 to 2.7)

Spasticity outcome - Modified Ashworth Scale at elbow - Polarity - Lower values are better
Physical function - upper limb - ARAT - mean change (95% CI) - Polarity - Higher values are better
Person/participant generic health-related quality of life - EQ5D- mean change - Polarity - Higher values are better
Pain - VAS score mean change - Polarity - Lower values are better
Stroke-specific Patient-Reported Outcome Measures Stroke Impact Scale domains - mean change - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Botoxvsusualcare-Spasticityoutcome-ModifiedAshworthScaleatelbow-MeanNineFivePercentCI-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to switching rate in the control group to treatment group)*
Overall bias and Directness	Overall Directness	Directly applicable

Botoxvsusualcare-Spasticityoutcome-ModifiedAshworthScaleatelbow-MeanNineFivePercentCI-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to switching rate in the control group to treatment group)*
Overall bias and Directness	Overall Directness	Directly applicable

Botoxvsusualcare-Physicalfunction-upperlimb-ARAT-meanchange(95%CI)-MeanNineFivePercentCI-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to switching rate in the control group to treatment group)*
Overall bias and Directness	Overall Directness	Directly applicable

Botoxvsusualcare-Physicalfunction-upperlimb-ARAT-meanchange(95%CI)-MeanNineFivePercentCI-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to switching rate in the control group to treatment group)*
Overall bias and Directness	Overall Directness	Directly applicable

Botoxvsusualcare-Person/participantgenerichealth-relatedqualityoflife-EQ5D-meanchange-MeanNineFivePercentCI-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to switching and unblinded pts with subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Botoxvsusualcare-Stroke-specificPatient-ReportedOutcomeMeasuresStrokeImpactScaledomains-meanchange-Strokerecovery-MeanNineFivePercentCI-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to switching and unblinded pts with subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Botoxvsusualcare-Stroke-specificPatient-ReportedOutcomeMeasuresStrokeImpactScaledomains-meanchange-Strokerecovery-MeanNineFivePercentCI-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to switching and unblinded pts with subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Botoxvsusualcare-Stroke-specificPatient-ReportedOutcomeMeasuresStrokeImpactScaledomains-meanchange-Physicaldomain-MeanNineFivePercentCI-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to switching and unblinded pts with subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Botoxvsusualcare-Stroke-specificPatient-ReportedOutcomeMeasuresStrokeImpactScaledomains-meanchange-Physicaldomain-MeanNineFivePercentCI-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to switching and unblinded pts with subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Botoxvsusualcare-Stroke-specificPatient-ReportedOutcomeMeasuresStrokeImpactScaledomains-meanchange-Participation/Handicap-MeanNineFivePercentCI-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to switching and unblinded pts with subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Botoxvsusualcare-Stroke-specificPatient-ReportedOutcomeMeasuresStrokeImpactScaledomains-meanchange-Participation/Handicap-MeanNineFivePercentCI-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to switching and unblinded pts with subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Botoxvsusualcare-Stroke-specificPatient-ReportedOutcomeMeasuresStrokeImpactScaledomains-meanchange-Handfunction-MeanNineFivePercentCI-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to switching and unblinded pts with subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

BotoxvsusualcareStroke-specificPatient-ReportedOutcomeMeasuresStrokeImpactScaledomains-meanchange-HandfunctionMeanNineFivePercentCI-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to switching and unblinded pts with subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

BotoxvsusualcareStroke-specificPatient-ReportedOutcomeMeasuresStrokeImpactScaledomains-meanchange-MobilityMeanNineFivePercentCI-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to switching and unblinded pts with subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

BotoxvsusualcareStroke-specificPatient-ReportedOutcomeMeasuresStrokeImpactScaledomains-meanchange-MobilityMeanNineFivePercentCI-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to switching and unblinded pts with subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Botoxvsusualcare-Stroke-specificPatient-ReportedOutcomeMeasuresStrokeImpactScaledomains-meanchange-ADL-MeanNineFivePercentCI-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to switching and unblinded pts with subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Botoxvsusualcare-Stroke-specificPatient-ReportedOutcomeMeasuresStrokeImpactScaledomains-meanchange-ADL-MeanNineFivePercentCI-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to switching and unblinded pts with subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Botoxvsusualcare-Stroke-specificPatient-ReportedOutcomeMeasuresStrokeImpactScaledomains-meanchange-Communication-MeanNineFivePercentCI-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to switching and unblinded pts with subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

BotoxvsusualcareStroke-specificPatient-ReportedOutcomeMeasuresStrokeImpactScaledomains-meanchange-Communication-MeanNineFivePercentCI-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to switching and unblinded pts with subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

BotoxvsusualcareStroke-specificPatient-ReportedOutcomeMeasuresStrokeImpactScaledomains-meanchange-Emotion-MeanNineFivePercentCI-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to switching and unblinded pts with subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

BotoxvsusualcareStroke-specificPatient-ReportedOutcomeMeasuresStrokeImpactScaledomains-meanchange-Emotion-MeanNineFivePercentCI-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to switching and unblinded pts with subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Botoxvsusualcare-Stroke-specificPatient-ReportedOutcomeMeasuresStrokeImpactScaledomains-meanchange-Memory-MeanNineFivePercentCI-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to switching and unblinded pts with subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Botoxvsusualcare-Stroke-specificPatient-ReportedOutcomeMeasuresStrokeImpactScaledomains-meanchange-Memory-MeanNineFivePercentCI-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to switching and unblinded pts with subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Botoxvsusualcare-Stroke-specificPatient-ReportedOutcomeMeasuresStrokeImpactScaledomains-meanchange-Strength-MeanNineFivePercentCI-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to switching and unblinded pts with subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Botoxvsusualcare-Pain-VASscoremeanchange-MeanNineFivePercentCI-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to switching and unblinded pts with subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Botoxvsusualcare-Pain-VASscoremeanchange-MeanNineFivePercentCI-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to switching and unblinded pts with subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Botoxvsusualcare-Person/participantgenerichealth-relatedqualityoflife-EQ5D-meanchange-MeanSD-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to switching and unblinded pts with subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Botoxvsusualcare-Person/participantgenerichealth-relatedqualityoflife-EQ5D-meanchange-MeanSD-Botulinum toxin type A and 4-week upper limb therapy programme-Control - 4-week upper limb therapy programme-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to switching and unblinded pts with subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Shin, 2008

Bibliographic Reference	Shin, H. K.; Cho, S. H.; Jeon, H. S.; Lee, Y. H.; Song, J. C.; Jang, S. H.; Lee, C. H.; Kwon, Y. H.; Cortical effect and functional recovery by the electromyography-triggered neuromuscular stimulation in chronic stroke patients; Neuroscience Letters; 2008; vol. 442 (no. 3); 174-9

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	NR

Study type	Randomised controlled trial (RCT)
Study location	Korea
Study setting	outpatients
Study dates	NR
Sources of funding	Supported by the Korea Science and Engineering foundation (KOSEF) grant funded by the Korean government
Inclusion criteria	≥1 year post stroke onset; plateau in the maximum motor recovery after a conventional neurorehabilitation programme; 3 the ability to voluntarily extend > 20 digresses against gravity from a 90 degrees flexed position at the metacarpophalangeal joint of the third finger; < grade 2 on the modified Ashworth scale and no visual problems and severe cognitive impairment (MMSE , 23).
Exclusion criteria	NR
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	NR
Intervention(s)	Patients received the EMG-stim treatment on the extensor digitorum communis with the walking man II EMG FES 3000 as one channel electrical stimulator, which consisted of 3 surface electrodes. Exact electrode placement was achieved by electrically stimulating a synergic group to find the target muscle. When the subjects initiated finger extension to a target threshold level of EMG actively, electrical stimulation was triggered to assist the muscle to reach a d full range of motion. the 4s ret period was set between contraction to limit fatigue. EMG treatment was performed for 2 sessions (30.session) a day, fiver times per week over 10 weeks. Both the EMG stim group and the control group were allowed to perform low - intensity physical activities.
Subgroup 1: Severity of spasticity (as stated by category or as measured by	Not stated/unclear

modified Ashworth scale [MAS])	
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	NA
Comparator	Both the EMG stim group and the control group were allowed to perform low - intensity physical activities. no additional details provided
Number of participants	14
Duration of follow-up	post intervention ? 10 weeks
Indirectness	NA
Additional comments	NR

1

Study arms

Neuromuscular electrical stimulation (NMES) (N = 7)
(EMG)-triggered neuromuscular electrical stimulation (NMES; EMG-stim)

Usual care (N = 7)
Control group- low intensity exercise only

Characteristics

Study-level characteristics

Characteristic	**Study (N = 14)**
Ethnicity Nominal	NR
Comorbidities Nominal	NR
Comorbidities No of events	n = NR ; % = NR
Severity of spasticity Nominal	NR
Type of spasticity Nominal	NR

Arm-level characteristics

Characteristic	Neuromuscular electrical stimulation (NMES) (N = 7)	Usual care (N = 7)
% Female Nominal	28.6	0
Mean age (SD) Mean (SD)	61 (7.5)	54.1 (3.9)
Time period after stroke months Mean (SD)	18.6 (4.2)	19.7 (7.7)

Outcomes

Study timepoints

- Baseline
- 10 week

EMG-stimulated NMES vs no treatment

Outcome	Neuromuscular electrical stimulation (NMES), Baseline, N = 7	Neuromuscular electrical stimulation (NMES), 10 week, N = 7	Usual care, Baseline, N = 7	Usual care, 10 week, N = 7
Physical function - upper limb - Box and block test 0-150 Mean (SD)	21.14 (4.09)	31.86 (4.77)	22.71 (3.87)	23 (3.24)

Physical function - upper limb - Box and block test - Polarity - Higher values are better
Final values

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

EMG-stimulatedNMESvsnotreatment-Physicalfunction-upperlimb-Boxandblocktest-MeanSD-(EMG)-triggered neuromuscular electrical stimulation (NMES; EMG-stim)-Control group- low intensity exercise only-t10

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to lack of details on randomisation process and no details on care provided to the control group so may be performance/adherence bias)*
Overall bias and Directness	Overall Directness	Directly applicable

Simpson, 1996

Bibliographic Reference	Simpson, D. M.; Alexander, D. N.; O'Brien, C. F.; Tagliati, M.; Aswad, A. S.; Leon, J. M.; Gibson, J.; Mordaunt, J. M.; Monaghan, E. P.; Botulinum toxin type A in the treatment of upper extremity spasticity: a randomized, double-blind, placebo-controlled trial; Neurology; 1996; vol. 46 (no. 5); 1306-10

Study details

Secondary publication of another included	NA

study- see primary study for details	
Other publications associated with this study included in review	NR
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Outpatient multicentre trial in 3 sites in the USA
Study dates	NR
Sources of funding	Supported from a grant from Allergan, Inc, who supplied the Botulinum Toxin and Placebo used in this stuudy
Inclusion criteria	At least 9 months post stroke and demonstrate an average wrist flexor tone of grade 2.5 or higher as measured by the MAS, with a minimum flexor score of 2 at both joints. Additionally, patients were required to have a stable clinical course for at least 2 months before the study and be willing to maintain ongoing spasticity treatments (e.g. medication, physiotherapy etc) throughout the study.
Exclusion criteria	Patients with a fixed contracture, previous treatment with BTXA, neurolytic or surgical procedures in the study limb, or a neuromuscular disease were excluded.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	NR
Intervention(s)	Patients were randomly assigned to receive either a low (75 units), medium (150 units) or high (300 units) total dose of BTXA. To monitor the safety of progressively escalating doses BTXA in this populations, the first four patients at each site received 75 units or placebo and the next four received 150 units or placebo, and the last 4 received 300 units of placebo.

	Study medication was prepared by the pharmacist or study nurse who has no role in evaluating or injecting patients. BTXA was supplied as a vacuum dried powder and reconstituted with sterile saline (0.9%) without preservatives. The amount of diluent added to the vials determined the dosage. A total volume of 3ml was injected into each patient. Study medication was injected into the biceps (four sites), flexor carpi radialis (one site), and flexor carpi ulnaris (one site) using a 2-guage teflon-coated needle with EMG guidance. The combination EMG-injection needle allowed recording if the muscle EMG activity via an audio and video signal and injection of study medication through the same needle.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Moderate (or MAS 2)
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	NA
Comparator	Patients were randomly assigned to receive either a low (75 units), medium (150 units) or high (300 units) total dose of BTXA. To monitor the safety of progressively escalating doses BTXA in this populations, the first four patients at each site received 75 units or placebo and the next four received 150 units or placebo, and the last 4 received 300 units of placebo.

	Study medication was prepared by the pharmacist or study nurse who has no role in evaluating or injecting patients. BTXA was supplied as a vacuum dried powder and reconstituted with sterile saline (0.9%) without preservatives. The amount of diluent added to the vials determined the dosage. A total volume of 3ml was injected into each patient. No additional details provided
Number of participants	39
Duration of follow-up	16 weeks
Indirectness	NA
Additional comments	NR

Study arms

Onobotulinum toxin A (BOTOX) (N = 27)

placebo (N = 10)

1 **Characteristics**

2 ***Study-level characteristics***

Characteristic	Study (N = 39)
% Female Nominal	57
Mean age (SD) Mean (SD)	59 (12)
Ethnicity Nominal	NR
Comorbidities Nominal	NR
Time period after stroke Range	9 to 133
Time period after stroke Mean (SD)	37 (NR)
Type of spasticity Nominal	NR

3

Arm-level characteristics

Characteristic	Onobotulinum toxin A (BOTOX) (N = 27)	placebo (N = 10)
Severity of spasticity Mean (SD)	2.73 (0.77)	2.85 (0.79)

Outcomes

Study timepoints

- Baseline
- 16 week

Botox A vs Placebo

Outcome	Onobotulinum toxin A (BOTOX), Baseline, N = 39	Onobotulinum toxin A (BOTOX), 16 week, N = 37	placebo, Baseline, N = 39	placebo, 16 week, N = 37
Spastcity outcome - Modified ashworth scale 0-4 (change score) Mean (SD)	2.73 (0.77)	0.25 (0.6)	2.85 (0.79)	0.45 (0.86)
Discontinuation due to adverse events Botox = 1 due to hypothyroidism, 1 = lymphoma No of events	n = 0 ; % = 0	n = 2 ; % = 7.41	n = 0 ; % = 0	n = 0 ; % = 0

Spastcity outcome - Modified ashworth scale - Polarity - Lower values are better

Discontinuation due to adverse events - Polarity - Lower values are better

discontinuation

Outcome	Onobotulinum toxin A (BOTOX), Baseline, N = 39	Onobotulinum toxin A (BOTOX), 16 week, N = 39	placebo, Baseline, N = 39	placebo, 16 week, N = 39
Discontinuation due to adverse events Botox = 1 due to hypothyroidism, 1 = lymphoma No of events	n = 0 ; % = 0	n = 2 ; % = 7.41	n = 0 ; % = 0	n = 0 ; % = 0

Discontinuation due to adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

BotoxAvsPlacebo-Spastcityoutcome-Modifiedashworthscale-MeanSD- botulinum toxin type A-placebo-t16

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Due to concerns regarding allocation concealment)*
Overall bias and Directness	Overall Directness	Directly applicable

BotoxAvsPlacebo-Discontinuationduetoadverseevents-NoOfEvents- botulinum toxin type A-placebo-t16

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Due to concerns regarding allocation concealment)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

discontinuation-Discontinuationduetoadverseevents-NoOfEvents- botulinum toxin type A-placebo-t16

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Due to concerns regarding allocation concealment)*
Overall bias and Directness	Overall Directness	Directly applicable

Simpson, 2009

Bibliographic Reference	Simpson, D. M.; Gracies, J. M.; Yablon, S. A.; Barbano, R.; Brashear, A.; Bo, N. T. T. Z. D. Study Team; Botulinum neurotoxin versus tizanidine in upper limb spasticity: a placebo-controlled study; Journal of Neurology, Neurosurgery & Psychiatry; 2009; vol. 80 (no. 4); 380-5

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with	NR

this study included in review	
Trial name / registration number	NCT00430196
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Multi centre trial. No additional details
Study dates	NR
Sources of funding	DMS of Mount Sinai School of Medicine is the sponsor of the study. The study was funded by an unrestricted grant by Allergan, Inc. Allergan had no influence on the design, interpretation or reporting of the study.
Inclusion criteria	Eligible participants were 18–85 years of age, with prior stroke (cerebrovascular accident with a neurological deficit persisting at least 24 h) or traumatic brain injury (TBI) > 3 months earlier, and spasticity of the wrist, as demonstrated by a score of >3 for wrist flexor tone on the modified Ashworth Scale (MAS),14 with 0 indicating normal tone and 5 rigid flexion. An additional criterion for enrolment was difficulty with hygiene or dressing, pain or malposition of the wrist, as evidenced by a score of >2 on the Disability Assessment Scale (DAS).2 One domain was chosen by the investigator and the participant or care giver as the Principal Therapeutic Target (PTT) as assessed at the time of initial screening. A score of 0 on the DAS indicates no disability, and 3 is severe disability.
Exclusion criteria	Exclusion criteria included severe contracture at the wrist (inability to passively move the joint by .10u); prior tendon transfer; prior phenol/alcohol nerve block in the study limb; BoNT injection into the target limb within 4 months; prior casting of the study limb within 2 weeks; severe muscle atrophy or infection in target sites; orthostatic hypotension or treatment with oral antispasticity agents within 14 days; impaired renal or hepatic function; or current anticoagulant therapy with INR>3.5. Women were excluded if they were pregnant or planning to become pregnant during the course of the study. Participants taking other CNS medications, (eg, antidepressants), were required to be on a stable dose for >2 months previously. Physical/ occupational therapy, if used, was required to be maintained unchanged throughout the study.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	NR

Intervention(s)	TZD + placebo group = TZD was supplied as 4 mg tablets. The dose of the blinded oral study medication (TZD or placebo) was initiated at 2 mg/day to a maximum of 36 mg/day. The oral study medication was taken twice per day, and titrated by 4 mg increments every 3–4 days as per telephone contact between the subject and study nurse/investigator. If a subject tolerated all dose increases, a maximum dose of 36 mg could be reached by day 27– 28. Any subject experiencing side effects was instructed to return to the previous tolerated dose and maintain it for three more days. Slower titration then occurred at 2 mg increments every 3– 4 days. If the subject again experienced any side effects, they returned to the previous tolerated dose and maintained it until the end of the treatment period (visit 6, week 18). BoN-A + placebo group = Each subject received an injection of BoNT-A or saline placebo at visit 2. Each phial of Botox contains 100 units (U) of BoNT-A, 0.5 mg of human albumin and 0.9 mg of sodium chloride in a sterile, vacuum-dried form without preservative. In order to maintain blinding, an individual other than the injecting and evaluating investigators prepared the phials for injection. BoNT-A was diluted with preservative-free normal saline. Based on our experience with BoNT-A volume/potency studies, suggesting a greater effectiveness of high-volume/dose injections in larger muscles,15 lyophilised Botox, 100 units (U)/ phial, was reconstituted with 5 cm3 of preservative-free saline for injections in muscles above the elbow (20 U/cm3) and with 2 cm3 of saline for muscles below the elbow (50 U/cm3). All subjects were required to receive a standardised dosage of Botox of 50 U (1.0 cm3)/muscle into each of the wrist flexors (flexor carpi radialis and ulnaris). The remainder of the affected upper-extremity muscles, from the shoulder to fingers, could be injected as per the investigator's discretion, based on the subject's disability, to a maximum total dose of 500 U. Injections employed a needle stimulation technique, with a monopolar injection electrode.16 Once the target muscle was identified, by obtaining an appropriate contraction with the lowest possible stimulus intensity, BoNT was injected into one to four sites, based on the size of the muscle. The study duration was 22–24 weeks and consisted of a 1-day to 2-week screening period (visit 1), an injection and oral treatment initiation visit (visit 2/baseline visit) and follow-up visits at weeks 3, 6, 12 and 18. At the end of the treatment period, subjects were monitored for a further 4 weeks.
Subgroup 1: Severity of spasticity (as stated by category or as measured by	Severe (or MAS 3)

modified Ashworth scale [MAS])	
Subgroup 2: Time period after stroke when trial starts	Mixed
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	NA
Comparator	Subjects in the control group were given an intramuscular placebo plus oral placebo as per the protocol above
Number of participants	60
Duration of follow-up	Week 3, Week 6, Week 12 Week 18, week 22
Indirectness	Study also includes TBI patients, however these are of less than 20% of the population
Additional comments	NR

Study arms

Onobotulinum toxin A (BOTOX) plus oral placebo (N = 20)

oral Tizanidine plus intramuscular placebo (N = 21)

Intramuscular placebo plus oral placebo (N = 19)

Characteristics

Study-level characteristics

Characteristic	Study (N = 60)
Comorbidities Nominal	NR
Type of spasticity Nominal	NR

Arm-level characteristics

Characteristic	Onobotulinum toxin A (BOTOX) plus oral placebo (N = 20)	oral Tizanidine plus intramuscular placebo (N = 21)	Intramuscular placebo plus oral placebo (N = 19)
% Female Nominal	37.5	44.4	64.3
Mean age (SD) Mean (SD)	57.2 (9.9)	54.5 (16.3)	54.3 (15.8)
Ethnicity	NR	NR	NR

Characteristic	Onobotulinum toxin A (BOTOX) plus oral placebo (N = 20)	oral Tizanidine plus intramuscular placebo (N = 21)	Intramuscular placebo plus oral placebo (N = 19)
Nominal			
Caucasian Nominal	64.7	66.7	71.4
Hispanic Nominal	5.9	5.6	0
Black Nominal	23.5	27.8	28.6
Unknown Nominal	5.9	0	0
Severity of spasticity wrist flexor Mean (SD)	3.4 (0.51)	3.44 (0.62)	3.14 (0.53)
Time period after stroke Mean (SD)	NR (NR)	NR (NR)	NR (NR)

1

Outcomes

Study timepoints

- Baseline
- 6 week
- 22 week

Botulinum Toxin A vs TZD vs placebo

Outcome	Onobotulinum toxin A (BOTOX) plus oral placebo, Baseline, N = 20	Onobotulinum toxin A (BOTOX) plus oral placebo, 6 week, N = 19	Onobotulinum toxin A (BOTOX) plus oral placebo, 22 week, N = 16	oral Tizanidine plus intramuscular placebo, Baseline, N = 21	oral Tizanidine plus intramuscular placebo, 6 week, N = 18	oral Tizanidine plus intramuscular placebo, 22 week, N = 13	Intramuscular placebo plus oral placebo, Baseline, N = 19	Intramuscular placebo plus oral placebo, 6 week, N = 19	Intramuscular placebo plus oral placebo, 22 week, N = 14
spasticity outcome - MAS - wrist flexor change score 0-4 change score Mean (SD)	3.4 (0.51)	-1.32 (0.89)	NR (NR)	3.44 (0.62)	-0.22 (0.88)	NR (NR)	3.14 (0.53)	-0.68 (1)	NR (NR)
spasticity	3.24 (0.83)	-1.37 (1.46)	NR (NR)	3.11 (0.83)	-0.39 (0.98)	NR (NR)	3.07 (1.07)	-0.26 (0.93)	NR (NR)

Outcome	Onobotulinum toxin A (BOTOX) plus oral placebo, Baseline, N = 20	Onobotulinum toxin A (BOTOX) plus oral placebo, 6 week, N = 19	Onobotulinum toxin A (BOTOX) plus oral placebo, 22 week, N = 16	oral Tizanidine plus intramuscular placebo, Baseline, N = 21	oral Tizanidine plus intramuscular placebo, 6 week, N = 18	oral Tizanidine plus intramuscular placebo, 22 week, N = 13	Intramuscular placebo plus oral placebo, Baseline, N = 19	Intramuscular placebo plus oral placebo, 6 week, N = 19	Intramuscular placebo plus oral placebo, 22 week, N = 14
outcome - MAS - Finger flexor change score Mean (SD)									

1 spasticity outcome - MAS - wrist flexor change score - Polarity - Lower values are better

2 ***Discontinuation***

Outcome	Onobotulinum toxin A (BOTOX) plus oral placebo, Baseline, N = 20	Onobotulinum toxin A (BOTOX) plus oral placebo, 6 week, N = 20	Onobotulinum toxin A (BOTOX) plus oral placebo, 22 week, N = 20	oral Tizanidine plus intramuscular placebo, Baseline, N = 21	oral Tizanidine plus intramuscular placebo, 6 week, N = 21	oral Tizanidine plus intramuscular placebo, 22 week, N = 21	Intramuscular placebo plus oral placebo, Baseline, N = 19	Intramuscular placebo plus oral placebo, 6 week, N = 19	Intramuscular placebo plus oral placebo, 22 week, N = 19
Discontinuation due to adverse events No of events	n = 0 ; % = 0	n = 1 ; % = 5	n = 3	n = 0 ; % = 0	n = 3	n = 4	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0

Discontinuation due to adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

botox-avsTZDvsplacebo-spasticityoutcome-MAS-wristflexorchangescore-MeanSD- intramuscular BoNT plus oral placebo-oral TZD plus intramuscular placebo-ntramuscular placebo plus oral placebo-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to high rates of missing data and bias in reporting of results)*
Overall bias and Directness	Overall Directness	Partially applicable *(population includes <20% TBI patients)*

botox-avsTZDvsplacebo-spasticityoutcome-MAS-wristflexorchangescore-MeanSD- intramuscular BoNT plus oral placebo-oral TZD plus intramuscular placebo-ntramuscular placebo plus oral placebo-t22

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to high rates of missing data and bias in reporting of results)*
Overall bias and Directness	Overall Directness	Partially applicable *(population includes <20% TBI patients)*

botox-avsTZDvsplacebo-spasticityoutcome-MAS-wristflexorchangescore-spasticityoutcome-MAS-Fingerflexorchangescore-MeanSD-intramuscular BoNT plus oral placebo-oral TZD plus intramuscular placebo-ntramuscular placebo plus oral placebo-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to high rates of missing data and bias in reporting of results)*
Overall bias and Directness	Overall Directness	Partially applicable *(population includes <20% TBI patients)*

botox-avsTZDvsplacebo-spasticityoutcome-MAS-wristflexorchangescore-spasticityoutcome-MAS-Fingerflexorchangescore-MeanSD-intramuscular BoNT plus oral placebo-oral TZD plus intramuscular placebo-ntramuscular placebo plus oral placebo-t22

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to high rates of missing data and bias in reporting of results)*
Overall bias and Directness	Overall Directness	Partially applicable *(population includes <20% TBI patients)*

Discontinuation-Discontinuationduetoadverseevents-NoOfEvents- intramuscular BoNT plus oral placebo-oral TZD plus intramuscular placebo-ntramuscular placebo plus oral placebo-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to differential rate of missingess)*
Overall bias and Directness	Overall Directness	Partially applicable *(population includes <20% TBI patients)*

Discontinuation-Discontinuationduetoadverseevents-NoOfEvents- intramuscular BoNT plus oral placebo-oral TZD plus intramuscular placebo-ntramuscular placebo plus oral placebo-t22

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to differential rate of missingess)*
Overall bias and Directness	Overall Directness	Partially applicable *(population includes <20% TBI patients)*

Sonde, 1998

Bibliographic Reference	Sonde, L.; Gip, C.; Fernaeus, S. E.; Nilsson, C. G.; Viitanen, M.; Stimulation with low frequency (1.7 Hz) transcutaneous electric nerve stimulation (low-tens) increases motor function of the post-stroke paretic arm; Scandinavian Journal of Rehabilitation Medicine; 1998; vol. 30 (no. 2); 95-9

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	Sonde 2000
Trial name / registration number	NR

Study type	Randomised controlled trial (RCT)
Study location	Sweden
Study setting	Outpatients
Study dates	NR
Sources of funding	Study was supported by funds from the The Regional Social Insurance Office in collaboration with the Stockholm County Council, The committee for the Health and Caring sciences, Karolinska Institute and Foundation for Stroke Research.
Inclusion criteria	44 non-demented patients who had a paretic arm (scored 0-5 points in the Fugl-Myer motor scale) following their first ever stroke occurring 6-12 months previously were randomised into 2 groups: a treatment group and a comparison group.
Exclusion criteria	No dementia
Recruitment / selection of participants	NR
Intervention(s)	The treatment group received low-TENS for 60 min, 5 days a week for 3 months, The treatment was initiated by a physiotherapist. After the third occasion Low-TENS treatments were performed at home by the patients themselves. The importance of distinct muscle contractions during the treatment was carefully reinforced. The TENS device used was a Cefar Dual unit, which at low frequency setting emits a stimulus frequency of 1.7hz in pulse trains (eight pulses with an interval of 14ms). Rubber electrodes with a surface area of 50x35 mm were attached by sticking tac gel on the wrist extensors of the affected arm, and in 21 out of 26 persons (80%) a pair of electrodes was also placed over the elbow extensors or shoulder abductors. Both groups received physiotherapy at the day centre, usually twice a week.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mild (or MAS 1)

Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	NA
Comparator	The control group received physiotherapy at the day centre, usually twice a week.
Number of participants	44
Duration of follow-up	3 months
Indirectness	NA
Additional comments	NA

Study arms

TENS - low intensity low frequency (1.7 Hz) transcutaneous electric nerve stimulation (N = 26)

Control - usual care physiotherapy (N = 18)

1 **Characteristics**

2 ***Study-level characteristics***

Characteristic	Study (N = 44)
Ethnicity Nominal	NR
Comorbidities Nominal	NR
Severity of spasticity Nominal	NR
Type of spasticity Nominal	NR

3

4 ***Arm-level characteristics***

Characteristic	TENS - low intensity low frequency (1.7 Hz) transcutaneous electric nerve stimulation (N = 26)	Control - usual care physiotherapy (N = 18)
% Female Nominal	26.92	55.56
Mean age (SD) Mean (SD)	71 (6)	73 (3.5)

Characteristic	TENS - low intensity low frequency (1.7 Hz) transcutaneous electric nerve stimulation (N = 26)	Control - usual care physiotherapy (N = 18)
Time period after stroke Mean (SD)	9.1 (2.2)	8.3 (2.1)

Outcomes

Study timepoints

- Baseline
- 3 month

TENS vs usual care

Outcome	TENS - low intensity low frequency (1.7 Hz) transcutaneous electric nerve stimulation, Baseline, N = 26	TENS - low intensity low frequency (1.7 Hz) transcutaneous electric nerve stimulation, 3 month, N = 26	Control - usual care physiotherapy, Baseline, N = 18	Control - usual care physiotherapy, 3 month, N = 18
Physical function - upper limb - Fugl Myer assessment 0-66 (change score) Mean (SD)	24.8 (14.5)	3.76 (4.06)	25.9 (16.8)	0.7 (2.67)

Physical function - upper limb - Fugl Myer assessment - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

TENSvsusualcare-Physicalfunction-upperlimb-FuglMyerassessment-MeanSD-TENS - low intensity low frequency (1.7 Hz) transcutaneous electric nerve stimulation-Control - usual care physiotherapy-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Due to missing data, lack of randomisation details and selection of reported results)*
Overall bias and Directness	Overall Directness	Directly applicable

Sonde, 2000

Bibliographic Reference	Sonde, L.; Kalimo, H.; Fernaeus, S. E.; Viitanen, M.; Low TENS treatment on post-stroke paretic arm: a three-year follow-up; Clinical Rehabilitation; 2000; vol. 14 (no. 1); 14-9

Study details

Secondary publication of another included study- see primary study for details	Sonde 1998 - see study for full details
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	Sweden
Study setting	Outpatients

Study dates	NR
Sources of funding	Study was supported by funds from the The Regional Social Insurance Office in collaboration with the Stockholm County Council, The committee for the Health and Caring sciences, Karolinska Institute and Foundation for Stroke Research.
Inclusion criteria	44 non-demented patients who had a paretic arm (scored 0-5 points in the Fugl-Myer motor scale) following their first ever stroke occurring 6-12 months previously were randomised into 2 groups: a treatment group and a comparison group.
Exclusion criteria	No dementia
Recruitment / selection of participants	NR
Intervention(s)	The treatment group received low-TENS for 60 min, 5 days a week for 3 months, The treatment was initiated by a physiotherapist. After the third occasion Low-TENS treatments were performed at home by the patients themselves. The importance of distinct muscle contractions during the treatment was carefully reinforced. The TENS device used was a Cefar Dual unit, which at low frequency setting emits a stimulus frequency of 1.7hz in pulse trains (eight pulses with an interval of 14ms). Rubber electrodes with a surface area of 50x35 mm were attached by sticking tac gel on the wrist extensors of the affected arm, and in 21 out of 26 persons (80%) a pair of electrodes was also placed over the elbow extensors or shoulder abductors. Both groups received physiotherapy at the day centre, usually twice a week.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mild (or MAS 1)
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)

Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	NA
Comparator	The control group received physiotherapy at the day centre, usually twice a week.
Number of participants	28
Duration of follow-up	3 years
Indirectness	NR
Additional comments	NR

Study arms

TENS - low intensity low frequency (1.7 Hz) transcutaneous electric nerve stimulation (N = 24)

Control - usual care physiotherapy (N = 18)

Outcomes

Study timepoints

- Baseline
- 3 month
- 3 year

TENS vs usual care

Outcome	TENS - low intensity low frequency (1.7 Hz) transcutaneous electric nerve stimulation, Baseline, N = 18	TENS - low intensity low frequency (1.7 Hz) transcutaneous electric nerve stimulation, 3 month, N = 18	TENS - low intensity low frequency (1.7 Hz) transcutaneous electric nerve stimulation, 3 year, N = 18	Control - usual care physiotherapy, Baseline, N = 10	Control - usual care physiotherapy, 3 month, N = 10	Control - usual care physiotherapy, 3 year, N = 10
spasticity outcome - MAS 0-4 Mean (SD)	1.6 (1.02)	1.6 (0.9)	2.2 (1.3)	1 (1.1)	1 (1.1)	1.4 (1.2)
Activities of daily living - Barthel Index Mean (SD)	80 (13.5)	81.9 (13.3)	78.1 (16.6)	79.5 (10.7)	79 (10.7)	66.5 (22.4)
physical function upper limb - Fugl Meyer	21.7 (14.8)	24.3 (16.7)	20.2 (13.9)	26.5 (18.9)	26.3 (17.6)	24.2 (17.4)

Outcome	TENS - low intensity low frequency (1.7 Hz) transcutaneous electric nerve stimulation, Baseline, N = 18	TENS - low intensity low frequency (1.7 Hz) transcutaneous electric nerve stimulation, 3 month, N = 18	TENS - low intensity low frequency (1.7 Hz) transcutaneous electric nerve stimulation, 3 year, N = 18	Control - usual care physiotherapy, Baseline, N = 10	Control - usual care physiotherapy, 3 month, N = 10	Control - usual care physiotherapy, 3 year, N = 10
assessment 0-66 Mean (SD)						

spasticity outcome - MAS - Polarity - Lower values are better
Activities of daily living - Barthel Index - Polarity - Higher values are better
physical function upper limb - Fugl Meyer assessment - Polarity - Higher values are better
Final values

discontinuation

Outcome	TENS - low intensity low frequency (1.7 Hz) transcutaneous electric nerve stimulation, Baseline, N = 26	TENS - low intensity low frequency (1.7 Hz) transcutaneous electric nerve stimulation, 3 month, N = 26	TENS - low intensity low frequency (1.7 Hz) transcutaneous electric nerve stimulation, 3 year, N = 26	Control - usual care physiotherapy, Baseline, N = 18	Control - usual care physiotherapy, 3 month, N = 18	Control - usual care physiotherapy, 3 year, N = 18
Discontinuation TENS = deceased = 3, major stroke = 3, deceased = 5, major stroke = 3 No of events	n = 0 ; % = 0	n = 2 ; % = 7.69	n = 6 ; % = 23.08	n = 0 ; % = 0	n = 0 ; % = 0	n = 8 ; % = 44.44

Discontinuation - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

TENSvsusualcare-spasticityoutcome-MAS-MeanSD-TENS - low intensity low frequency (1.7 Hz) transcutaneous electric nerve stimulation-Control - usual care physiotherapy-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to issues with randomisation and missingness)*
Overall bias and Directness	Overall Directness	Directly applicable

TENSvsusualcare-physicalfunctionupperlimb-FuglMeyerassessment-MeanSD-TENS - low intensity low frequency (1.7 Hz) transcutaneous electric nerve stimulation-Control - usual care physiotherapy-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to issues with randomisation and missingness)*
Overall bias and Directness	Overall Directness	Directly applicable

TENSvsusualcare-physicalfunctionupperlimb-FuglMeyerassessment-MeanSD-TENS - low intensity low frequency (1.7 Hz) transcutaneous electric nerve stimulation-Control - usual care physiotherapy-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to issues with randomisation and missingness)*
Overall bias and Directness	Overall Directness	Directly applicable

TENSvsusualcar-Activitiesofdailyliving-BarthelIndex-MeanSD-TENS - low intensity low frequency (1.7 Hz) transcutaneous electric nerve stimulation-Control - usual care physiotherapy-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to issues with randomisation and missingness)*
Overall bias and Directness	Overall Directness	Directly applicable

TENSvsusualcare-Activitiesofdailyliving-BarthelIndex-MeanSD-TENS - low intensity low frequency (1.7 Hz) transcutaneous electric nerve stimulation-Control - usual care physiotherapy-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to issues with randomisation and missingness)*
Overall bias and Directness	Overall Directness	Directly applicable

TENSsusualcare-spasticityoutcome-MAS-MeanSD-TENS - low intensity low frequency (1.7 Hz) transcutaneous electric nerve stimulation-Control - usual care physiotherapy-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to issues with randomisation and missingness)*
Overall bias and Directness	Overall Directness	Directly applicable

discontinuation-Discontinuation-NoOfEvents-TENS - low intensity low frequency (1.7 Hz) transcutaneous electric nerve stimulation-Control - usual care physiotherapy-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to issues with randomisation and missingness)*
Overall bias and Directness	Overall Directness	Directly applicable

discontinuation-Discontinuation-NoOfEvents-TENS - low intesity low frequency (1.7 Hz) transcutaneous electric nerve stimulation-Control - usual care physiotherapy-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to issues with randomisation and missingness)*
Overall bias and Directness	Overall Directness	Directly applicable

Tan, 2021

Bibliographic Reference	Tan, B.; Jia, L.; Ultrasound-Guided BoNT-A (Botulinum Toxin A) Injection Into the Subscapularis for Hemiplegic Shoulder Pain: A Randomized, Double-Blind, Placebo-Controlled Trial; Stroke; 2021; trokeaha121034049

Study details

Secondary publication of another included	NR

study- see primary study for details	
Other publications associated with this study included in review	NR
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	outpatients department of rehabilitation medicine
Study dates	June 2019 - December 2019
Sources of funding	This research was supported in part by the National Natural Science Foundation of China, The natural Science foundation of Chongquing, the medical scientific research projects foundation of ChongQuing, the traditional Chinese medicine science and technology project of ChongQing and the Chongquing health commission projects.
Inclusion criteria	An age over 18 years old; spastic hemiparesis due to a cerebral vascular accident >2 months ago; moderate-severe spastic shoulder pain with a VAS score for pain >4; a MAS of 1+ or more points for spasticity in external rotation and abduction; limited passive ROM of the shoulder defined as 10-30 degrees less ROM in external rotation and abduction than that of the opposite side and the ability to understand and agree to the trial procedures and to sig an informed consent form in accordance with the nation legislation.
Exclusion criteria	Having received a BoNT-A injection into the affected shoulder within the previous 6 months; the presence of another obvious explanation for the pain (eg. fracture); a prior surgery to either the shoulder or neck region; patient immobility involving confinement to bed for >50% of the daytime house; any mediation condition that might increase the risk to the subject on exposure to BoNT-! (eg AMS); a known allergy or sensitivity to any component of BoNT-A; the presence of an unstable medical condition or an uncontrolled know systemic disease; concurrent participation in another drug or device study or participation in such a study during the 30 days before enrolment; the use of aminoglyscoside antibiotics, or any other agent that might interfere with neuromuscular function; any condition or situation that might place the subject at significant risk; and anticoagulant use.

Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	Participants were recruited with flyers posted in stroke and rehabilitation medicine outpatient clinic waiting areas.
Intervention(s)	One vial of 100U of BoNT-A was reconstituted with 2.0ml of saline at a concentration of 50U/ml before injection. A dose of 100 U was selected as being both optimal and cost effective based on a previous pilot study using Botox. The shoulder was placed in flexion and external rotation to give the ultrasound access to the posterior axillary fold. All subscapularis sonographic images were evaluated by the same experience physician who was certified by the nation health commission of the peoples republic of China. The physician performed musculoskeletal sonography using a 6- to 13-mhx linear array transducer. Then a 10 cm 18- gauge needle was inserted into the subscapularis under direct ultrasound guidance. BoNT-A (2ml 100U/ml) was injected at 2 points, with each injection point receiving 50 U and the maximum total dose per patient was 100 U. All patients received a standard course of exercise therapy (stretching, increasing active motion)and physiotherapy (hot pack interferential current therapy) during the 4 - week period after injection with a minimum of 2 visits per week by a physical therapist blinded to the group.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Severe (or MAS 3)
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	not applicable

Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	NA
Comparator	The control group received 2.0 ml saline injection at 2 points and a 1-ml injection of saline at each point. All patients received a standard course of exercise therapy (stretching, increasing active motion)and physiotherapy (hot pack interferential current therapy) during the 4 - week period after injection with a minimum of 2 visits per week by a physical therapist blinded to the group.
Number of participants	36
Duration of follow-up	4 week
Indirectness	NA
Additional comments	NA

Study arms

Onabotulinum toxin A (BOTOX) + physiotherapy (N = 18)

Placebo + physiotherapy (N = 18)

1 **Characteristics**

2 ***Study-level characteristics***

Characteristic	Study (N =)
Ethnicity Nominal	NR
Comorbidities Nominal	NR
Type of spasticity Nominal	NR

3

4 ***Arm-level characteristics***

Characteristic	Onabotulinum toxin A (BOTOX) + physiotherapy (N = 18)	Placebo + physiotherapy (N = 18)
% Female Nominal	16.7	33.3
Mean age (SD) Mean (SD)	51.1 (11.4)	53.9 (13)
Severity of spasticity Mean (SE)	NR (*empty data*)	NR (NR)
Severity of spasticity Mean (SD)	3.3 (0.48)	3.4 (0.51)

Outcomes

Study timepoints

- Baseline
- 4 week
- 24 week

Botulinum Toxin A vs Placebo

Outcome	Onabotulinum toxin A (BOTOX) + physiotherapy, Baseline, N = 18	Onabotulinum toxin A (BOTOX) + physiotherapy, 4 week, N = 18	Onabotulinum toxin A (BOTOX) + physiotherapy, 24 week, N = 18	Placebo + physiotherapy, Baseline, N = 18	Placebo + physiotherapy, 4 week, N = 18	Placebo + physiotherapy, 24 week, N = 18
Spastcity outcome - Modified ashworth scale (final values) 0-4 Mean (SD)	3.3 (0.48)	1.78 (0.59)	2.42 (0.56)	3.4 (0.51)	2.36 (0.6)	2.64 (0.81)
Physical function - upper limb - FMA-UE (final values) 0-66 Mean (SD)	18.72 (7.98)	29.67 (12.46)	NR (NR)	17.44 (8.23)	23.94 (10.06)	NR (NR)
Pain - VAS (final values) 0-10	7.11 (0.96)	2.83 (1.2)	4.22 (1.7)	7.33 (1.14)	4.22 (1.06)	5.17 (1.34)

Outcome	Onabotulinum toxin A (BOTOX) + physiotherapy, Baseline, N = 18	Onabotulinum toxin A (BOTOX) + physiotherapy, 4 week, N = 18	Onabotulinum toxin A (BOTOX) + physiotherapy, 24 week, N = 18	Placebo + physiotherapy, Baseline, N = 18	Placebo + physiotherapy, 4 week, N = 18	Placebo + physiotherapy, 24 week, N = 18
Mean (SD)						
Stroke specific patient reported outcome measures (final values) 49-245 Mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Energy Mean (SD)	8 (2.52)	9.89 (2.68)	NR (NR)	7.72 (2.63)	9.33 (2.61)	NR (NR)
family Mean (SD)	6.61 (3.18)	6.94 (3.22)	*empty data*	6.72 (3.58)	7.11 (3.56)	*empty data*
Language Mean (SD)	19.67 (6.37)	21.61 (5.21)	*empty data*	18.83 (6.2)	21 (4.7)	*empty data*
Mobility Mean (SD)	16.44 (4.32)	22 (5.38)	*empty data*	15.77 (4.5)	20.94 (4.7)	*empty data*
Mood Mean (SD)	17.44 (4.82)	18.94 (5.03)	*empty data*	16.83 (5.08)	17.89 (5.09)	*empty data*
Personality Mean (SD)	10.56 (3.29)	10.72 (3.25)	*empty data*	10.72 (2.76)	10.89 (2.95)	*empty data*

Outcome	Onabotulinum toxin A (BOTOX) + physiotherapy, Baseline, N = 18	Onabotulinum toxin A (BOTOX) + physiotherapy, 4 week, N = 18	Onabotulinum toxin A (BOTOX) + physiotherapy, 24 week, N = 18	Placebo + physiotherapy, Baseline, N = 18	Placebo + physiotherapy, 4 week, N = 18	Placebo + physiotherapy, 24 week, N = 18
social roles Mean (SD)	7.89 (1.18)	8.78 (1.63)	*empty data*	7.5 (1.85)	8.94 (1.55)	*empty data*
Vision Mean (SD)	13.78 (1.35)	13.83 (1.2)	*empty data*	13.83 (1.15)	13.94 (1.06)	*empty data*
Work Mean (SD)	4.44 (2.77)	8.28 (3)	*empty data*	7.11 (2.56)	7.78 (2.88)	*empty data*
self care Mean (SD)	13.56 (3.55)	19.44 (3.97)	*empty data*	13 (3.66)	18.44 (3.94)	*empty data*
thinking Mean (SD)	9.28 (2.05)	10.17 (2.07)	*empty data*	9.17 (1.58)	10.39 (1.85)	*empty data*
Upper extremity Mean (SD)	13.22 (3.08)	19.28 (3.54)	*empty data*	11.5 (3.59)	16.33 (3.99)	*empty data*
Discontinuation - due to adverse events No of events	n = 0 ; % = 0	n = 0 ; % = 0	*empty data*	n = 0 ; % = 0	n = 0 ; % = 0	*empty data*

1 Spastcity outcome - Modified ashworth scale - Polarity - Lower values are better
2 Physical function - upper limb - FMA-UE - Polarity - Higher values are better
3 Pain - VAS - Polarity - Lower values are better

Stroke specific patient reported outcome measures - Polarity - Higher values are better
Discontinuation - due to adverse events - Polarity - Lower values are better
Final values

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

BotoxAvsPlacebo-Strokespecificpatientreportedoutcomemeasures-Upperextremity-MeanSD-BoNT-A (botulinum toxin A) + physiotherapy-Placebo + physiotherapy-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

BotoxAvsPlacebo-Discontinuation-duetoadverseevents-NoOfEvents-BoNT-A (botulinum toxin A) + physiotherapy-Placebo + physiotherapy-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

BotoxAvsPlacebo-Strokespecificpatientreportedoutcomemeasures-thinking-MeanSD-BoNT-A (botulinum toxin A) + physiotherapy-Placebo + physiotherapy-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

BotoxAvsPlacebo-Strokespecificpatientreportedoutcomemeasures-selfcare-MeanSD-BoNT-A (botulinum toxin A) + physiotherapy-Placebo + physiotherapy-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

BotoxAvsPlacebo-Strokespecificpatientreportedoutcomemeasures-Work-MeanSD-BoNT-A (botulinum toxin A) + physiotherapy-Placebo + physiotherapy-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

BotoxAvsPlacebo-StrokespecificpatientreportedoutcomemeasuresVision-MeanSD-BoNT-A (botulinum toxin A) + physiotherapy-Placebo + physiotherapy-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

BotoxAvsPlacebo-Strokespecificpatientreportedoutcomemeasuressocialroles-MeanSD-BoNT-A (botulinum toxin A) + physiotherapy-Placebo + physiotherapy-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

BotoxAvsPlacebo-StrokespecificpatientreportedoutcomemeasuresPersonality-MeanSD-BoNT-A (botulinum toxin A) + physiotherapy-Placebo + physiotherapy-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

BotoxAvsPlacebo-Strokespecificpatientreportedoutcomemeasures-Mood-MeanSD-BoNT-A (botulinum toxin A) + physiotherapy-Placebo + physiotherapy-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

BotoxAvsPlacebo-Strokespecificpatientreportedoutcomemeasures-Mobility-MeanSD-BoNT-A (botulinum toxin A) + physiotherapy-Placebo + physiotherapy-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

BotoxAvsPlacebo-Strokespecificpatientreportedoutcomemeasures-Language-MeanSD-BoNT-A (botulinum toxin A) + physiotherapy-Placebo + physiotherapy-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

BotoxAvsPlacebo-Strokespecificpatientreportedoutcomemeasures-family-MeanSD-BoNT-A (botulinum toxin A) + physiotherapy-Placebo + physiotherapy-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

BotoxAvsPlacebo-Strokespecificpatientreportedoutcomemeasures-Energy-MeanSD-BoNT-A (botulinum toxin A) + physiotherapy-Placebo + physiotherapy-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

BotoxAvsPlacebo-Discontinuation-duetoadverseevents-NoOfEvents-BoNT-A (botulinum toxin A) + physiotherapy-Placebo + physiotherapy-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

BotoxAvsPlacebo-Pain-VAS-MeanSD-BoNT-A (botulinum toxin A) + physiotherapy-Placebo + physiotherapy-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

BotoxAvsPlacebo-Pain-VAS-MeanSD-BoNT-A (botulinum toxin A) + physiotherapy-Placebo + physiotherapy-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

BotoxAvsPlacebo-Physicalfunction-upperlimb-FMA-UE-MeanSD-BoNT-A (botulinum toxin A) + physiotherapy-Placebo + physiotherapy-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

BotoxAvsPlacebo-Spastcityoutcome-Modifiedashworthscale-MeanSD-BoNT-A (botulinum toxin A) + physiotherapy-Placebo + physiotherapy-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

BotoxAvsPlacebo-Spastcityoutcome-Modifiedashworthscale-MeanSD-BoNT-A (botulinum toxin A) + physiotherapy-Placebo + physiotherapy-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Tao, 2015

Bibliographic Reference	Tao, W.; Yan, D.; Li, J. H.; Shi, Z. H.; Gait improvement by low-dose botulinum toxin A injection treatment of the lower limbs in subacute stroke patients; Journal of Physical Therapy Science; 2015; vol. 27 (no. 3); 759-62

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with	NR

this study included in review	
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Stroke/neurology units or rehabilitation department of Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University
Study dates	NR
Sources of funding	NR
Inclusion criteria	The inclusion criteria for the patients were as follows: 1. They were over the age of 18 and less than 80 years and had had a stroke within 6 weeks. 2. They had slight spasticity of the triceps surae as defined by a score of 1–1+ on the MAS or ankle clonus (+). 3. They had sufficient cognitive and communication ability as defined by an MMSE (mini-mental state examination) sore >25. 4. They could not dorsiflex the ankle and their LEMI (Lower Extremity Motor Index)< 109) . 5. They were not receiving concurrent aminoglycoside antibiotics or oral anti-spasticity medication.
Exclusion criteria	NR
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	Patients were recruited from the stroke/neurology units or rehabilitation department of Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University
Intervention(s)	An experienced physician injected 200 units BTX-A (Allergan, 1 ml dilution per vial) by electrical stimulation-guided (Dantec CLAVISTM, REF 9015A0011) into the gastrocnemius (medial and lateral head of the gastrocnemius, 100 units), the soleus (50 units), and the posterior tibial muscle (50 units). There was no other specific treatment other than the injections. Both groups received comprehensive rehabilitation. This included physiotherapy (45 minutes every workday) and occupational therapy (30 minutes every workday). Gait training was also performed. The therapy combined elements of the neurodevelopmental technique and motor relearning program.

Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mixed
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb
Population subgroups	NA
Comparator	patients received the same volume of placebo solution into the same number of injections of the same muscles. There was no other specific treatment other than the injections. Both groups received comprehensive rehabilitation. This included physiotherapy (45 minutes every workday) and occupational therapy (30 minutes every workday). Gait training was also performed. The therapy combined elements of the neurodevelopmental technique and motor relearning program.
Number of participants	23
Duration of follow-up	8 weeks
Indirectness	NA
Additional comments	NR

Study arms

Onabotulinum toxin A (BOTOX) (N = 11)

Placebo injection (N = 12)

Characteristics

Study-level characteristics

Characteristic	Study (N = 23)
Ethnicity Nominal	NR
Comorbidities Nominal	NR
Type of spasticity Nominal	NR

Arm-level characteristics

Characteristic	Onabotulinum toxin A (BOTOX) (N = 11)	Placebo injection (N = 12)
% Female	36.36	33.33

Characteristic	Onabotulinum toxin A (BOTOX) (N = 11)	Placebo injection (N = 12)
Nominal		
Mean age (SD) Mean (SD)	55 (12)	58 (14)
Severity of spasticity Nominal	NR	NR
Time period after stroke (days) Mean (SD)	24.2 (12.2)	23.2 (17.2)

Outcomes

Study timepoints

- Baseline
- 8 week

Botox A vs Placebo

Outcome	Onabotulinum toxin A (BOTOX), Baseline, N = 11	Onabotulinum toxin A (BOTOX), 8 week, N = 11	Placebo injection, Baseline, N = 12	Placebo injection, 8 week, N = 12
Physical Function - lower limb - FMA (final values) 0-34 Mean (SD)	22.5 (5.1)	29 (3.3)	21.1 (4.1)	27.8 (5.5)

Outcome	Onabotulinum toxin A (BOTOX), Baseline, N = 11	Onabotulinum toxin A (BOTOX), 8 week, N = 11	Placebo injection, Baseline, N = 12	Placebo injection, 8 week, N = 12
Activities of daily living - Barthel Index (final values) 0-100 Mean (SD)	38.8 (7.7)	65.5 (9.5)	37.5 (5.9)	50.1 (11.8)
Discontinuation due to adverse events Nominal	0	0	0	0
Discontinuation due to adverse events No of events	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0

Physical Function - lower limb - FMA - Polarity - Higher values are better
Activities of daily living - Barthel Index - Polarity - Higher values are better
Discontinuation due to adverse events - Polarity - Lower values are better
Final values

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

BotoxAvsPlacebo-Discontinuationduetoadverseevents-Nominal-botulinum toxin A-Placebo injection-t8

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

BotoxAvsPlacebo-Activitiesofdailyliving-BarthelIndex-MeanSD-botulinum toxin A-Placebo injection-t8

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

BotoxAvsPlacebo-PhysicalFunction-lowerlimb-FMA-MeanSD-botulinum toxin A-Placebo injection-t8

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Tavakol, 2021

Bibliographic Reference	Tavakol, Z.; Shariat, A.; Ansari, N. N.; Ghannadi, S.; Honarpishe, R.; Dommerholt, J.; Noormohammadpour, P.; Ingle, L.; A double-blind randomized controlled trial for the effects of dry needling on upper limb dysfunction in patients with stroke; Acupuncture and Electro-Therapeutics Research; 2021; vol. 45 (no. 2-4); 115-124

1 **Study details**

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	Iran
Study setting	Sports Medicine Research Center, Tehran University of Medical Sciences, Iran
Study dates	August and October 2018
Sources of funding	This study was supported by the Sports Medicine Research Center, Neuroscience Institute, Tehran University of Medical Sciences.
Inclusion criteria	The inclusion criteria were: 1) age between 18≥; 2) at least six months since the stroke; 3) the first-ever stroke resulted in hemiplegia; 4) wrist flexor Modified Modified Ashworth Scale (MMAS) score ≥1; 5) not taking any medications for spasticity, and 6) able to understand and follow instructions.
Exclusion criteria	The exclusion criteria were: 1) having any contraindication to dry needling; 2) history of neurological pain; 3) fixed muscle contracture of the affected wrist; 4) currently receiving other treatment protocols, and 5) unwillingness to participate in the study.
Stratification - Type of spasticity	Focal spasticity

Recruitment / selection of participants	The trial was conducted between August and October 2018 in the Sports Medicine Research Center, Tehran University of Medical Sciences, Iran.
Intervention(s)	Dry needling was delivered for three sessions, separated by a 48-hours interval between sessions. An experienced physiotherapist, blinded to the patient allocation, preformed the assessments. Dry needling was performed with the patient in the supine position, the affected arm alongside the trunk, the shoulder at 45° abduction, the elbow was extended, and the forearm in supination. Disposable sterile stainless-steel needles (size: 0.25 mm x 25 mm; SMC, Seoul, Korea) were used with the fast-in and fast-out cone shape technique. Target muscles were the flexor carpi radialis (FCR) and flexor carpi ulnaris (FCU). The FCR was needled in the medial forearm 4 cm below and 1 cm medially from the midpoint of the elbow crease. The FCU was needled at the midpoint of the proximal third segment of a line connecting the medial epicondyle to the ulnar styloid process. Each muscle was needled for 1 minute. An experienced sports medicine specialist not involved in the assessment of the patients completed the treatments All patients were instructed not to have any other treatments during the study and follow up period, including other physical therapy treatments, medications, acupuncture, or dry needling.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mild (or MAS 1)
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)

Subgroup 3: Acupuncture/dry needling	Dry needling
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	NR
Comparator	Baseline clinical characteristics, including age, sex, body mass index (BMI), time since stroke, hemiplegic side, co-morbidities, and medication usage were recorded. Sham needling was delivered for three sessions, separated by a 48-hours interval between sessions. An experienced physiotherapist, blinded to the patient allocation, preformed the assessments. In the control group, the same protocol was carried out using a sham needle. All patients were instructed not to have any other treatments during the study and follow up period, including other physical therapy treatments, medications, acupuncture, or dry needling.
Number of participants	24
Duration of follow-up	post intervention - approx 1 week and 4 weeks after
Indirectness	NR
Additional comments	NA

1

Study arms

Acupuncture/dry needling (N = 12)
Dry needling

Sham therapy (N = 12)
Sham needling

Characteristics

Study-level characteristics

Characteristic	Study (N = 24)
% Female Nominal	29.17
Mean age (SD) Mean (SD)	57 (9.6)
Ethnicity Nominal	NR
Comorbidities Nominal	NR
Time period after stroke Nominal	NR

Characteristic	Study (N = 24)
Type of spasticity Nominal	NR

1

2 ***Arm-level characteristics***

Characteristic	Acupuncture/dry needling (N = 12)	Sham therapy (N = 12)
Severity of spasticity (%) Nominal	NR	NR
MAS 0 Nominal	0	0
MAS 1 Nominal	50	25
MAS 2 Nominal	25	41.7
MAS 3 Nominal	25	33.3
MAS 4 Nominal	0	0

3

Outcomes

Study timepoints

- Baseline
- 5 week

Dry needling vs Sham needling

Outcome	Acupuncture/dry needling, Baseline, N = 12	Acupuncture/dry needling, 5 week, N = 12	Sham therapy, Baseline, N = 12	Sham therapy, 5 week, N = 12
Physical function - upper limb - Box and block test (final values) 0-150 Mean (SD)	6.34 (9.28)	6.84 (9.54)	3.41 (3.05)	3.25 (2.77)
Discontinuation due to adverse events No of events	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0

Physical function - upper limb - Box and block test - Polarity - Higher values are better
Discontinuation due to adverse events - Polarity - Lower values are better
Final values

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

DryneedlingvsShamneedling-Physicalfunction-upperlimb-Boxandblocktest-MeanSD-Dry needling-Sham needling-t5

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

DryneedlingvsShamneedling-Discontinuationduetoadverseevents-NoOfEvents-Dry needling-Sham needling-t5

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Tekeoglu, 1998

Bibliographic Reference	Tekeoglu, Y.; Adak, B.; Goksoy, T.; Effect of transcutaneous electrical nerve stimulation (TENS) on Barthel Activities of Daily Living (ADL) index score following stroke; Clinical Rehabilitation; 1998; vol. 12 (no. 4); 277-80

Study details

Secondary publication of another included study- see primary study for details	NR

Other publications associated with this study included in review	NR
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	Turkey
Study setting	Medical Faculty of Yüzüncü Yy'l University
Study dates	NR
Sources of funding	NR
Inclusion criteria	1) stroke with hemiplegia or hemiparesis; 2) diagnosis determined by physical and laboratory examination including radiological examination, computerized tomography and blood screen; 3) informed consent for participation in the study; 4) patients affected by discrete loss of motor function but able to stand and walk if assisted.
Exclusion criteria	NR
Stratification - Type of spasticity	Multifocal spasticity
Recruitment / selection of participants	The subjects included in the study were inpatients of the clinical research programme for hemiplegia after stroke in the Medical Faculty of Yüzüncü Yy'l University.
Intervention(s)	TENS stimulation was performed by means of a portable Acutens stimulator unit (Sa lam Electronics, Turkey), with digital display of peak current and voltage. Square pulses of 0.2 m s duration were delivered at a frequency of 100 per second. The two stimulating surface electrodes (3 . 5 cm × 5 cm) were placed on the extensor muscles of elbow (musculus triceps brachii). These are antagonistic to the spastic elbow flexor muscles. Spasticity in the elbow, knee and ankle was measured using the Ashworth Scale.5 The other two electrodes were attached to the skin over the common peroneal nerve posterior to the head of the fibula on the hemiparetic leg. This nerve supplies the muscles antagonistic to the spastic calf muscles. The sensory threshold was determined by the intensity of stimulation, which was gradually increased to the bearable level. Intensity was set at the level of bearable pain threshold

	All the patients were treated using the Todd–Davies exercise programme, which is a basic neurophysiological treatment programme.4 The study lasted eight weeks for total of 40 sessions. Both groups of patients received the same type of exercise programme every day in the morning, and in the afternoon group 1 underwent TENS stimulation and group two received placebo T E N S .
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mild (or MAS 1)
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Mixed
Population subgroups	NR
Comparator	Patients undergoing sham stimulation were connected to the stimulator with a resistor at the output. While the stimulator display showed that the stimulator was functioning, the patient received no current. The stimulation or placebo was administered for half an hour each day, Monday through Friday.

	All the patients were treated using the Todd–Davies exercise programme, which is a basic neurophysiological treatment programme.4 The study lasted eight weeks for total of 40 sessions. Both groups of patients received the same type of exercise programme every day in the morning, and in the afternoon group 1 underwent TENS stimulation and group two received placebo T E N S .
Number of participants	60
Duration of follow-up	8 weeks
Indirectness	NA
Additional comments	NR

Study arms

TENS with frequency of 100 Hz (N = 30)

Placebo TENS (N = 30)

Characteristics

Study-level characteristics

Characteristic	**Study (N = 60)**
Ethnicity Nominal	NR

Characteristic	Study (N = 60)
Type of spasticity Nominal	NR

1

2 ***Arm-level characteristics***

Characteristic	TENS with frequency of 100 Hz (N = 30)	Placebo TENS (N = 30)
% Female Nominal	43.33	53.33
Mean age (SD) Mean (SD)	55.9 (7)	52.2 (5.4)
Comorbidities shoulder pain Sample size	n = 8 ; % = 22	n = 6 ; % = 20
Severity of spasticity Mean (SD)	1.96 (1.35)	1.9 (1.47)
Time period after stroke days Mean (SD)	40.8 (11.4)	44.3 (13.1)

3

Outcomes

Study timepoints

- Baseline
- 8 week

TENS vs placebo

Outcome	TENS with frequency of 100 Hz, Baseline, N = 30	TENS with frequency of 100 Hz, 8 week, N = 30	Placebo TENS, Baseline, N = 30	Placebo TENS, 8 week, N = 30
spasticity outcome - MAS (final values) 0-4 Mean (SD)	1.96 (1.35)	0 (0)	1.9 (1.47)	0.93 (1.41)
Activities of daily living - Barthel Index (final values) 0-100 Mean (SD)	30.4 (22.1)	80.4 (10)	44.7 (17)	60.4 (13.3)

spasticity outcome - MAS - Polarity - Lower values are better
Activities of daily living - Barthel Index - Polarity - Higher values are better
Final values

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

TENSvsplacebo-Activitiesofdailyliving-BarthelIndex-MeanSD-TENS with frequency of 100 Hz-Placeboo TENS-t8

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to missing data and concerns with randomisation process)*
Overall bias and Directness	Overall Directness	Directly applicable

TENSvsplacebo-spasticityoutcome-MAS-MeanSD-TENS with frequency of 100 Hz-Placeboo TENS-t8

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to missing data and concerns with randomisation process)*
Overall bias and Directness	Overall Directness	Directly applicable

Turcu-Stiolica, 2021

Bibliographic Reference	Turcu-Stiolica, A.; Subtirelu, M. S.; Bumbea, A. M.; Can Incobotulinumtoxin-A Treatment Improve Quality of Life Better Than Conventional Therapy in Spastic Muscle Post-Stroke Patients? Results from a Pilot Study from a Single Center; Brain Sciences; 2021; vol. 11 (no. 7); 15

Study details

Secondary publication of another included	NA

study- see primary study for details	
Other publications associated with this study included in review	NR
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	Romania
Study setting	The patients were enrolled from the Neurology Hospital of Craiova, Romania, during the period from May 2020 to February 2021.
Study dates	May 2020 to February 2021.
Sources of funding	This research received no external funding
Inclusion criteria	Inclusion criteria were: age ≥ 18; ischemic or haemorrhagic stroke (as documented radiologically by a computerized tomography scan or magnetic resonance imaging; subarachnoid hemorrhage excluded); time since stroke onset ≥3 months (the limit of 3 months was chosen because spasticity occurs at least 6 weeks after the onset of stroke); Ashworth scale ≥ 2; no previous focal treatment of post-stroke spasticity with botulinum toxin; no other antispastic medications (including muscle relaxants).
Exclusion criteria	Exclusion criteria were: neurologically, cardiological, or respiratory unstable patients were not admitted, respiratory pathology was excluded because the risk of respiratory depression may be amplified by the administration of botulinum toxin; other orthopedic conditions involving the affected limbs. Patients who had contraindications to botulinum toxin injection were excluded, such as patients receiving anticoagulant therapy, patients with myasthenia, or patients with skin disorders at the injection site.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	The patients were enrolled from the Neurology Hospital of Craiova, Romania, during the period from May 2020 to February 2021.

Intervention(s)	BOT group, which received physiotherapy and applied focal spasticity therapy using botulinum toxin type A: incobotulinumtoxin-A (INCO, Xeomin®). The BOT group received a specific program of stretching exercises for the spastic muscles of the upper limb. Focal spasticity therapy consisted of injecting therapeutic doses of INCO into the target muscles. The injection was performed only on the upper spastic limb. The administration of botulinum toxin followed the corresponding dose of 200 U for INCO. The BOT patients were in the hospitalized system only for administration of INCO and they also received kinetotherapy. For both arms, anti-spasticity therapy was applied by physical and medication therapy. The difference between the groups consisted of the type of medication therapy applied.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mixed
Subgroup 2: Time period after stroke when trial starts	Not stated/unclear
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	NA

Comparator	The CON group received physiotherapy and oral drug treatment of spasticity: baclofen (started from 10 mg up to 60 mg daily). Patients in the CON group received physical therapy and the specific physiotherapy program for spasmodic muscles with the readjustment of the physical program at 3 months to respect the study design. The CON group, which were in the hospitalized system, received a specific classic specific physical kinetic treatment which consisted of electrotherapy to stimulate the paralyzed muscles combined with elements of kinetotherapy and stretching applied to the spastic muscles and antispastic drug treatment of baclofen. For both arms, anti-spasticity therapy was applied by physical and medication therapy. The difference between the groups consisted of the type of medication therapy applied.
Number of participants	34
Duration of follow-up	6 months
Indirectness	NA
Additional comments	NR

Study arms

Incobotulinum toxin type A (Xeomin) + physiotherapy (N = 17)

Baclofen + physiotherapy (N = 17)
started from 10 mg up to 60 mg daily

1 **Characteristics**

2 ***Study-level characteristics***

Characteristic	Study (N = 34)
Ethnicity Nominal	NR
Time period after stroke Nominal	NR
Type of spasticity Nominal	NR

3

4 ***Arm-level characteristics***

Characteristic	Incobotulinum toxin type A (Xeomin) + physiotherapy (N = 17)	Baclofen + physiotherapy (N = 17)
% Female Nominal	47.1	52.9
Mean age (SD) Mean (SD)	59.53 (8.94)	60.91 (12.86)
Comorbidities Nominal	NR	NR
Ischemic heart disease Nominal	82.4	100

Characteristic	Incobotulinum toxin type A (Xeomin) + physiotherapy (N = 17)	Baclofen + physiotherapy (N = 17)
Hypertension Nominal	94.1	100
Diabetes Nominal	11.8	52.9
Severity of spasticity Nominal	NR	NR
MAS 1 Nominal	0	11.8
MAS 2 Nominal	5.9	64.7
MAS 3 Nominal	58.8	17.7
MAS 3/4 Nominal	35.3	5.9

Outcomes

Study timepoints

- Baseline
- 6 month

Botulinum Toxin A a vs Baclofen

Outcome	Incobotulinum toxin type A (Xeomin) + physiotherapy, Baseline, N = 17	Incobotulinum toxin type A (Xeomin) + physiotherapy, 6 month, N = 17	Baclofen + physiotherapy, Baseline, N = 17	Baclofen + physiotherapy, 6 month, N = 17
Person/participant generic health-related quality of life - Romanian version of the general instrument 15D (final values) unknown scale Mean (SD)	0.57 (0.12)	0.72 (0.14)	0.57 (0.09)	0.68 (0.12)
Spasticity outcome - Tardieu scale (final values) 0-4 Mean (SD)	2.53 (0.62)	2.18 (0.81)	2.29 (0.52)	2.21 (0.64)
physical function - upper limb - muscle strength (final values) 0-5 Mean (SD)	2.35 (0.7)	3 (0)	2.41 (0.82)	2.74 (0.75)
Activities of daily living - Barthel Index (final values) 0-100 Mean (SD)	42.94 (9.36)	52.94 (11.6)	42.5 (15.82)	47.35 (17.81)

Person/participant generic health-related quality of life - Romanian version of the general instrument 15D - Polarity - Higher values are better

Spasticity outcome - Tardieu scale - Polarity - Lower values are better

physical function - upper limb - muscle strength - Polarity - Higher values are better
Activities of daily living - Barthel Index - Polarity - Higher values are better
Final values

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

BOTavsBaclofen-Person/participantgenerichealth-relatedqualityoflife-Romanianversionofthegeneralinstrument15D-MeanSD-botulinum toxin type A + physiotherapy-Baclofenum + physiotherapy-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Due to no information on missing data and issue with randomisation)*
Overall bias and Directness	Overall Directness	Directly applicable

BOTavsBaclofen-Activitiesofdailyliving-BarthelIndex-MeanSD-botulinum toxin type A + physiotherapy-Baclofenum + physiotherapy-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Due to no information on missing data and issue with randomisation)*
Overall bias and Directness	Overall Directness	Directly applicable

BOTavsBaclofen-physicalfunction-upperlimb-musclestrength-MeanSD-botulinum toxin type A + physiotherapy-Baclofenum + physiotherapy-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Due to no information on missing data and issue with randomisation)*
Overall bias and Directness	Overall Directness	Directly applicable

BOTavsBaclofen-Spasticityoutcome-Tardieuscale-MeanSD-botulinum toxin type A + physiotherapy-Baclofenum + physiotherapy-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Due to no information on missing data and issue with randomisation)*
Overall bias and Directness	Overall Directness	Directly applicable

Wallace, 2020

Bibliographic Reference	Wallace, A. C.; Talelli, P.; Crook, L.; Austin, D.; Farrell, R.; Hoad, D.; O'Keeffe, A. G.; Marsden, J. F.; Fitzpatrick, R.; Greenwood, R.; Rothwell, J. C.; Werring, D. J.; Exploratory Randomized Double-Blind Placebo-Controlled Trial of Botulinum Therapy on Grasp Release After Stroke (PrOMBiS); Neurorehabilitation & Neural Repair; 2020; vol. 34 (no. 1); 51-60

Study details

Secondary publication of another included	NR

study- see primary study for details	
Other publications associated with this study included in review	NR
Trial name / registration number	PrOMBiS The study is registered on the EU Clinical Trial Register (EudraCT: 2009-009357-22)
Study type	Randomised controlled trial (RCT)
Study location	UK
Study setting	Focal spasticity clinics at the National Hospital for Neurology and Neurosurgery
Study dates	2009-2014
Sources of funding	The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Study funding: Supported by UK Stroke Association (TSA 2008/01)
Inclusion criteria	Inclusion criteria were the following: (1) confirmed diagnosis of stroke more than 1 month previously; (2) established focal finger or wrist spasticity that the multidisciplinary team felt could be interfering with active grasp and release function and had the potential to benefit from treatment with onabotulinumtoxinA (this included an assessment on whether the potential participant presented with sufficient residual strength and motor control for rehabilitation to be effective); (3) score of 2 or more in the modified Ashworth Scale (MAS) in the joints of interest; and (4) ability to transport the assessment cup to at least 1 of the target positions and release it at baseline.
Exclusion criteria	Exclusion criteria were the following: onabotulinumtoxinA injections to any site within the previous 3 months; contraindications to onabotulinumtoxinA; fixed contracture in the upper limb; additional neurological impairment not related to stroke; uncontrolled upper-limb pain; cognitive impairment preventing informed consent or the ability to follow task instructions.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	Patients presenting to focal spasticity clinics at the National Hospital for Neurology and Neurosurgery were screened for eligibility by the multidisciplinary team, including members of the independent research team.

Intervention(s)	Injection sites were identified using standard neurophysiological technique (electromyography [EMG] and electrical stimulation) using a portable handheld device (Clavis; Medtronic, Minneapolis, MN).18 The doses and distribution of the injections were guided by the clinical and neurophysiological evaluation (including the magnitude of the audible stretch response and degree of resting muscle overactivity) per standard clinical practice. Allergan Botox, diluted as 100 units in 2 mL of saline, was injected through a fine-bore EMG needle electrode into the muscles identified by the multidisciplinary assessment as likely to be hindering function. Treatment and placebo solutions looked identical and were reconstituted out of sight of the injecting doctor, treating physiotherapist, and the participant. Physiotherapy - The original protocol consisted of daily sessions over 10 consecutive working days. For this study, it was modified to occur over 4 weeks to focus training during the peak action of the drug and reflect current clinical practice of outpatient therapy provision. The total session time ranged from 45 minutes up to 1.5 hours to accommodate each patient's need to complete the tasks, rest, and stretch without affecting the overall intensity (repetitions) of the therapy. In summary, the protocol included both strength training (3 different muscle groups) and functional task practice (3 different tasks). Strength training consisted of 3 sets of 10 repetitions of wrist extension, finger extension, and grip strength at 60% to 80% of maximal isometric voluntary contraction measured in midrange and was recalibrated every 3 training days. Functional training tasks were chosen by the participant relevant to their personal treatment goals. The intervention was tailored to the individual's impairment level, so that the intensity of intervention was standardized despite differing impairment levels at enrolment. Participants were encouraged to stretch whenever needed throughout the strength and functional training.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Not stated/unclear
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable

Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	
Comparator	Injection sites were identified in the same way as the treatment group. The doses and distribution of the injections were guided by the clinical and neurophysiological evaluation (including the magnitude of the audible stretch response and degree of resting muscle overactivity) per standard clinical practice. A saline placebo was injected through a fine-bore EMG needle electrode into the muscles identified by the multidisciplinary assessment as likely to be hindering function. Treatment and placebo solutions looked identical and were reconstituted out of sight of the injecting doctor, treating physiotherapist, and the participant. Physiotherapy - The original protocol consisted of daily sessions over 10 consecutive working days. For this study, it was modified to occur over 4 weeks to focus training during the peak action of the drug and reflect current clinical practice of outpatient therapy provision. The total session time ranged from 45 minutes up to 1.5 hours to accommodate each patient's need to complete the tasks, rest, and stretch without affecting the overall intensity (repetitions) of the therapy. In summary, the protocol included both strength training (3 different muscle groups) and functional task practice (3 different tasks). Strength training consisted of 3 sets of 10 repetitions of wrist extension, finger extension, and grip strength at 60% to 80% of maximal isometric voluntary contraction measured in midrange and was recalibrated every 3 training days. Functional training tasks were chosen by the participant relevant to their personal treatment goals. The intervention was tailored to the individual's impairment level, so that the intensity of intervention was standardized despite differing impairment levels at enrolment. Participants were encouraged to stretch whenever needed throughout the strength and functional training.
Number of participants	28
Duration of follow-up	5 weeks
Indirectness	NA

Additional comments	NR

Study arms

Onabotulinum toxin A (BOTOX) (N = 14)
Onabotulinum toxin A (BOTOX) combined with standardized physiotherapy

Placebo (N = 14)
Placebo combined with standardized physiotherapy

Characteristics

Study-level characteristics

Characteristic	**Study (N = 28)**
Ethnicity Nominal	NR
Comorbidities Nominal	NR
Severity of spasticity (MAS) Nominal	NR

Arm-level characteristics

Characteristic	Onabotulinum toxin A (BOTOX) (N = 14)	Placebo (N = 14)
% Female Nominal	35.71	28.57
Mean age (SD) Mean (SD)	50 (18)	48 (14)
Time period after stroke months Mean (SD)	83 (118)	50 (46)

Outcomes

Study timepoints

- Baseline
- 5 week

Onabotulinum toxin A (BOTOX) vs Placebo

Outcome	Onabotulinum toxin A (BOTOX), Baseline, N = 14	Onabotulinum toxin A (BOTOX), 5 week, N = 14	Placebo, Baseline, N = 14	Placebo, 5 week, N = 14
Person/participant generic health-related quality of life - EQ5D (change score) 0-100 Mean (SD)	0.62 (0.14)	-0.01 (0.11)	0.64 (0.17)	0.043 (0.11)

Outcome	Onabotulinum toxin A (BOTOX), Baseline, N = 14	Onabotulinum toxin A (BOTOX), 5 week, N = 14	Placebo, Baseline, N = 14	Placebo, 5 week, N = 14
physical function - upper limb ARAT (final values) 0-57 Mean (SD)	24.14 (0.8)	29.23 (9.76)	23.43 (9.97)	25.57 (10.38)
Discontinuation due to adverse events No of events	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0

Person/participant generic health-related quality of life - EQ5D - Polarity - Higher values are better
physical function - upper limb ARAT - Polarity - Higher values are better
Discontinuation due to adverse events - Polarity - Lower values are better
Final values

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

BotoxAvsPLacebo-DiscontinuationduetoadverseeventsNoOfEvents- OnabotulinumtoxinA combined with standardized physiotherapy-Placebo combined with standardized physiotherapy-t5

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

BotoxAvsPLacebo-physicalfunction-upperlimbARAT-MeanSD- OnabotulinumtoxinA combined with standardized physiotherapy-Placebo combined with standardized physiotherapy-t5

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

BotoxAvsPLacebo-Person/participantgenerichealth-relatedqualityoflife-EQ5D-MeanSD- OnabotulinumtoxinA combined with standardized physiotherapy-Placebo combined with standardized physiotherapy-t5

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Wang, 2019

Bibliographic Reference	Wang, H. Q.; Hou, M.; Bao, C. L.; Min, L.; Li, H.; Effects of Acupuncture Treatment on Lower Limb Spasticity in Patients Following Hemorrhagic Stroke: A Pilot Study; European Neurology; 2019; vol. 81 (no. 12); 5-12

Study details

Secondary publication of another included study- see primary study for details	NR

Other publications associated with this study included in review	pilot study but main study not included in this review
Trial name / registration number	ChiCTR-TRC-08000225
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Department of Rehabilitation at Yueyang hospital
Study dates	NR
Sources of funding	Supported by the scientific research fund of Traditional Chinese Medicine of Shanghai Municipal Health and Family Planning Commission (no. 2018LP016)
Inclusion criteria	Inclusion criteria were: Hemorrhagic stroke confirmed by CT scan, time since stroke more than 30 days and less than 90 days, unilateral lower limb extensor spasticity, Brunnstrom stages III-V, conscious and stable vital signs.
Exclusion criteria	Exclusion criteria were: patients after surgery severe primary cardiovascular, liver, kidney or hematopoietic diseases, systemic bone, or joint disorders, taking anti-spastic drugs, pregnancy, and cognitive impairment or communicative disorders influencing assessment.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	participants were recruited from the acupuncture department and rehabilitation department of Yueyang hospital.
Intervention(s)	In addition to conventional therapy the treatment group received acupuncture treatment. the main points for this study are Baihui and Tauyang. Baihui and the 2 intermediate points were punctured in the direction of Tauyang. Tauyang itself was punctured backwards and downwards. The following limb points were selcted; Yinmen, Fuxi, Xiyangguan, Yanglingquan, Zusanli, Tiaokou, Taichong. Needles of 0.25mm diametere and to-70mm long were used in this study. Each needle was first punctured, perpendicularly until it passed the galea aponeurotica or skin, and then it went forward 30 mm obliquely or perpendicularly as appropriate.

	the needle was twisted swiftly at <200 rev/min for 5 min. This manipulation was repeated 3 times with 2 intervals of 5 min. After the manipulation, a sensation of soreness, numbness and distension defined as de qi was obtained by the the patient. Patients received 6 consecutive sessions of acupuncture treatments for 4 weeks. The acupuncture treatment was administer by 2 acupuncturists with a doctors degree in acupuncture and mire than 5 years experience. Both the treatment and control groups received standard routine internal medicine care, including blood pressure control and treatment of complications. In additional patients were required to complete the following exercises: passive joint movements, anti-spasm limb positioning, trunk muscle distraction, sit-to-stand transfer, sitting and sanding balance, and gait training. these exercises tool place once a day for 4 minutes, 6 consecutive days per week for 4 weeks. All physicians and therapists were blinded to the allocation.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Moderate (or MAS 2)
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	Acupuncture
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb
Population subgroups	NR

Comparator	Both the treatment and control groups received standard routine internal medicine care, including blood pressure control and treatment of complications. In additional patients were required to complete the following exercises: passive joint movements, anti-spasm limb positioning, trunk muscle distraction, sit-to-stand transfer, sitting and sanding balance, and gait training. these exercises tool place once a day for 4 minutes, 6 consecutive days per week for 4 weeks. All physicians and therapists were blinded to the allocation.
Number of participants	59
Duration of follow-up	4 weeks
Indirectness	NA
Additional comments	NR

Study arms

acupuncture treatment combined with conventional treatment (N = 30)

Conventional treatment only (N = 29)

Characteristics

Study-level characteristics

Characteristic	**Study (N = 59)**
Ethnicity Nominal	NR

Characteristic	Study (N = 59)
Comorbidities Nominal	NR
Type of spasticity Nominal	NR

1

2 ***Arm-level characteristics***

Characteristic	acupuncture treatment combined with conventional treatment (N = 30)	Conventional treatment only (N = 29)
% Female Nominal	36.7	44.8
Mean age (SD) Mean (SD)	56.7 (7.02)	59 (7.51)
Severity of spasticity Nominal	NR	NR
Severity of spasticity Mean (SD)	2.25 (0.82)	2.28 (0.77)
Time period after stroke (days) Mean (SD)	59.53 (17.49)	55.72 (15.78)

Outcomes

Study timepoints

- Baseline
- 28 day

Acupuncture vs conventional therapy

Outcome	acupuncture treatment combined with conventional treatment, Baseline, N = 30	acupuncture treatment combined with conventional treatment, 28 day, N = 30	Conventional treatment only, Baseline, N = 29	Conventional treatment only, 28 day, N = 29
Spasticity outcome - modified Ashworth scale (0-4) change score Mean (SD)	2.25 (0.82)	1.55 (0.65)	2.28 (0.77)	1.92 (0.74)
Physical function - lower limb- FMA lower limb (final values) 0-34 Mean (SD)	14.33 (6.7)	25.33 (6.94)	16.34 (6.24)	19.57 (8.18)
Activities of daily - Barthel indexliving (final values) 0-100 Mean (SD)	46.83 (20.99)	70.67 (23)	44.66 (20.35)	66.55 (25.74)

Outcome	acupuncture treatment combined with conventional treatment, Baseline, N = 30	acupuncture treatment combined with conventional treatment, 28 day, N = 30	Conventional treatment only, Baseline, N = 29	Conventional treatment only, 28 day, N = 29
Discontinuation due to adverse events No of events	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0

Spasticity outcome - modified Ashworth scale - Polarity - Lower values are better
Physical function - lower limb- FMA lower limb - Polarity - Higher values are better
Activities of daily - Barthel indexliving - Polarity - Higher values are better
Discontinuation due to adverse events - Polarity - Lower values are better
Final values

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

NMESvsconventionaltherapy-Discontinuationduetoadverseevents-NoOfEvents-acupuncture treatment combined with conventional treatment-Conventional treatment only-t28

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

NMESvsconventionaltherapy-Physicalfunction-lowerlimb-FMAlowerlimb-MeanSD-acupuncture treatment combined with conventional treatment-Conventional treatment only-t28

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

NMESvsconventionaltherapy-Spasticityoutcome-modifiedAshworthscale-MeanSD-acupuncture treatment combined with conventional treatment-Conventional treatment only-t28

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

NMESvsconventionaltherapy-Activitiesofdaily-Barthelindexliving-MeanSD-acupuncture treatment combined with conventional treatment-Conventional treatment only-t28

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Wang, 2016

Bibliographic Reference	Wang, Y. H.; Meng, F.; Zhang, Y.; Xu, M. Y.; Yue, S. W.; Full-movement neuromuscular electrical stimulation improves plantar flexor spasticity and ankle active dorsiflexion in stroke patients: a randomized controlled study; Clinical Rehabilitation; 2016; vol. 30 (no. 6); 577-86

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Rehabilitation hospital
Study dates	NR
Sources of funding	This study was supported by the Rehabilitation Center of Qilu hospital of Shandong University. This work was founded by the National Natural Science Foundation of China [grant No. 81000855 and No. 81272155] and the Natural Science Foundation of Shandong [grant No. ZR2010HQ021].
Inclusion criteria	Patients were enrolled in the study if they met all of the following criteria: (1) stroke patients with first hemorrhagic or ischemic stroke in the cerebral hemisphere (not in the brain stem or cerebellum, which was confirmed by computed

	tomography scan); (2) 30– 70years old; (3) stable vital signs, clear consciousness, and no functional cognitive disturbances. All participants were assessed by the Mini-Mental State Examination before being enrolled in the study;19 (4) “sub-acute” stroke: time from stroke onset within the first two weeks to six weeks post-stroke; (5) normal cardio-respiratory function and normal lower extremity skin; (6) Brunnstrom stage ⩾ III (increased muscle tone with active movements mainly in rigid extension synergy) in the affected lower extremity with plantar flexor spasticity; (7) not taking any medications to relieve spasticity.
Exclusion criteria	Patients with complications that could influence spasticity severity and patients with systemic diseases that could cause peripheral neuropathy were excluded.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	After the initial screening evaluation, patients were enrolled in the study if they met all of the inclusion criteria.
Intervention(s)	Patients in the NMES groups received 30-minute sessions of neuromuscular electrical stimulation (Japan) twice a day, five days per week for four weeks. Treatment was delivered by surface electrodes (2.5×5 cm) positioned on the motor points of extensor hallucis and digitorum longus and the skin of fibular head . The stimulation parameters were as follows: pulse width=200 microseconds; on time=5seconds; off time=5seconds; frequency=20Hz; waveform=symmetrical biphasic square wave. The stimulation intensity was adjusted according to each treatment group. All intensities were comfortable for the patients and did not induce fatigue. In the sensory threshold—neuromuscular electrical stimulation group, the stimulation intensity was set to the sensory threshold, and the patients could only feel comfortable electric stimulation. There was no movements observed. In the motor threshold—neuromuscular electrical stimulation group, the stimulation intensity was set to the movement threshold. Therefore, the visible hallucis and digitorum dorsiflexion movements were observed. In the full-movement neuromuscular electrical stimulation group, the movements and range of the hallucis and digitorum dorsiflexion were as large as possible, while the patient remained subjectively comfortable. There was no movement of the strephenopodia showing up. The motor points are in the skin area located above the muscle in which an electrical pulse can evoke a muscle twitch with the least injected current. The pen electrode, which is the active electrode, was 1×1cm in size and was placed over the skin of extensor hallucis and digitorum longus, and the reference electrode was placed over the skin of the fibular head to close the stimulation current loop. The purpose of this procedure was to identify the motor points or motor line in which the same electrical pulse can evoke the largest toe dorsiflexion activities without ankle inversion activity. At the

	beginning, the stimulating frequency and intensity was very low (starting from 1–2Hz and 1mA using a biphasic wave). The pulse width was 200microseconds. The operator lightly pressed the pen-electrode on a specific skin area overlying the extensor hallucis and digitorum longus for approximately three seconds. The pen electrode was then moved across the skin to adjacent locations to compare the contractile responses. If no location reacted to the low current level, the stimulation amplitude was slowly increased (with steps of 0.5mA), and the skin scanning was repeated until a clear muscle contraction was observed or perceived by manual palpation. Thereafter, the stimulation current was decreased to a value providing a minimal twitch response only on the muscle motor points. In addition to the different interventions, all patients participated in conventional rehabilitation therapy by physical therapists as basic therapy, even during the follow-up period. Conventional rehabilitation therapy included exercise of the ankle joint (range of movement), stretch of the spastic plantar flexors, and neurodevelopment facilitation techniques.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Moderate (or MAS 2)
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb

Population subgroups	NA
Comparator	The control group only received conventional rehabilitation therapy and no neuromuscular electrical stimulation treatment.
Number of participants	72
Duration of follow-up	post intervention and 2 weeks after intervention
Indirectness	NR
Additional comments	NR

Study arms

NMES: neuromuscular electrical stimulation: sensory threshold, motor threshold and full movement threshold (N = 54)
3 types of NMES combined for the purpose of this review.

control - conventional rehabilitation (N = 18)

Characteristics

Study-level characteristics

Characteristic	**Study (N = 72)**
Ethnicity Nominal	NR

Characteristic	Study (N = 72)
Comorbidities Nominal	NR
Type of spasticity Mean (SD)	NR (NR)

1

2 ***Arm-level characteristics***

Characteristic	NMES: neuromuscular electrical stimulation: sensory threshold, motor threshold and full movement threshold (N = 54)	control - conventional rehabilitation (N = 18)
% Female Nominal	68.75	64
Mean age (SD) Mean (SD)	49.76 (9.67)	51.81 (10.41)
Severity of spasticity Composite Spasticity scale Mean (SD)	10.82 (1.72)	10.69 (1.66)
Time period after stroke days Mean (SD)	29.93 (8.83)	29.88 (9.42)

Outcomes

Study timepoints

- Baseline
- 6 week

NMES vs control

Outcome	NMES: neuromuscular electrical stimulation: sensory threshold, motor threshold and full movement threshold, Baseline, N = 54	NMES: neuromuscular electrical stimulation: sensory threshold, motor threshold and full movement threshold, 6 week, N = 50	control - conventional rehabilitation, Baseline, N = 18	control - conventional rehabilitation, 6 week, N = 16
Spasticity outcome - Composite Spasticity Scale (final values) 0-16 Mean (SD)	10.82 (1.72)	9.48 (1.43)	10.69 (1.66)	9.81 (0.98)
physical function - lower limb - timed up and go (seconds) final values Mean (SD)	22.14 (8.83)	15.07 (5.2)	22.52 (8.44)	16.04 (5.6)

Spasticity outcome - Composite Spasticity Scale - Polarity - Lower values are better
physical function - lower limb - timed up and go - Polarity - Lower values are better
Final values

discontinuation

Outcome	NMES: neuromuscular electrical stimulation: sensory threshold, motor threshold and full movement threshold, Baseline, N = 50	NMES: neuromuscular electrical stimulation: sensory threshold, motor threshold and full movement threshold, 6 week, N = 50	control - conventional rehabilitation, Baseline, N = 18	control - conventional rehabilitation, 6 week, N = 18
Discontinuation due to adverse events reasons: control group = discharge, NMES = 1 discharge, 3 lost to FU No of events	n = 0 ; % = 0	n = 4 ; % = 7.41	n = 0 ; % = 0	n = 2 ; % = 11.1

Discontinuation due to adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

NMESvscontrol-physicalfunction-lowerlimb-timedupandgo-MeanSD-NMES: neuromuscular electrical stimulation: sensory threshold, motor threshold and full movement threshold-control - conventional rehabilitation-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

NMESvscontrol-Spasticityoutcome-CompositeSpasticityScale-MeanSD-NMES: neuromuscular electrical stimulation: sensory threshold, motor threshold and full movement threshold-control - conventional rehabilitation-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

discontinuation-Discontinuationduetoadverseevents-NoOfEvents-NMES: neuromuscular electrical stimulation: sensory threshold, motor threshold and full movement threshold-control - conventional rehabilitation-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Ward, 2014

Bibliographic Reference	Ward, A. B.; Wissel, J.; Borg, J.; Ertzgaard, P.; Herrmann, C.; Kulkarni, J.; Lindgren, K.; Reuter, I.; Sakel, M.; Satero, P.; Sharma, S.; Wein, T.; Wright, N.; Fulford-Smith, A.; Group, Best Study; Functional goal achievement in post-stroke spasticity patients: the BOTOX R Economic Spasticity Trial (BEST); Journal of Rehabilitation Medicine; 2014; vol. 46 (no. 6); 504-13

Study details

Secondary publication of another included	NR

study- see primary study for details	
Other publications associated with this study included in review	Borg J, Ward AB, Wissel J, Kulkarni J, Sakel M, Ertzgaard P, et al. Rationale and design of a multicentre, double-blind, prospective, randomized, European and Canadian study: evaluating patient outcomes and costs of managing adults with post-stroke focal spasticity. J Rehabil Med 2011; 43: 15–22 protocol only
Trial name / registration number	BEST trial
Study type	Randomised controlled trial (RCT)
Study location	Multi site - Germany, Sweden, the United Kingdom, and Canada (Phase IV)
Study setting	Multi site rehabilitation centres
Study dates	October 2007 and July 2009
Sources of funding	Professor Anthony B. Ward has participated in research studies, for which unrestricted grants have been provided by Allergan. He has been the recipient of honoraria and fees for presentations at meetings and congresses and for participating in Advisory Boards. He has also received, in the past, honoraria and fees from Ipsen, Medtronic and Merz for presentations at meetings and congresses. Professor Jörg Wissel has participated in research studies, for which unrestricted grants have been provided by Allergan, Elan, Merz and Ipsen. He has been the recipient of honoraria and fees for presentations at meetings and congresses and for participating in Advisory Boards from Allergan, Eisai, Ipsen, Merz and Medtronic. Professor Jörgen Borg has been the recipient of honoraria and fees for presentations at meetings and congresses and for participating in Advisory Boards. Dr Christoph Herrmann has participated in research studies, for which unrestricted grants have been provided by Allergan. He has been the recipient of honoraria and fees from Allergan, Ipsen, Medtronic and Merz for presentations at meetings and congresses. Professor Jai Kulkarni has been the recipient of honoraria and fees from Allergan and Ipsen for presentations at meetings and congresses. Dr Kristina Lindgren has no conflicts of commercial interest in this study. Dr Mohamed Sakel has been the recipients of honoraria and fees from Allergan and Ipsen for presentations at meetings and congresses. Dr Per Ertzgaard has been the recipient of honoraria and fees from Allergan and Medtronic for presentations at meetings and congresses and for participating in Advisory Boards. Dr Iris Reuter has received honoraria and fees from Allergan, Ipsen, Merz and Medtronic for presentations at meetings and

	congresses and for participating in Advisory Boards. Dr Patrik Säterö has received honoraria and fees from Allergan for presentations at meetings and congresses. Dr Satyendra Sharma has no conflicts of commercial interest in this study. He has received honoraria and fees from Allergan and Merz for presentations at meetings and congresses, and for serving as a faculty member in an educational programme sponsored by Allergan. Dr Theodore Wein has participated in research studies for which unrestricted grants have been provided by Allergan, Sanofi, Bristol Myers Squibb, Pfizer and the National Institutes of Health. He has received honoraria for participating in congresses, Advisory Boards and accredited CME activities from Allergan, Bristol Myers Squibb, Sanofi, Pfizer and Servier. In addition, he has received consultancy fees from Allergan.
Inclusion criteria	Consecutive patients at each centre were considered for the study. Participation in the study was limited to men and women aged 18–85 years who: had experienced a stroke due to a primary cerebral haemorrhage/infarction or subarachnoid haemorrhage, leading to a hemiplegia/ hemiparesis, ≥ 3 months before the screening visit, were considered as suitable and had the potential for functional gains following treatment with OnabotulinumtoxinA for upper or lower limb spasticity
Exclusion criteria	Patients with a fixed contracture as a result of spasticity and with causes of spasticity other than stroke were excluded.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	Consecutive patients at each centre were considered for the study
Intervention(s)	During the double-blind period, patients received either a single injection of onabotulinumtoxinA or placebo, with a second dose at a minimum of 12 weeks, if the treating physician thought they would benefit from a second treatment. During the open-label phase, all patients were eligible to receive onabotulinumtoxinA injections, with a minimum inter-injection interval of 12 weeks. A maximum of 800 U of study medication was available to the investigator for any single treatment session. While minimum doses for each muscle were recommended in the study protocol, the principal investigators agreed that, in order to reflect clinical practice, individual patients' dosing was to be at each investigator's discretion based upon their clinical experience. This may not have reflected the manufacturer's label. All study participants received standard care. Each participating centre individually determined SC in terms of available resources and usual practice in that centre. Therefore SC was anticipated to differ between individual patients and centres

	across the study but for some, this may well have been a more intensive programme of care than prior to study entry, e.g., physical therapy, occupational therapy and SC focussed on their active functional goal achievement.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Moderate (or MAS 2)
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Mixed
Population subgroups	na
Comparator	During the double-blind period, patients received a single injection of placebo, with a second dose at a minimum of 12 weeks, if the treating physician thought they would benefit from a second treatment. All study participants received standard care. Each participating centre individually determined SC in terms of available resources and usual practice in that centre. Therefore SC was anticipated to differ between individual patients and centres across the study but for some, this may well have been a more intensive programme of care than prior to study entry, e.g., physical therapy, occupational therapy and SC focussed on their active functional goal achievement.

Number of participants	274
Duration of follow-up	24 and 52 weeks
Indirectness	NA
Additional comments	NR

Study arms

Onabotulinum Toxin A (BOTOX) (N = 139)
Onabotulinum Toxin A (BOTOX) + standard of care

Placebo (N = 135)
Placebo + standard of care

Characteristics

Study-level characteristics

Characteristic	**Study (N = 274)**
Comorbidities Nominal	NR
Type of spasticity Nominal	NR

Arm-level characteristics

Characteristic	Onabotulinum Toxin A (BOTOX) (N = 139)	Placebo (N = 135)
% Female Nominal	38.8	43.7
Mean age (SD) Median (IQR)	64.11 (22.6 to 81.2)	61.86 (26.8 to 82.4)
Caucasian Nominal	97.8	96.3
Other Nominal	2.2	3.7
Severity of spasticity mild Nominal	5	5.9
Moderate Nominal	74.1	74.8
Severe Nominal	20.9	18.5
Time period after stroke months Median (IQR)	24.05 (2.9 to 252.3)	21.29 (3 to 402.6)

Outcomes

Study timepoints

- Baseline
- 24 week
- 52 week

Onabotulinum toxin (BOTOX) vs Placebo

Outcome	Onabotulinum Toxin A (BOTOX), Baseline, N = 62	Onabotulinum Toxin A (BOTOX), 24 week, N = 62	Onabotulinum Toxin A (BOTOX), 52 week, N =	Placebo, Baseline, N = 62	Placebo, 24 week, N = 62	Placebo, 52 week, N =
Spastcity outcome - Resistance to passive movement (REPAS) - upper limb 0-64 (change score Mean (SD)	20.1 (8.29)	*empty data*	*empty data*	21.2 (8.4)	*empty data*	*empty data*
Spastcity outcome - Resistance to passive movement (REPAS) - upper limb 0-64 (change score Mean (95% CI)	*empty data* (*empty data* to *empty data*)	-4.3 (-5.7 to -2.8)	*empty data* (*empty data* to *empty data*)	*empty data* (*empty data* to *empty data*)	-1.7 (-2.9 to -0.4)	*empty data* (*empty data* to *empty data*)

Spastcity outcome - Resistance to passive movement (REPAS) - upper limb - Polarity - Lower values are better
OnabotulinumtoxianA vs Placebo

discontinuation

Outcome	Onabotulinum Toxin A (BOTOX), Baseline, N = 139	Onabotulinum Toxin A (BOTOX), 24 week, N = 139	Onabotulinum Toxin A (BOTOX), 52 week, N = 139	Placebo, Baseline, N = 135	Placebo, 24 week, N = 135	Placebo, 52 week, N = 135
Discontinuation Discontininued onabotulinumtoxin A + SC (n=8) Patients request/withdrew consent (n=5) Non-compliance with study visits (n=1) Administrative reasons (n=1) Lost to follow-up (n=1). Discontinued placebo + SC (n=13) Serious adverse event (n=2) Patients request/withdrew consent (n=4) Administrative reasons (n=2) Died (n=5) No of events	n = 0 ; % = 0	n = 0 ; % = 0	n = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 7 ; % = 0

Discontinuation - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

discontinuation-Discontinuation-NoOfEvents-OnabotulinumtoxinA + standard of care-Placebo + standard of care-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

discontinuation-Discontinuation-NoOfEvents-OnabotulinumtoxinA + standard of care-Placebo + standard of care-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

OnabotulinumtoxianAvsPlacebo-Spastcityoutcome-Resistancetopassivemovement(REPAS)-upperlimb-MeanNineFivePercentCI-OnabotulinumtoxinA + standard of care-Placebo + standard of care-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to bias in selection of reported results)*
Overall bias and Directness	Overall Directness	Directly applicable

OnabotulinumtoxianAvsPlacebo-Spastcityoutcome-Resistancetopassivemovement(REPAS)-upperlimb-MeanSD-OnabotulinumtoxinA + standard of care-Placebo + standard of care-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to bias in selection of reported results)*
Overall bias and Directness	Overall Directness	Directly applicable

1 Wayne, 2005

Bibliographic Reference	Wayne, P. M.; Krebs, D. E.; Macklin, E. A.; Schnyer, R.; Kaptchuk, T. J.; Parker, S. W.; Scarborough, D. M.; McGibbon, C. A.; Schaechter, J. D.; Stein, J.; Stason, W. B.; Acupuncture for upper-extremity rehabilitation in chronic stroke: a randomized sham-controlled study; Archives of Physical Medicine & Rehabilitation; 2005; vol. 86 (no. 12); 2248-55

2

3 **Study details**

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Spaulding Rehabilitation Hospital’s Stroke Service
Study dates	NR
Sources of funding	Supported by an anonymous philanthropic foundation grant to the New England School of Acupuncture
Inclusion criteria	To be eligible, patients were required to have moderate UE dysfunction from a first stroke incurred at least 6 months earlier. Moderate UE dysfunction was defined as at least some weakness or functional limitation, but not so severe as to prevent a patient from being able to raise the impaired arm from a hanging position to a table top while seated (knees 15.2 cm [6in]

	under table). Other inclusion criteria were the ability to arise independently from a chair and the ability to walk independently with or without a cane or walker.
Exclusion criteria	Exclusion criteria were: (1) previous experience with acupuncture; (2) contraindications to electroacupuncture, including wearing of pacemakers or embedded neural stimulators, cardiac arrhythmia, epilepsy, or women who were pregnant or trying to conceive32,33; (3) comorbidities that would prohibit participation in study procedures, including active renal dialysis, metastatic cancer, or extremity fracture within the past 6 months; (4) simultaneous participation in other forms of physical or occupational therapy; (5) enrolment in other studies that involved active interventions; or (6) cognitive impairment that would interfere with one's ability to give informed consent.
Stratification - Type of spasticity	Generalised spasticity
Recruitment / selection of participants	Patient recruitment was coordinated through Spaulding Rehabilitation Hospital's Stroke Service and targeted people in the greater Boston area. Recruitment included use of hospital databases; letters to local hospital neurologists, nursing homes, and stroke support group leaders; and newspaper advertising.
Intervention(s)	Treatments were administered twice weekly for 10 weeks by 2 licensed TCM-style acupuncturists who were trained in China and had an average of 20 years of clinical experience treating stroke patients in China and the United States. Active acupuncture intervention. A flexible, yet standardized and replicable, protocol was followed using the manualisation process used in other acupuncture RCTs. The protocol was based on TCM-style acupuncture and consisted of a combination of traditional acupuncture points on the body surface and a modern system of "scalp" acupuncture. Both manual and electrostimulation were applied to the body points, while manual stimulation only was applied to the scalp points. Body and scalp acupuncture protocols were alternated on a weekly basis. All patients received a TCM evaluation at each visit based on the "4 examinations": interrogation, looking, smelling and listening, and palpation. These evaluations determined the specific acupuncture points and stimulation strategies to be applied during the visit. Manual stimulation was applied on body parts until a characteristic response referred to as de qi was obtained. De qi has a sensory component perceived by the patient as a heaviness or ache in the tissue surrounding the needle, and a biomechanical component perceived by the practitioner as a needle grasp. Additionally, electric stimulation was applied to points on the affected limbs. Scalp acupuncture was directed at sensory and motor components of the affected limb. A total of 2 to 3 acupuncture scalp lines were selected per session (57 needles in total). Needling was performed on the side opposite the affected limb, and thus, on the side of the stroke. For both body and scalp treatments, needles were left in place for 20 to 30 minutes. Each session lasted approximately 60 minutes. We used stainless steel disposable, pre-sterilized needles (34 gauge; length, 3040mm) for all active treatments.

Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mild (or MAS 1)
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	NA
Comparator	Treatments were administered twice weekly for 10 weeks by 2 licensed TCM-style acupuncturists who were trained in China and had an average of 20 years of clinical experience treating stroke patients in China and the United States. For the sham acupuncture, a sham acupuncture needle was used developed by Streitberger and Kleinhenz. The device works like a magician's sword: the patient sees and feels the acupuncture needle, but as it is applied to the skin, the needle retracts and slides up the needle shaft rather than penetrating the skin. For body points, a 1 cm-diameter plastic ring, covered and held in place with paper surgical tape, supported needles in a vertical position. At each body treatment visit, 4 to 6 sham needles were placed at predetermined locations at least 1cm away from any acupuncture point. One to 2 needles were located on each affected arm and leg. In addition, 1 needle each was placed on both the healthy arm and leg. Sham electroacupuncture was administered to arm needles, using wires that were severed and re-taped so as to leave a

	gap, and thus not conduct electricity. We also used sham needles for the sham scalp acupuncture. Two sham needles were located 2cm from active scalp lines. To further reduce the chance that patients in the sham group would correctly guess their treatment group assignment, 1 real needle was administered in a visible location adjacent to Ren 6, on the abdomen without the use of a sham ring and tape. In addition, to avoid un-blinding resulting from patients in different groups comparing their experiences, rings and tape were used on 1 needle in the active group at every session. Patients were told that the tape and rings were used on some points to ensure accuracy. Finally, to minimize nonspecific differences between active and sham protocols, we developed a standard operating procedure that was in all practitioner-patient interactions.
Number of participants	33
Duration of follow-up	2 weeks and 3 months
Indirectness	NA
Additional comments	NR

Study arms

Active acupuncture (N = 16)

Sham acupuncture (N = 17)

Characteristics

Study-level characteristics

Characteristic	**Study (N = 33)**
Ethnicity	NR

Characteristic	Study (N = 33)
Nominal	
Ethnicity Mean (SD)	NR (NR)
Comorbidities Nominal	NR
Type of spasticity Nominal	NR

Arm-level characteristics

Characteristic	Active acupuncture (N = 16)	Sham acupuncture (N = 17)
% Female Nominal	25	30
Mean age (SD) Mean (SD)	NR (NR)	NR (NR)
Mean age (SD) Median (IQR)	63 (28 to 89)	54 (42 to 69)
Severity of spasticity elbow MAS - mean Mean (SD)	1.7 (NR)	2.3 (NR)

Characteristic	Active acupuncture (N = 16)	Sham acupuncture (N = 17)
Time period after stroke (Months) results are mean (range) Median (IQR)	66 (12 to 292)	41 (10 to *empty data*)

Outcomes

Study timepoints

- Baseline
- 3 month

Acupuncture vs placebo

Outcome	Active acupuncture vs Sham acupuncture, Baseline, N2 = 16, N1 = 17	Active acupuncture vs Sham acupuncture, 3 month, N2 = 11, N1 = 8
spasticity outcome - MAS - elbow mean difference Mean (95% CI)	NR (NR to NR)	-0.2 (-1.4 to 1)
Wrist unsure if these could be combined Mean (95% CI)	NR (NR to NR)	-0.57 (-1.5 to -0.4)
Physical function - upper limb - Fugl Myer assessment 0-66	NR (NR to NR)	0.05 (-4.2 to 4.1)

Outcome	Active acupuncture vs Sham acupuncture, Baseline, N2 = 16, N1 = 17	Active acupuncture vs Sham acupuncture, 3 month, N2 = 11, N1 = 8
Mean (95% CI)		
Activities of daily living - Barthel Index 0-20 Mean (95% CI)	NR (NR to NR)	0.11 (-3.4 to 3.6)
HRQOL - part I of the Nottingham Health Profile 0-100 Mean (95% CI)	NR (NR to NR)	-1.27 (-7.5 to 4.9)

spasticity outcome - MAS - elbow - Polarity - Lower values are better
Physical function - upper limb - Fugl Myer assessment - Polarity - Higher values are better
Activities of daily living - Barthel Index - Polarity - Higher values are better
HRQOL - part I of the Nottingham Health Profile - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Acupuncturevsplacebo-spasticityoutcome-MAS-elbow-MeanNineFivePercentCI-Active acupuncture-Sham acupuncture-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Acupuncturevsplacebo-spasticityoutcome-MAS-elbow-Wrist-MeanNineFivePercentCI-Active acupuncture-Sham acupuncture-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Acupuncturevsplacebo-Physicalfunction-upperlimb-FuglMyerassessment-MeanNineFivePercentCI-Active acupuncture-Sham acupuncture-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Acupuncturevsplacebo-Activitiesofdailyliving-BarthelIndex-MeanNineFivePercentCI-Active acupuncture-Sham acupuncture-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Acupuncturevsplacebo-HRQOL-partIoftheNottinghamHealthProfile-MeanNineFivePercentCI-Active acupuncture-Sham acupuncture-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to missing data and reporting of data)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Wein, 2018

Bibliographic Reference	Wein, T.; Esquenazi, A.; Jost, W. H.; Ward, A. B.; Pan, G.; Dimitrova, R.; OnabotulinumtoxinA for the Treatment of Poststroke Distal Lower Limb Spasticity: A Randomized Trial; Pm & R; 2018; vol. 10 (no. 7); 693-703

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	(NCT01575054).
Study type	Randomised controlled trial (RCT)
Study location	Sixty study centers across North America, Europe, Russia, the United Kingdom, and South Korea.
Study setting	Sixty study centers across North America, Europe, Russia, the United Kingdom, and South Korea.
Study dates	May 2012 - July 2015

Sources of funding	Funding source: Allergan plc (Dublin, Ireland)
Inclusion criteria	Adults (18-85 years) with PSLLS (MAS score ≥3) with equinus or equinovarus foot deformity, and most recent stroke occurring ≥3 months before screening were enrolled. Patients were botulinum toxin treatment - naive or treated with botulinum toxin >20 weeks before study day 1 for other indications. Patients receiving muscle relaxants or oral medication for spasticity were on a stable dose for ≥2 months before study day 1; those receiving antiepileptic medications were on a stable dose for ≥1 months before study day 1 and were not permitted to have dose adjustments during the double-blind phase of the study.
Exclusion criteria	Patients were excluded if they had lower limb spasticity with aetiology other than stroke; spasticity that required treatment in the contralateral leg; fixed ankle contracture in the study leg (i.e., MAS=4); profound atrophy pf the muscles to be injected; or previous surgical intervention, phenol block, ethanol block, or muscle afferent block before screening in muscles eligible for treatment or < 6 months before screening for any other upper or lower limb muscles. in addition patients were excluded if they were non ambulatory; has the study limb casted < months before study day 1 or planned to cast the limb during the double-blind phase; had an injection of the skin, soft tissue or joint in the injection area; were pregnant; or had a known allergy or sensitivity to study medication.
Stratification - Type of spasticity	Multifocal spasticity
Recruitment / selection of participants	NR
Intervention(s)	Study drugs (OnabotulinumtoxinA and placebo) were provided in sterile, vacuum-dried form without any preservative in identical packaging. Study personnel with no patient interaction prepared the study drugs and filled the syringes. The injector and patient were blinded to treatment allocation. The dose for each muscle was evenly distributed across the number of specified injection sites for that muscle, including 3 sites for each of the mandatory ankle muscles (ie medial and lateral gastrocnemius, soleus, tibialis posterior). An optional total additional dose ≤100U was injected into additional muscles (ie, flexor digitorum longus, brevis, flexor hallucis longus, rectus femoris), if clinically indicated. Muscles were injected via instrumented muscle localisation techniques (ie, electromyography, electrical - stimulation, sonography) that targeted the motor endplate region. Eligible patients who completed the 12week double blind phased entered the open-label phase, in which they could receive ≤400 U of OnabotulinumtoxinA at approximately 12-week intervals. Targets muscles for the open-label phase included all mandatory and additional muscles in the double-blind phase plus the hamstrings. To receive treatment the identified muscles required a MAS score of ≥1+. Each muscle has a maximum dose and number

Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Severe (or MAS 3)
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb
Population subgroups	NA
Comparator	identical process as with the onabotulinumtoxinA but patients instead received the placebo injection.
Number of participants	468
Duration of follow-up	6 weeks
Indirectness	NA
Additional comments	NR

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Study arms

Onabotulinum toxin A (BOTOX) treatment (N = 233)

Placebo (N = 235)

Characteristics

Study-level characteristics

Characteristic	Study (N = 468)
Ethnicity Nominal	NR
Comorbidities Nominal	NR
Type of spasticity Nominal	NR

Arm-level characteristics

Characteristic	Onabotulinum toxin A (BOTOX) treatment (N = 233)	Placebo (N = 235)
% Female Nominal	34.7	34

Characteristic	Onabotulinum toxin A (BOTOX) treatment (N = 233)	Placebo (N = 235)
Mean age (SD) Mean (SD)	56 (12.6)	57 (11.9)
Severity of spasticity Nominal	NR	NR
Mild Nominal	9.9	10.6
Moderate Nominal	68.7	63.8
Severe Nominal	21.5	25.5
Time period after stroke Mean (SD)	67.1 (74.4)	61.6 (73.9)

Outcomes

Study timepoints

- Baseline
- 6 week

Onobotulinum Toxin A (BOTOX) vs placebo

Outcome	Onabotulinum toxin A (BOTOX) treatment, Baseline, N = 233	Onabotulinum toxin A (BOTOX) treatment, 6 week, N = 223	Placebo, Baseline, N = 235	Placebo, 6 week, N = 227
Spasticity outcome- MAS average change score from baseline to weeks 4 and 6 (0-4) Mean (SD)	NR (NR)	-0.81 (0.87)	NR (NR)	0.61 (0.84)

Spasticity outcome- MAS - Polarity - Lower values are better

discontinuation

Outcome	Onabotulinum toxin A (BOTOX) treatment, Baseline, N = 233	Onabotulinum toxin A (BOTOX) treatment, 6 week, N = 233	Placebo, Baseline, N = 235	Placebo, 6 week, N = 235
Discontinuation Botox reasons = adverse events - 4, Placebo reasons = adverse event- 1 No of events	n = 0 ; % = 0	n = 4 ; % = 1.72	n = 0 ; % = 0	n = 1 ; % = 0.43

Discontinuation - Polarity - Lower values are better

adverse events

Outcome	Onabotulinum toxin A (BOTOX) treatment, Baseline, N = 233	Onabotulinum toxin A (BOTOX) treatment, 6 week, N = 231	Placebo, Baseline, N = 235	Placebo, 6 week, N = 226
Adverse events all treatment emergent adverse events No of events	n = 0 ; % = 0	n = 154 ; % = 66.7	n = 0 ; % = 0	n = 118 ; % = 52.2

Outcome	Onabotulinum toxin A (BOTOX) treatment, Baseline, N = 233	Onabotulinum toxin A (BOTOX) treatment, 6 week, N = 231	Placebo, Baseline, N = 235	Placebo, 6 week, N = 226
Treatment related adverse events No of events	n = 0 ; % = 0	n = 23 ; % = 10	n = 0 ; % = 0	n = 16 ; % = 7.1

Adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

BotoxAvsplacebo-Spasticityoutcome-MAS-MeanSD-Onabotulinumtoxin A treatment-Placebo-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Due to bias in reporting results)*
Overall bias and Directness	Overall Directness	Directly applicable

discontinuation-Discontinuation-NoOfEvents-Onabotulinumtoxin A treatment-Placebo-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

adverseevents-Adverseevents-NoOfEvents-Onabotulinumtoxin A treatment-Placebo-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

adverseevents-Adverseevents-Treatmentrelatedadverseevents-NoOfEvents-Onabotulinumtoxin A treatment-Placebo-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Wolf, 2012

Bibliographic Reference	Wolf, S. L.; Milton, S. B.; Reiss, A.; Easley, K. A.; Shenvi, N. V.; Clark, P. C.; Further assessment to determine the additive effect of botulinum toxin type A on an upper extremity exercise program to enhance function among individuals with chronic stroke but extensor capability; Archives of Physical Medicine & Rehabilitation; 2012; vol. 93 (no. 4); 578-87

Study details

Secondary publication of another included study- see primary study for details	NR

Other publications associated with this study included in review	NR
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Department of Rehabilitation Medicine, Emory University School of Medicine, Atlanta
Study dates	NR
Sources of funding	Supported by Allergan, Inc (grant no. IIT-000121)
Inclusion criteria	Inclusion criteria included (1) a documented history of a haemorrhagic or ischemic stroke within the past 3 to 24 months resulting in unilateral, upper extremity focal spasticity in the wrist or finger musculature but with the ability to initiate wrist extension of at least 10° from a fully flexed position with the forearm supported in a pronated position; (2) active shoulder flexion and abduction to 45° and no less than –30° of elbow extension; (3) the ability to repeat these movements 3 times within 1 minute; (4) electromyographic evidence of volitional activation of wrist and finger extensor and flexor muscles; (5) a Mini-Mental State Exam of 24 or greater; (6) the ability to follow study instructions and complete all required visits; and (7) not receiving concurrent occupational or physical therapy treatment to the impaired upper extremity.
Exclusion criteria	Additionally, individuals were ineligible to participate if they (1) had received BTX-A or any other botulinum toxin serotype within the last year, or phenol or alcohol block in the study limb within the previous 6 months; (2) had limb casting; (3) had fixed joint contractures; (4) had an allergy or sensitivity to the study medication; (5) had infection or dermatologic conditions at anticipated injection sites; (6) were participating in another clinical study; (7) had become pregnant or were women planning to conceive; or (8) anticipated use of other spasticity-reducing therapies.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	Ten women and 15 men, aged 23 to 76 years, who underwent evaluation at a university research clinic constituted a nonrandom sample.

Intervention(s)	Both BTX-A and saline were provided by Allergan in 100-U vials which, along with identical vials of saline, were stored in a secured refrigerator at a temperature of 35° to 45°F. The BTX-A was diluted with 1 mL of normal saline per 100U of the drug. Each vial was secured and controlled by the study nurse not involved in participant evaluations. Unlabelled 1-mL syringes were filled with BTX-A or pure saline solutions. One physician (S.B.M.) blinded to treatment assignment administered up to 300U of fluid within wrist and finger muscles. The amount injected was documented and determined from the physician's impression regarding tone within a given muscle. Exercise Intervention Procedure - The 2 therapists, also blinded to treatment assignment, administered the therapeutic exercise program after undergoing standardization for exercise delivery to ensure consistency. Three sessions were scheduled per week beginning approximately 1 month after injections and continued until 12 to 16 treatment sessions were completed. Briefly, each session was divided into 3 components. First, activities addressed stability and mobility at the shoulder, progressing to general movement at the wrist and digits. The second portion addressed strengthening and repetition of movement (pre-functional phase), while the last segment emphasized functional activities relevant to the participant. All activities were documented to ensure correct distribution of training segments.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Not stated/unclear
Subgroup 2: Time period after stroke when trial starts	Mixed
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal	Upper limb (including shoulder girdle)

spasticity only, area affected	
Population subgroups	NA
Comparator	Saline in identical was provided by Allergan in 100-U vials which, were stored in a secured refrigerator at a temperature of 35° to 45°F. Each vial was secured and controlled by the study nurse not involved in participant evaluations. Unlabelled 1-mL syringes were filled pure saline solutions. One physician (S.B.M.) blinded to treatment assignment administered up to 300U of fluid within wrist and finger muscles. The amount injected was documented and determined from the physician's impression regarding tone within a given muscle. Both groups received the exercises intervention detailed above.
Number of participants	25
Duration of follow-up	15 weeks
Indirectness	NA
Additional comments	The primary analysis was performed using an intention-to-treat approach

Study arms

Onabotulinum toxin type A (BOTOX) (N = 12)
Onabotulinum toxin type A (BOTOX) and a standardized exercise protocol

Placebo (N = 13)
Placebo and the same exercise program

Characteristics

Study-level characteristics

Characteristic	Study (N = 25)
Comorbidities Nominal	NR
Severity of spasticity Nominal	NR
Time period after stroke Nominal	NR
Type of spasticity % focal Nominal	100

Arm-level characteristics

Characteristic	Onabotulinum toxin type A (BOTOX) (N = 12)	Placebo (N = 13)
% Female Nominal	41.7	38.5
Mean age (SD) Mean (SD)	48.8 (15.6)	49.8 (13.7)

Characteristic	Onabotulinum toxin type A (BOTOX) (N = 12)	Placebo (N = 13)
Ethnicity Nominal	NR	NR
White (not Hispanic) Nominal	0	15.4
Black (not Hispanic) Nominal	91.7	84.6
Asian or Pacific Islander Nominal	8.3	0

Outcomes

Study timepoints

- Baseline
- 15 week

Botox-A vs placebo

Outcome	Onabotulinum toxin type A (BOTOX), Baseline, N = 12	Onabotulinum toxin type A (BOTOX), 15 week, N = 12	Placebo, Baseline, N = 13	Placebo, 15 week, N = 13
Discontinuation Botox = Lost to follow-up (n=1) Discontinued intervention (n=1) No of events	n = 0 ; % = 0	n = 2 ; % = 16.67	n = 0 ; % = 0	n = 0 ; % = 0

Discontinuation - Polarity - Lower values are better

Final values

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Botox-Avsplacebo-Discontinuation-NoOfEvents-Botulinum toxin type A (BTX-A) and a standardized exercise protocol-Placebo and the same exercise program-t15

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Yan, 2009

Bibliographic Reference	Yan, T.; Hui-Chan, C. W.; Transcutaneous electrical stimulation on acupuncture points improves muscle function in subjects after acute stroke: a randomized controlled trial; Journal of Rehabilitation Medicine; 2009; vol. 41 (no. 5); 312-6

1 **Study details**

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Department of Rehabilitation Medicine, China
Study dates	NR
Sources of funding	This study was supported by a grant from The Hong Kong Polytechnic University to C. W. Y Hui-Chan and a scholarship to T. Yan.
Inclusion criteria	Patients were diagnosed by computed tomography as having had a unilateral stroke in the carotid artery system. Stratifications included age (45–59, 60–75 and 76–85 years), gender, type of stroke, side of hemiplegia, and muscle strength of affected hip flexors (grade of < 2 or of 2–3 according to the manual muscle strength test). Patients were independent in daily activities before stroke. Those with a second stroke were recruited if they were able to walk independently and to look after themselves after the first stroke, with paralysis of the same extremity as the first one.
Exclusion criteria	Exclusion criteria were brainstem or cerebellar lesions, medical co-morbidity, receptive dysphasia, or cognitive impairment.
Stratification - Type of spasticity	Focal spasticity

Recruitment / selection of participants	Sixty-two patients, age range 45–85 years, 9.2 (standard deviation (SD) 3.4) days post-stroke, were recruited.
Intervention(s)	In the TES group, model 120Z® TES stimulator (ITO Co Ltd, Tokyo, Japan) was applied with 0.2 ms pulses, at 100 Hz in the constant mode within the subject's tolerance level, via (5 × 3.5 cm) electrodes attached to the following acupuncture points on the affected lower extremity: St 36, Lv 3, GB 34, and Bl 60 (Fig. 2). PS was applied using the same electrodes, locations and device, with the circuit disconnected. To ensure similar mental set, subjects were told that they might or might not feel the simulation. Treatment for TENS lasted 60 min per session, 5 days a week for 3 weeks. All subjects received the same SR including both physiotherapy and occupational therapy, each lasting for 60 min. Neither therapist knew to which group a subject being treated had been assigned.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mild (or MAS 1)
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb

Population subgroups	NA
Comparator	Placebo stimulation was applied using the same electrodes, locations and device, with the circuit disconnected. To ensure similar mental set, subjects were told that they might or might not feel the simulation. Treatment for both TES and PS lasted 60 min per session, 5 days a week for 3 weeks. Subjects in the control group received only standard rehabilitation including both physiotherapy and occupational therapy, each lasting for 60 min. All subjects received the same SR including both physiotherapy and occupational therapy, each lasting for 60 min. Neither therapist knew to which group a subject being treated had been assigned.
Number of participants	56
Duration of follow-up	8 weeks
Indirectness	NA
Additional comments	NR

Study arms

Transcutaneous electrical nerve stimulation (TENS) (N = 21)

Placebo stimulation (N = 21)

Standard Rehabilitation (N = 20)

Characteristics

Study-level characteristics

Characteristic	Study (N = 56)
Ethnicity Nominal	NR
Comorbidities Range	NR to *empty data*
Type of spasticity Nominal	NR

Arm-level characteristics

Characteristic	Transcutaneous electrical nerve stimulation (TENS) (N = 21)	Placebo stimulation (N = 21)	Standard Rehabilitation (N = 20)
% Female Nominal	52.6	47.4	50
Mean age (SD)	68.4 (9.6)	72.8 (7.4)	70.4 (7.6)

Characteristic	Transcutaneous electrical nerve stimulation (TENS) (N = 21)	Placebo stimulation (N = 21)	Standard Rehabilitation (N = 20)
Mean (SD)			
Severity of spasticity CSS Median (IQR)	4.5 (5.8 to NR)	4 (5 to NR)	4 (5 to NR)
Time period after stroke days Mean (SD)	9.2 (4.4)	9.9 (2.6)	8.7 (3.3)

Outcomes

Study timepoints

- Baseline
- 8 week

TENS vs Placebo vs Usual care

Outcome	Transcutaneous electrical nerve stimulation (TENS) , Baseline, N = 21	Transcutaneous electrical nerve stimulation (TENS) , 8 week, N = 19	Placebo stimulation, Baseline, N = 21	Placebo stimulation, 8 week, N = 19	Standard Rehabilitation, Baseline, N = 20	Standard Rehabilitation, 8 week, N = 18
Spastcity outcome - Composite	4.5 (5.8)	7.5 (6.2)	4 (5)	10 (11)	4 (6)	11 (8)

Outcome	Transcutaneous electrical nerve stimulation (TENS) , Baseline, N = 21	Transcutaneous electrical nerve stimulation (TENS) , 8 week, N = 19	Placebo stimulation, Baseline, N = 21	Placebo stimulation, 8 week, N = 19	Standard Rehabilitation, Baseline, N = 20	Standard Rehabilitation, 8 week, N = 18
spastcity scale (final values) only reports median interquartile (1-3) Custom value						
physical function - lower limb - timed up and go (seconds) final values Mean (SD)	67.5 (13.7)	15.2 (8.4)	55.5 (14.8)	34.5 (28.5)	46.4 (19.6)	36.3 (25.3)

Spastcity outcome - Composite spastcity scale - Polarity - Lower values are better
physical function - lower limb - timed up and go - Polarity - Lower values are better
Final values

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

TENSvsPlacebovsUsualcare-physicalfunction-lowerlimb-timedupandgo-MeanSD-Transcutaneous electrical nerve stimulation (TENS) - Placebo stimulation-Standard Rehabilitation-t8

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

TENSvsPlacebovsUsualcare-Spastcityoutcome-Compositespastcityscale-CustomValue0-Transcutaneous electrical nerve stimulation (TENS) -Placebo stimulation-Standard Rehabilitation-t8

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(study reports median and interquartile for this outcome only)*
Overall bias and Directness	Overall Directness	Directly applicable

Yan, 2005

Bibliographic Reference	Yan, T.; Hui-Chan, C. W.; Li, L. S.; Functional electrical stimulation improves motor recovery of the lower extremity and walking ability of subjects with first acute stroke: a randomized placebo-controlled trial; Stroke; 2005; vol. 36 (no. 1); 80-5

Study details

Secondary publication of	NR

another included study- see primary study for details	
Other publications associated with this study included in review	Nr
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Department of Rehabilitation Sciences China
Study dates	NR
Sources of funding	This study was supported by an Area of Strategic Development grant from the Hong Kong Polytechnic University to C. W. Y. Hui-Chan and a scholarship to T. Yan.
Inclusion criteria	Subjects were included if they had a unilateral stroke within the carotid artery system according to computerized tomography, aged 45 to 85 years old, and were independent in daily activities before stroke
Exclusion criteria	Exclusion criteria were brain stem or cerebella lesions, medical comorbidity, receptive dysphasia, or cognitive impairment denoted by scoring <7 of 10 on the Abbreviated Mental Test.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	Forty-six subjects with first acute stroke were recruited.
Intervention(s)	FES - Two dual-channel stimulators (Respond Select; Empi Inc) were connected with a program timer to form one stimulating unit for FES. Surface electrodes were applied on quadriceps, hamstring, tibialis anterior (TA), and medial gastrocnemius (MG) with subject side-lying and the affected lower extremity supported by sling. FES was delivered with 0.3-ms pulses at 30 Hz, maximum tolerance intensity (20 to 30 mA),3,4 using an activation sequence that mimicked normal

	gait. Subjects were treated within 3 days after being transferred from the acute hospital, 30 minutes per day, 5 days per week for 3 weeks. All subjects received the same SR including 60 minutes each of physiotherapy based on the neurodevelopmental facilitation approach and of occupational therapy focused on activities of daily living, given once per day, 5 days per week for 3 weeks.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mild (or MAS 1) measured by CSS
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	Not stated/unclear
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb
Population subgroups	NR
Comparator	The placebo group received stimulation from an electrical stimulation device with disconnected circuit. Treatment frequency and period were identical to those of the FES group, except for the longer duration (60 minutes) thought to optimize placebo

	effects.15,16 To promote similar mental set, subjects were told before treatment that they might or might not feel the stimulation. The control group received only SR. All subjects received the same SR including 60 minutes each of physiotherapy based on the neurodevelopmental facilitation approach and of occupational therapy focused on activities of daily living, given once per day, 5 days per week for 3 weeks.
Number of participants	46
Duration of follow-up	8 weeks
Indirectness	NA
Additional comments	Nr

Study arms

Functional electrical stimulation (FES) (N = 13)

Placebo (N = 15)

standard rehabilitation (N = 13)

Characteristics

Study-level characteristics

Characteristic	Study (N = 46)
Ethnicity Nominal	NR
Comorbidities Nominal	NR
Type of spasticity Nominal	NR

Arm-level characteristics

Characteristic	Functional electrical stimulation (FES) (N = 13)	Placebo (N = 15)	standard rehabilitation (N = 13)
% Female Nominal	46.2	53.3	53.8
Mean age (SD) Mean (SD)	68.2 (7.7)	73.3 (8.1)	70.4 (7.6)
Severity of spasticity (0-16) CSS	7.3 (3.1)	5.9 (2.7)	6.1 (2.6)

Characteristic	Functional electrical stimulation (FES) (N = 13)	Placebo (N = 15)	standard rehabilitation (N = 13)
Mean (SD)			

Outcomes

Study timepoints

- Baseline
- 8 week

FES vs placebo vs standard rehabilitation

Outcome	Functional electrical stimulation (FES), Baseline, N = 15	Functional electrical stimulation (FES), 8 week, N = 13	Placebo, Baseline, N = 16	Placebo, 8 week, N = 15	standard rehabilitation, Baseline, N = 15	standard rehabilitation, 8 week, N = 13
Spastcity outcome - Composite spasticity scale (CSS) (change) % increase (scale 0-16) Mean (SD)	7.3 (3.1)	41.8 (93.5)	5.9 (2.7)	56 (91.2)	6.1 (2.9)	78.6 (64.7)
Functional outcome - lower limb - timed up and go (seconds) change score Mean (SD)	66 (29.5)	28.4 (21)	49.7 (22.9)	31.7 (27.9)	56.6 (33.7)	39.7 (30.1)

Spastcity outcome - Composite spasticity scale (CSS) - Polarity - Lower values are better
Functional outcome - lower limb - timed up and go - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

FESvsplacebovsstandardrehabilitation-Spastcityoutcome-Compositespasticityscale(CSS)-MeanSD-Function electrical stimulation (FES)-Placebo-standard rehabilitation-t8

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

FESvsplacebovsstandardrehabilitation-Functionaloutcome-lowerlimb-timedupandgo-MeanSD-Function electrical stimulation (FES)-Placebo-standard rehabilitation-t8

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Yang, 2018

Bibliographic Reference	Yang, Y. R.; Mi, P. L.; Huang, S. F.; Chiu, S. L.; Liu, Y. C.; Wang, R. Y.; Effects of neuromuscular electrical stimulation on gait performance in chronic stroke with inadequate ankle control - A randomized controlled trial; PLoS ONE [Electronic Resource]; 2018; vol. 13 (no. 12); e0208609

1 **Study details**

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	his trial was registered in http://www.anzctr.org.au/ (ACTRN12617000 786392) on May 29th, 2017
Study type	Randomised controlled trial (RCT)
Study location	Taiwan
Study setting	Taipei Veterans General Hospital, Taipei Taiwan
Study dates	August 2013 to June 2014
Sources of funding	This work was supported by grants from the National Science Council (NSC 100-2314-B010-022-MY2) to RYW
Inclusion criteria	To be included in the study, participants with stroke had to satisfy the following criteria: (1) diagnosis of first-ever stroke with unilateral motor deficits at least 6 months, (2) with inadequate ankle control during gait (defined as maximum position of ankle dorsiflexion less than -5˚ at heel strike and plantarflexion less than 10˚ at push off, 0˚ was set as neutral position), (3) with passive range of motion (PROM) of ankle dorsiflexion at least to neutral position (defined as 0˚), (4) ability to walk at least 10 m with or without assistive devices, and (5) a detectable surface EMG signal (>5 μV) from the tibialis anterior (TA) and medial gastrocnemius (MG) muscles of the affected leg.
Exclusion criteria	The exclusion criteria included (1) surface sensory loss of affected lower leg, (2) insufficient cognition to communicate (Mini-Mental State Examination < 24), (3) contraindications to NMES, such as a pacemaker or tumour, and (4) a history of orthopaedic or other neurologic disorders affecting walking function (5) a history of surgery to correct drop foot
Stratification - Type of spasticity	Focal spasticity

Intervention(s)	Participants in the NMES groups received 20 minutes of NMES on either TA (NMES-TA) or MG (NMES-MG) and then 15 minutes of ambulation training. An EMG-triggered NMES (Myomed 932, Enraf Nonius, Netherlands) with two surface electrodes was used for ES in this study. Participants were in sitting position with feet off the ground during NMES sessions. For the NMES-TA group, the cathode electrode was placed on the motor points of TA, and the anode electrode was located at the mid-muscle belly on one third of the line between fibular head and medial malleolus. For the NMES-MG group, both electrodes were placed on the muscle belly of MG. The cathode electrode was located at about 2 cm medial to the midline of shank and 5 finger-widths distal to the popliteal fossa, and the anode electrode was placed on 2 cm distal to the cathode electrode. The reference electrode was placed on the distal part of the targeted muscles. The frequency of NMES was set at 50 Hz with a 0.2 ms pulse width. Biphasic square wave was chosen to provide a specific waveform, and the stimulation duty cycle was 5:15 (on:off) in seconds for 20 minutes. The intensity of stimulation was set from 50 mV to 0 mV to induce full range of motion of ankle dorsiflexion or plantarflexion without causing any discomfort [11]. EMG signals of the targeted muscles were recorded and displayed on the screen of NMES machine with auditory feedbacks. EMG signals of maximal voluntary contraction of ankle dorsiflexion (NMES-TA group) or plantarflexion (NMES-MG group) subtracting 2 uV was used as the initial training goal in every session. When receiving NMES, participants were asked to actively dorsiflex (NMES-TA group) or plantarflex (NMES-MG group) the ankle joint to reach the initial training goal that activated the ES. After completing five successful cycles of active ankle dorsiflexion or plantarflexion, the training goal was increased by 2 uV progressively. The NMES training lasted for 20 minutes, followed by ambulation training focusing on ankle control for another 15 minutes. Verbal cues were provided to enhance ankle movement during walking. For instance, participants were instructed to “elevate your foot more (dorsiflexion)”, “please do more foot eversion”, and “heel contacts floor first instead of forefoot”. Both groups received the 15 minutes of ambulation training focused on ankle movement and ankle control with verbal cues. All training sessions occurred 3 times per week for 7 weeks which were conducted by the same physical therapist.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Moderate (or MAS 2)

Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb
Population subgroups	NA
Comparator	Participants in the control group received 20 minutes of range of motion and stretching exercises, followed by 15 minutes of ambulation training (ambulation training focused on ankle movement and ankle control with verbal cues). All training sessions occurred 3 times per week for 7 weeks which were conducted by the same physical therapist. Exercise of the affected lower extremity for 20 minutes, including stretching for 5 minutes, PROM exercise for 5 minutes, and AROM exercise for 10 minutes. The 15 minutes of ambulation training, was the same as described in the NMES groups.
Number of participants	25
Duration of follow-up	7 weeks
Indirectness	NA
Additional comments	NR

1

Study arms

Neuromuscular electrical stimulation (NMES) (N = 17)

Usual care (N = 8)
Control group - exercises

Characteristics

Study-level characteristics

Characteristic	Study (N = 25)
Ethnicity Nominal	NR
Comorbidities Nominal	NR
Type of spasticity Nominal	NR

Arm-level characteristics

Characteristic	Neuromuscular electrical stimulation (NMES) (N = 17)	Usual care (N = 8)
% Female Nominal	50	50

Characteristic	Neuromuscular electrical stimulation (NMES) (N = 17)	Usual care (N = 8)
Mean age (SD) Mean (SD)	53.1 (4.4)	50.8 (3.8)
Severity of spasticity Mean (SD)	2.24 (0.34)	1.9 (0.4)
Time period after stroke months Mean (SD)	44.7 (8.4)	31.8 (6.1)

Outcomes

Study timepoints

- Baseline
- 7 week

NMES vs control

Outcome	Neuromuscular electrical stimulation (NMES) , Baseline, N = 17	Neuromuscular electrical stimulation (NMES) , 7 week, N = 17	Usual care, Baseline, N = 8	Usual care, 7 week, N = 8
Spasticity outcome - modified Ashworth scale (final values) 0-5 (reported by study) Mean (SD)	2.24 (0.34)	1.61 (0.32)	1.9 (0.4)	1.5 (0.1)

Outcome	Neuromuscular electrical stimulation (NMES) , Baseline, N = 17	Neuromuscular electrical stimulation (NMES) , 7 week, N = 17	Usual care, Baseline, N = 8	Usual care, 7 week, N = 8
Withdrawl due to adverse events No of events	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0

Spasticity outcome - modified Ashworth scale - Polarity - Lower values are better
Withdrawl due to adverse events - Polarity - Lower values are better
Final values

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

NMESvscontrol-Spasticityoutcome-modifiedAshworthscale-MeanSD-Neuromuscular electrical stimulation (NMES) -Control group - exercises-t7

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

NMESvscontrol-Discontinuation-NoOfEvents-Neuromuscular electrical stimulation (NMES) -Control group - exercises-t7

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Yazdchi, 2013

Bibliographic Reference	Yazdchi, M.; Ghasemi, Z.; Moshayedi, H.; Rikhtegar, R.; Mostafayi, S.; Mikailee, H.; Najmi, S.; Comparing the efficacy of botulinum toxin with tizanidine in upper limb post stroke spasticity; Iranian Journal of Neurology; 2013; vol. 12 (no. 2); 47-50

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	Iran
Study setting	Imam Reza University Hospital and Neurology Clinic
Study dates	July 2010 to December 2012

Sources of funding	NR
Inclusion criteria	Patients older than 35 years who had experienced stroke (ischemic or haemorrhagic that documented by computed tomography or magnetic resonance imaging) with onset of at least 3 months ago, were evaluated by Modified Ashworth Scale (MAS) for their upper limb spasticity. And patients with minimum score of 2 on the MAS were included.
Exclusion criteria	Patients who suffered from severe dementia or impaired consciousness were excluded from the study. In addition, patients who received BoNT injection into affected muscles in at least 3 months before recruitment and those who were older than 70 years old were excluded.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	Since July 2010 to December 2012, 68 eligible patients with our inclusive and exclusive criteria were recruited (that are mentioned below thoroughly) and came to follow up visits to Imam Reza University Hospital and Neurology Clinic and were randomly allocated into two equal groups.
Intervention(s)	In BoNT group, patients received injections into dominant spastic muscles of the upper extremities according to the same neurologist at baseline and week 12. In this study, Dysport 500U including clostridium botulinum type A and toxin-hemagglutinin complex, IPSEN Ltd were used and each vial diluted with 2.5ml sodium chloride 0.9%. Approximately, biceps brachii (150-200U), flexor carpi radialis (50-100U), flexor carpi ulnaris (50-100U) and flexor digitorum profundus (100-150U) were the most common injected muscles, respectively in all the patients. The maximum dosage of 1000U was limitation point in each time for an upper extremity. All the patients offered to have rehabilitative treatments with the same program at the same university physical therapy center. The physiotherapy program consisted of 45-60 min of strengthening, stretching and passive range of motion exercises, electrical stimulation and endurance exercise three times a week throughout the study.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Severe (or MAS 3)

Subgroup 2: Time period after stroke when trial starts	Not stated/unclear
Subgroup 3: Acupuncture/dry needling	Not stated/unclear
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	NR
Comparator	In TZN group, patients were administrated with Sirdalude (Novartis) with initiated dosage of 2mg and gradual increase of 2 mg weekly to reach 24 mg at week 12 and continued the same dosage of 24 mg to week 24 to the end of the study. All the patients offered to have rehabilitative treatments with the same program at the same university physical therapy centre. The physiotherapy program consisted of 45-60 min of strengthening, stretching and passive range of motion exercises, electrical stimulation and endurance exercise three times a week throughout the study.
Number of participants	68
Duration of follow-up	12 and 24 weeks
Indirectness	NA
Additional comments	NA

1

Study arms

Abobotulinum toxin A (Dysport) (N = 34)

Oral tizanidine (TZD) (N = 34)

Characteristics

Study-level characteristics

Characteristic	Study (N = 68)
Ethnicity Nominal	NR
Comorbidities Nominal	NR
Time period after stroke Nominal	NR
Type of spasticity Nominal	NR

Arm-level characteristics

Characteristic	Abobotulinum toxin A (Dysport) (N = 34)	Oral tizanidine (TZD) (N = 34)
% Female Nominal	38.24	47.06
Mean age (SD) Range	35 to 70	51 to 68
Mean age (SD) Mean (SD)	67.5 (NR)	64.7 (NR)
Severity of spasticity Mean (SD)	3.22 (4.68)	2.78 (0.41)

Outcomes

Study timepoints

- Baseline
- 24 week

Botulinum toxin vs Tizanidine

Outcome	Abobotulinum toxin A (Dysport), Baseline, N = 34	Abobotulinum toxin A (Dysport), 24 week, N = 34	Oral tizanidine (TZD), Baseline, N = 34	Oral tizanidine (TZD), 24 week, N = 34
Spastcity outcome- Modified ashworth scale (combined scores) (final values) 0-4 Mean (SD)	3.22 (0.61)	1.68 (0.47)	2.78 (0.41)	2.32 (0.56)
Physical function - upper limb- ARAT (final values) 0-57 Mean (SD)	1.79 (3.38)	10.79 (4.57)	11.02 (5.45)	11.35 (5.85)
Discontinuation/adverse events (narrative outcome) No statistical analysis was done for adverse effects, even though 20 patients ended up in side effects of TZD and quitted study. Other eligible participants were replaced to prevent reduction and sample loss in sample size. Seven patients could not tolerate the dosage of 12 mg and 13 out of 20 discontinued receiving TZD when the dosage reached to 24 mg. Sedation and dizziness were the main causes of adverse effects in 17 patients. Besides, three patients could not continue receiving TZD due to abdominal pain and nausea. No adverse effect was found at BoNT group. This showed that BoNT was safe at the used dosages of this study. No of events	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 20 ; % = 20

Spastcity outcome- Modified ashworth scale (combined scores) - Polarity - Lower values are better
Physical function - upper limb- ARAT - Polarity - Higher values are better
Discontinuation/adverse events - Polarity - Lower values are better
Final values

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

botulinumtoxinvstizanidine-Physicalfunction-upperlimb-ARAT-MeanSD-Botulinum (BoNT) toxin type A-Oral tizanidine (TZD)-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(20 drop outs were reported in the TZD group however these were replaced with other eligible participants)*
Overall bias and Directness	Overall Directness	Directly applicable

botulinumtoxinvstizanidine-Discontinuation/adverseevents-NoOfEvents-Botulinum (BoNT) toxin type A-Oral tizanidine (TZD)-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(20 drop outs were reported in the TZD group however these were replaced with other eligible participants)*
Overall bias and Directness	Overall Directness	Directly applicable

botulinumtoxinvstizanidine-Spastcityoutcome-Modifiedashworthscale(combinedscores)-MeanSD-Botulinum (BoNT) toxin type A-Oral tizanidine (TZD)-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(20 drop outs were reported in the TZD group however these were replaced with other eligible participants)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

You, 2014

Bibliographic Reference	You, G.; Liang, H.; Yan, T.; Functional electrical stimulation early after stroke improves lower limb motor function and ability in activities of daily living; Neurorehabilitation; 2014; vol. 35 (no. 3); 381-9

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	Department of Rehabilitation Medicine, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China
Study setting	Stroke rehabilitation department
Study dates	NR

Sources of funding	Supported by grants from the Guangdong Provincial Department of Science and Technology
Inclusion criteria	Inclusion criteria were: the first diagnosis was the first time primary cerebral infarction or Haemorrhage that was confirmed by CT or MRI imaging; they were ages between 45 and 80 years old; time since the incident was less than 3 months; strength of muscles induced ankle dorsiflexion was less than grade 3/5 in a manual muscle test; without serious cognitive impairment as confirmed by a score of at least 7/10 on the abbreviated mental test; and willing to sign the informed consent form.
Exclusion criteria	Patients were excluded if they had one of the following conditions: progressive stroke, or subarachnoid haemorrhage. severe heat, liver or kidney disease, or infection, traumatic brain injury or tumour, a cardiac pacemaker, skin lesion at the site of the stimulation electrode.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	All Subjects were in patients with stroke in the department of rehabilitation medicine or of neurology at the hospital in China.
Intervention(s)	Functional electrical stimulation was given to patients in the FES group using a dual-channel stimulator (KR&, Ito, Japan). the surface electrodes were placed over the motor points of the tibialis anterior to provoke ankle dorsiflexion and the peroneus brevis and peroneus longus to provoke ankle eversion. Patients in both groups received necessary drugs and the standard rehabilitation programme including 60 minutes of physiotherapy based on the neurodevelopmental facilitation approach and of the occupational therapy focused on activities of daily living (5 days per week).
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Not stated/unclear

Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Lower limb
Population subgroups	
Comparator	The control group received standard rehabilitation only as below. Patients in both groups received necessary drugs and the standard rehabilitation programme including 60 minutes of physiotherapy based on the neurodevelopmental facilitation approach and of the occupational therapy focused on activities of daily living (5 days per week).
Number of participants	37
Duration of follow-up	3 weeks
Indirectness	N/A
Additional comments	NR

1

Study arms

FES + Standard rehabilitation (N = 19)

Standard rehabilitation (N = 18)

Characteristics

Study-level characteristics

Characteristic	Study (N = 37)
Ethnicity Nominal	NR
Comorbidities Nominal	NR
Severity of spasticity Nominal	NR
Type of spasticity Nominal	NR

Arm-level characteristics

Characteristic	FES + Standard rehabilitation (N = 19)	Standard rehabilitation (N = 18)
% Female Nominal	42.1	44.4
Mean age (SD) Mean (SD)	60.8 (10.8)	64.1 (9.7)
Time period after stroke days Mean (SD)	25.9 (21.3)	22.7 (16.6)

Outcomes

Study timepoints

- Baseline
- 3 week

FES + standard rehabilitation vs standard rehabilitation

Outcome	FES + Standard rehabilitation , Baseline, N = 21	FES + Standard rehabilitation , 3 week, N = 19	Standard rehabilitation , Baseline, N = 21	Standard rehabilitation , 3 week, N = 18
spastcity outcome - CSS (composite spastcity scale) (final	9.9 (2.8)	10.9 (1.8)	9.9 (2.8)	13.1 (0.6)

Outcome	FES + Standard rehabilitation , Baseline, N = 21	FES + Standard rehabilitation , 3 week, N = 19	Standard rehabilitation , Baseline, N = 21	Standard rehabilitation , 3 week, N = 18
values) 1-16 Mean (SD)				
Physical function - Fugl Meyer assessment (final values) ?scale Mean (SD)	11.3 (4.8)	22.3 (7.9)	11.4 (5.9)	17.2 (7.2)
Physical function - lower limb - Berg balance scale (final values) 0-56 Mean (SD)	15.9 (17.3)	30.8 (5.1)	18.3 (10)	28.4 (6.2)
Activities of daily living (final values) 0-100 Mean (SD)	41.4 (20.1)	78.8 (18.4)	46.4 (21.3)	70 (11.6)

spastcity outcome - CSS (composite spastcity scale) - Polarity - Lower values are better
Physical function - Fugl Meyer assessment - Polarity - Higher values are better
Physical function - lower limb - Berg balance scale - Polarity - Higher values are better
Activities of daily living - Polarity - Higher values are better
Final values

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

FES+standardrehabilitationvsstandardrehabilitation-Physicalfunction-lowerlimb-Bergbalancescale-MeanSD-FES + Standard rehabilitation -Standard rehabilitation -t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

FES+standardrehabilitationvsstandardrehabilitation-Activitiesofdailyliving-MeanSD-FES + Standard rehabilitation -Standard rehabilitation -t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

FES+standardrehabilitationvsstandardrehabilitation-Physicalfunction-FuglMeyerassessment-MeanSD-FES + Standard rehabilitation - Standard rehabilitation -t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

FES+standardrehabilitationvsstandardrehabilitation-spastcityoutcome-CSS(compositespastcityscale)-MeanSD-FES + Standard rehabilitation -Standard rehabilitation -t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Yun, 2011

Bibliographic Reference	Yun, G. J.; Chun, M. H.; Park, J. Y.; Kim, B. R.; The synergic effects of mirror therapy and neuromuscular electrical stimulation for hand function in stroke patients; Annals of Rehabilitation Medicine; 2011; vol. 35 (no. 3); 316-21

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)

Study location	Korea
Study setting	Department of Rehabilitation Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul.
Study dates	March 1, 2009 and March 30, 2010
Sources of funding	NR
Inclusion criteria	The study was conducted on 60 patients who were admitted or transferred to the Department of Rehabilitation at the medical center due to hemiparesis caused by stroke between March 1, 2009 and March 30, 2010. No further details provided.
Exclusion criteria	The studies excluded those who were expected to be uncooperative due to cognitive impairment, were medically unstable, and had neurologic deficit, or patients with neglect.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	The study was conducted on 60 patients who were admitted or transferred to the Department of Rehabilitation at the medical center due to hemiparesis caused by stroke between March 1, 2009 and March 30, 2010.
Intervention(s)	Electrical stimulation (Microstim® Model GmbH, Stanberg, Germany) was applied at 30-70 mA intensity, 250 μsec amplitude, and 35 Hz frequency. It lasted for five seconds and then stopped for five seconds. The intensity of stimulation was determined so that the subjects could feel muscle contraction while not feeling tired. It was applied to the common extensor digitorum muscle and extensor polliics brevis of the paretic arm with an aim at hand extension movements. For the mirror and NMES therapy group and NMES only group, patients extended their paretic wrists and hands and at the same time extended non-paretic wrists and hands to electrical stimuli. They also actively conducted nonparetic wrist and hand flexion when bending the paretic wrist and hand with their paretic wrist and hand not extended, which was caused by absence of electrical stimuli. The NMES therapy group looked into an opaque wooden board while conducting the same thing as the mirror and NMES therapy group did. The mirror therapy group repeated bending and extending their paretic wrists and hands at an interval of five seconds while looking into the mirror when they were conducting flexion and extension movements of non-paretic wrists and hands. The patient with right hemiparesis had NMES on her right wrist and

	hand extensor muscle and simultaneously underwent flexion and extension of her fingers and wrist while looking at the reflection of her left hand on the mirror. All three groups received the same conventional rehabilitation programs and additionally, had each of their own therapies for thirty minutes, five days a week for three weeks.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mild (or MAS 1)
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	not applicable
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	The mirror therapy group repeated bending and extending their paretic wrists and hands at an interval of five seconds while looking into the mirror when they were conducting flexion and extension movements of non-paretic wrists and hands. All three groups received the same conventional rehabilitation programs and additionally, had each of their own therapies for thirty minutes, five days a week for three weeks.

Comparator	For the mirror therapy group, with their paretic arm put behind the mirror, they kept bending and extending the nonparetic-side wrist and hand while patients looked into the mirror watching the movements of their non-paretic hand and imagined their paretic-side wrist and hand were doing exactly the same thing. All three groups received the same conventional rehabilitation programs and additionally, had each of their own therapies for thirty minutes, five days a week for three weeks.
Number of participants	60
Duration of follow-up	3 weeks
Indirectness	Intervention indirectness - No control group so for the purpose of this review the mirror therapy only group has been used as a control group
Additional comments	NR

Study arms

Neuromuscular electrical stimulation (NMES) (N = 40)
Mirror + NMES and NMES only. 2 treatment groups combined for the purposes of this review

Usual care (N = 20)
Mirror therapy only

1 **Characteristics**

2 ***Study-level characteristics***

Characteristic	Study (N = 60)
Ethnicity Nominal	NR
Comorbidities Nominal	NR
Type of spasticity Nominal	NR

3

4 ***Arm-level characteristics***

Characteristic	Neuromuscular electrical stimulation (NMES) (N = 40)	Usual care (N = 20)
% Female Nominal	37.5	30
% Female Mean (SD)	37.5 (*empty data*)	30 (*empty data*)
Mean age (SD) Mean (SD)	63.45 (10.92)	63.1 (7.3)
Severity of spasticity Mean (SD)	0.4 (0.5)	0.2 (0.4)

Characteristic	Neuromuscular electrical stimulation (NMES) (N = 40)	Usual care (N = 20)
Time period after stroke days Mean (SD)	26.85 (13.68)	23.9 (10.5)

Outcomes

Study timepoints

- Baseline
- 3 week

Mirror therapy + NMES and NMES vs Mirror therapy

Outcome	Neuromuscular electrical stimulation (NMES), Baseline, N = 20	Neuromuscular electrical stimulation (NMES), 3 week, N = 20	Usual care, Baseline, N = 20	Usual care, 3 week, N = 20
Spastcity outcome - Modified ashworth scale (final values) scale 0-4 Mean (SD)	0.4 (0.5)	0.7 (0.5)	0.2 (0.4)	0.7 (0.5)
physical function - general - summation of Fugl Meyer (final values) 0-66 Mean (SD)	4.8 (4.4)	18 (6.6)	5.3 (5.8)	11.2 (6.9)

Spastcity outcome - Modified ashworth scale - Polarity - Lower values are better
physical function - general - summation of Fugl Meyer - Polarity - Higher values are better
Final values

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Mirrortherapy+NMESandNMESvsMirrortherapy-Spastcityoutcome-Modifiedashworthscale-MeanSD-Mirror + NMES and NMES only-Mirror therapy only-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(no information on missing data)*
Overall bias and Directness	Overall Directness	Partially applicable

Mirrortherapy+NMESandNMESvsMirrortherapy-physicalfunction-general-summationofFuglMeyer-MeanSD-Mirror + NMES and NMES only-Mirror therapy only-t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(no information on missing data)*
Overall bias and Directness	Overall Directness	Partially applicable

Zhang, 2021

Bibliographic Reference	Zhang, Y.; Li, M.; Ouyang, G.; Observation on the clinical curative effect of acupuncture for stroke Hemiplegia according to Muscle Tension Evolution Rule; Acupuncture and Electro-Therapeutics Research; 2021; vol. 46 (no. 3); 225-237

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Inpatients in the Second Afficiated Hospital of Nanjing Medical University
Study dates	Oct 16- Dec 19
Sources of funding	Science and Development Fund of Nanjing Medical University (2016NJMU038)
Inclusion criteria	Diagnosis of stroke, cerebral haemorrhage and atherosclerotic thrombotic cerebral infarction; patients with relatively stable conditions after a stroke; patients with hemiplegia after a stroke for the first time within one months; patients who had no severe cognitive dysfunction and could cooperate to complete the scale measurement; and patients who provided signed informed consent.
Exclusion criteria	Patients with serious disease of other systems; patients with severe arthritis or joint pain; patients with motor dysfunction caused by non- stroke factors such as cerebral embolisms, subarachnoid haemorrhage, brain tumour, train trauma or parasitic brain disease.
Stratification - Type of spasticity	Focal spasticity

Recruitment / selection of participants	Inpatients in the Second Afficiated Hospital of Nanjing Medical University
Intervention(s)	Traditional acupuncture - Patients lay in the supine position. the Shuigou point was punctured using the bird-pecking method, preferably with moist eyes. For Jiquan point, acupuncture was performed at 2 cms below the heart meridian. The needle was vertically punctured, using the lifting and thrusting method, taking the patients upper extremity numbness and twitching as the degree. Chise and Weizhong were vertically punctured using the lifting ad thrusting of the needle to make the limbs twitch. KWD-808 Pulse electrotherapy Apparatus was used for puncture after manual acupuncture brought about the desired sensation. Jianyu, Shoudanli, Zusanli and Xeici received electroacupuncture using a continuous wave. The frequency was 2Hx, the intensity was determined based based on patient comfort and duration was 20 minutes at a time. Acupuncture was performing once a day for 28 days as a course of treatment. Staging Acupuncture - Acupuncture points were determined in stages according to the changes in muscle tension. The conventional rehabilitation treatments, treatment time, and course of treatment were the same as those in the traditional acupuncture group. Flaccid paralysis period: The points in the upper limbs used in this period were those in the hand Yin meridian and Hand Yang meridians, while the points in the lower limbs used in this period were those in the Foot Yangming, Foot Taiyang and Foot Shaoyang meridians. The points in the upper limb and hand were punctured first, bloating and numbness were the desired sensations but twitching was better. Jianyu, Binao, Shoudanli, Waiguan, Biguan, Futu, Yinmen, Chengfu, Yanglingquan and Waiqui received electroacupuncture, continuous wave, with a frequency of 2 Hz. Intensity was based on patient comfort. Ounctures would continue until mild dorsiflexion of the wrist or extension of the fingers was observed when connecting the electroacupuncture at the Shousanli and Waiguan points. All patients were treated according to the routine internal medicine treatment plans of stroke and received symptomatic treatment and supportive treatment such as drugs. All participants received basic rehabilitation exercise therapy including comprehensive training of hemiplegic limbs and balance training.
Subgroup 1: Severity of	Not stated/unclear

spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	Acupuncture
Subgroup 4: For focal and multifocal spasticity only, area affected	Mixed
Population subgroups	NA
Comparator	Patients received basic rehabilitation exercises therapy, including comprehensive training of hemiplegic limbs, balance training and daily living ability training.
Number of participants	125
Duration of follow-up	4 weeks
Indirectness	NA
Additional comments	NR

1

Study arms

Acupuncture (Convention acupuncture and staging acupuncture combined) (N = 83)
The 2 groups of conventional acupuncture and staging acupuncture according to level of tension were combined for the purposes of this review. Staging acupuncture participants received rehabilitation exercises 1 x per day for 4 weeks

Control group - conventional rehabilitation therapy (N = 40)

Characteristics

Study-level characteristics

Characteristic	**Study (N = 125)**
Ethnicity Nominal	NR
Comorbidities Nominal	NR
Severity of spasticity Nominal	NR

Arm-level characteristics

Characteristic	Acupuncture (Convention acupuncture and staging acupuncture combined) (N = 83)	Control group - conventional rehabilitation therapy (N = 40)
% Female Nominal	43.04	42.5
Mean age (SD) Mean (SD)	65.2 (10.99)	64.88 (11.45)
Time period after stroke (days) Mean (SD)	21.96 (6.38)	21.98 (6.67)

Outcomes

Study timepoints

- Baseline
- 28 day

Acupuncture + conventional rehabilitation vs conventional rehabilitation

Outcome	Acupuncture (Convention acupuncture and staging acupuncture combined), Baseline, N = 83	Acupuncture (Convention acupuncture and staging acupuncture combined), 28 day, N = 79	Control group - conventional rehabilitation therapy, Baseline, N = 42	Control group - conventional rehabilitation therapy, 28 day, N = 40
Physical Function - General - FMA	31.01 (16.23)	55.56 (17.55)	32.25 (17.46)	42.35 (18.33)

Outcome	Acupuncture (Convention acupuncture and staging acupuncture combined), Baseline, N = 83	Acupuncture (Convention acupuncture and staging acupuncture combined), 28 day, N = 79	Control group - conventional rehabilitation therapy, Baseline, N = 42	Control group - conventional rehabilitation therapy, 28 day, N = 40
(final values) 0-100 Mean (SD)				
Activities of daily living - Barthel Index (final values) 0-100 Mean (SD)	27.83 (14.04)	54.48 (17.43)	28.9 (14.45)	42.58 (16.28)

1 Physical Function - General - FMA - Polarity - Higher values are better
2 Activities of daily living - Barthel Index - Polarity - Higher values are better
3 Final values

4 ***Discontinuation***

Outcome	Acupuncture (Convention acupuncture and staging acupuncture combined), Baseline, N = 83	Acupuncture (Convention acupuncture and staging acupuncture combined), 28 day, N = 83	Control group - conventional rehabilitation therapy, Baseline, N = 42	Control group - conventional rehabilitation therapy, 28 day, N = 42
Discontinuation due to adverse events no reasons cited No of events	n = 0 ; % = 0	n = 4 ; % = 4.82	n = 0 ; % = 0	n = 2 ; % = 4.76

5 Discontinuation due to adverse events - Polarity - Lower values are better

6

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Acupuncture+conventionalrehabilitationvsconventionalrehabilitation-PhysicalFunction-General-FMA-MeanSD-Acupuncture (Convention acupuncture and staging acupuncture combined)-Control group - conventional rehabilitation therapy-t28

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Acupuncture+conventionalrehabilitationvsconventionalrehabilitation-Activitiesofdailyliving-BarthelIndex-MeanSD-Acupuncture (Convention acupuncture and staging acupuncture combined)-Control group - conventional rehabilitation therapy-t28

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Discontinuation-Discontinuationduetoadverseevents-NoOfEvents-Acupuncture (Convention acupuncture and staging acupuncture combined)-Control group - conventional rehabilitation therapy-t28

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Zhang, 2021

Bibliographic Reference	Zhang, Zengqiao; Wang, Wu; Song, Yongjia; Zhai, Tianjun; Zhu, Yan; Jiang, Liming; Li, Qunfeng; Jin, Lei; Li, Kunpeng; Feng, Wei; Immediate Effect of Dry Needling at Myofascial Trigger Point on Hand Spasticity in Chronic Post-stroke Patients: A Multicenter Randomized Controlled Trial.; Frontiers in neurology; 2021; vol. 12; 745618

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	ChiCTR1900022379.
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	The Seventh People's Hospital Affiliated with the Shanghai University of traditional Chinese medicine, Shanghai Second rehabilitation hospital, and Shanghai Hudong hospital
Study dates	NR
Sources of funding	This work was supported by the Shanghai Science and Technology Commission (grant number 18401900300), the National Natural Science Foundation of China (grant number 81873328), and the Shanghai Characteristic Diagnosis and Treatment Technology Improvement Project of Traditional Chinese Medicine [grant number YZ (2018-2020)-ZYJS-04].

Inclusion criteria	1 Clinically diagnosed with stroke (13); 2 Brunnstrom stages ranged from II to IV; 3 spasticity of the hand [Modified Ashworth Scale (MAS) score 1+-3); 4 aged between 50 and 70 years; 5 could understand the content of the scale and cooperate with the evaluation and treatment; 6 agreed to engage in the trial and signed the informed consent.
Exclusion criteria	1 Secondary Parkinson's disease; 2 aphasia, conscious, or cognitive impairment; 3 severe bleeding tendency or infection of treatment site; 4 received other related treatment in the past 3 months; 5 other causes of hand spasticity; 6 combined with muscle contracture or joint deformity; 7 pregnant and lactating women; 8 fear of acupuncture or fainting.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	Participants were recruited from the Seventh People's Hospital Affiliated with the Shanghai University of traditional Chinese medicine, Shanghai Second rehabilitation hospital, and Shanghai Hudong hospital through the web platform, outpatient, and inpatient clinical poster advertisements.
Intervention(s)	Acupuncture/dry needling (Dry needling) N=70 Participants in this group were treated with dry needling at myofascial trigger point five times a week (30 min each time) for 4 weeks. After routine disinfection, the operator inserted a sterile needle (0.3 mmx25 mm) vertically into the myofascial trigger point. The success criteria of acupuncture were local pain, distal finger pain, and finger twitch. The needle was kept for 30 min following the induction of a convulsive reaction. Concomitant therapy: All people received routine rehabilitation therapy, five times a week for 4 weeks. This included recumbent positioning, neurodevelopmental treatment, activities of daily living treatment and routine anti-stroke treatment.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mild (or MAS 1)
Subgroup 2: Time period after stroke when trial starts	Chronic (>6 months)

Subgroup 3: Acupuncture/dry needling	Dry needling
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	NR
Comparator	Placebo/sham (sham dry needling) N=70 Participants in this group received sham dry acupuncture five times a week (30 min each time) for 4 weeks. The acupuncture needle was inserted 2 mm lateral to myofascial trigger point to a depth of 2 mm without manual stimulation. Concomitant therapy: All people received routine rehabilitation therapy, five times a week for 4 weeks. This included recumbent positioning, neurodevelopmental treatment, activities of daily living treatment and routine anti-stroke treatment. Usual care N=70 Usual care only. Concomitant therapy: All people received routine rehabilitation therapy, five times a week for 4 weeks. This included recumbent positioning, neurodevelopmental treatment, activities of daily living treatment and routine anti-stroke treatment.
Number of participants	210

Duration of follow-up	4 weeks
Indirectness	NR
Additional comments	NR

Study arms

Acupuncture/dry needling (Dry needling) (N = 70)
Participants in this group were treated with dry needling at myofascial trigger point five times a week (30 min each time) for 4 weeks. After routine disinfection, the operator inserted a sterile needle (0.3 mmx25 mm) vertically into the myofascial trigger point. The success criteria of acupuncture were local pain, distal finger pain, and finger twitch. The needle was kept for 30 min following the induction of a convulsive reaction. Concomitant therapy: All people received routine rehabilitation therapy, five times a week for 4 weeks. This included recumbent positioning, neurodevelopmental treatment, activities of daily living treatment and routine anti-stroke treatment.

Placebo/sham (sham dry needling) (N = 70)
Participants in this group received sham dry acupuncture five times a week (30 min each time) for 4 weeks. The acupuncture needle was inserted 2 mm lateral to myofascial trigger point to a depth of 2 mm without manual stimulation. Concomitant therapy: All people received routine rehabilitation therapy, five times a week for 4 weeks. This included recumbent positioning, neurodevelopmental treatment, activities of daily living treatment and routine anti-stroke treatment.

Usual care (N = 70)
Usual care only. Concomitant therapy: All people received routine rehabilitation therapy, five times a week for 4 weeks. This included recumbent positioning, neurodevelopmental treatment, activities of daily living treatment and routine anti-stroke treatment.

1 **Characteristics**

2 ***Arm-level characteristics***

Characteristic	Acupuncture/dry needling (Dry needling) (N = 70)	Placebo/sham (sham dry needling) (N = 70)	Usual care (N = 70)
% Female Sample size	n = 23 ; % = 32.9	n = 26 ; % = 37.1	n = 22 ; % = 31.4
Mean age (SD) Mean (SD)	66.17 (9.84)	62.97 (11.53)	65.07 (8.5)
Ethnicity Nominal	NR	NR	NR
Comorbidities Nominal	NR	NR	NR
Severity of spasticity Nominal	NR	NR	NR
Time period after stroke (Months) Mean (SD)	12.67 (3.09)	13.41 (2.98)	12.54 (3.04)
Type of spasticity Nominal	NR	NR	NR

3

Outcomes

Study timepoints

- Baseline
- 4 week

Dichotomous outcomes

Outcome	Acupuncture/dry needling (Dry needling), Baseline, N = 70	Acupuncture/dry needling (Dry needling), 4 week, N = 70	Placebo/sham (sham dry needling), Baseline, N = 70	Placebo/sham (sham dry needling), 4 week, N = 70	Usual care, Baseline, N = 70	Usual care, 4 week, N = 70
Withdrawal due to adverse events No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 1 ; % = 0.7	n = NA ; % = NA	n = 0 ; % = 0

Withdrawal due to adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomousoutcomes-Withdrawalduetoadverseevents-NoOfEvents-Dry needling-Sham dry needling + usual care-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Zhong, 2002

Bibliographic Reference	Zhong, C. M.; Liu, Q. F.; Jin, H. Y.; Liu, H. M.; Effects of acupuncture and balance facilitation of muscular tension on the early rehabilitation of patients with stroke and hemiplegia; Chinese Journal of Clinical Rehabilitation; 2002; vol. 6 (no. 23); 3612-3613

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	NR
Study dates	Jan 1998 - May 2000
Sources of funding	NR
Inclusion criteria	49 males and 47 females were randomly divided into the 2 groups. The limit was 1 month, and reject light patients such as TIA and RIND and patients complicated with severe diseases with dysnoesia and conscious disturbance. All cases were diagnosed according to the diagnostic standard of cerebrovascular disease made by Chine Medical Association, and assured by skull CT.

Exclusion criteria	The limit was 1 month, and reject light patients such as TIA and RIND and patients complicated with severe diseases with dysnoesia and conscious disturbance.
Stratification - Type of spasticity	Focal spasticity
Recruitment / selection of participants	NR
Intervention(s)	Stab negative channels and points of upper limb paralysis side in flaccid paralysis stage in the intervention group were chosen. take positive channel and points of the lower limb and apply strong stimulation manoeuvre such as twirling and lifting or thrusting the needle. kept the needle for 15-20 mins or turn on the electricity of 200hz with rarefied and dense waves for half and hour. The therapy went on for a week to make the muscular tension of the flexor muscle of the upper limb and extensor muscle of the lower limb increase and promote congenerous movement. at the same time stab the same points on the healthy side to enhance the effect. in Bronston stage 2 when the tension was from grade 0 to 1 the congenerous movement of anti gravity muscles appeared and enhanced, part of muscles near end contracted voluntarily. at this stage stab positive points of upper limb of paralyses side to excite extensor muscles. the purpose was enhancing the excitation of motor neuron and a motor neuron of antagonists of anti gravity muscles. then enhance the muscular tension and promote antagonists of antigravity muscles to move. this went on for 1 week. in Brunstrom stage 3 (for 1-2 weeks) tension of both side was enhanced but the muscle tension still gained advantage. the phase was rather key for recover of motor function, main therapy was also enabling the tension of antagonists, balance and coordination therapy of channel and points was going on. The purpose was to reduce congenerous movement and enhance separated movement and transited into Brunstrom 5. At this time separated movement was key. The coordinate movement disappeared on the whole and normal motor pattern hd been established. Remove the acupuncture, induce and enhance the normal motor training until it was nearly normal (Brunstrom stage 6). the therapy went on for 4 weeks. (translated directly from text) All cases were given corresponding drugs regularly. After the condition was stable, cases of the 2 groups were performed basal rehabilitation therapy, including good position of limbs, turn the body over and clap the back, joint movement of the whole range, wipe and manage the muscles and knock the muscular tendon, treating with modern rehabilitation technique

	such as Brunnstrom promoting method, Bobath, Rood method, and proprioception method of promoting nerves and muscles (PNF).
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mild (or MAS 1)
Subgroup 2: Time period after stroke when trial starts	Not stated/unclear
Subgroup 3: Acupuncture/dry needling	Acupuncture
Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	NA
Comparator	All cases were given corresponding drugs regularly. After the condition was stable, cases of the 2 groups were performed basal rehabilitation therapy, including good position of limbs, turn the body over and clap the back, joint movement of the whole range, wipe and manage the muscles and knock the muscular tendon, treating with modern rehabilitation technique such as Brunnstrom promoting method, Bobath, Rood method, and proprioception method of promoting nerves and muscles (PNF).
Number of participants	96
Duration of follow-up	4 weeks

Indirectness	majority of patients score 0 on MAS
Additional comments	nr

Study arms

acupuncture (N = 48)

usual care (N = 48)

Characteristics

Study-level characteristics

Characteristic	**Study (N = 96)**
% Female Nominal	48.96
Mean age (SD) Nominal	NR
Ethnicity Nominal	NR
Comorbidities Nominal	NR

Characteristic	Study (N = 96)
Type of spasticity Nominal	NR

1

2 ***Arm-level characteristics***

Characteristic	acupuncture (N = 48)	usual care (N = 48)
Severity of spasticity Nominal	NR	NR
MAS grade 0 Nominal	42	43
MAS grade 1 Nominal	0	0
MAS grad 1+ Nominal	2	3
MAS grade 2 Nominal	2	1
MAS grade 3 Nominal	2	1
MAS grade 4	0	*empty data*

Characteristic	acupuncture (N = 48)	usual care (N = 48)
Nominal		
Time period after stroke Nominal	NR	NR
Time period after stroke Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- Baseline
- 4 week

Acupuncture vs usual rehabilitation

Outcome	acupuncture, Baseline, N = 48	acupuncture, 4 week, N = 48	usual care, Baseline, N = 48	usual care, 4 week, N = 48
motor function - FMA final values Mean (SD)	25.4 (19.5)	69.4 (27.1)	20.2 (20.1)	31.7 (24.1)
Activities of daily living - Barthel Index final values Mean (SE)	17.3 (3.1)	82.5 (16.9)	18.3 (1.4)	50 (16.9)

motor function - FMA - Polarity - Higher values are better
Activities of daily living - Barthel Index - Polarity - Higher values are better
Final values

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

acupuncturevsusualrehabilitation-motorfunction-FMA-MeanSD-acupuncture-usual care-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to issues with randomisation and adhering to the intervention)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(most pts have MAS scores of 0 at baseline)*

acupuncturevsusualrehabilitation-Activitiesofdailyliving-BarthelIndex-MeanSE-acupuncture-usual care-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to issues with randomisation and adhering to the intervention)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(most pts have MAS scores of 0 at baseline)*

Zhou, 2018

Bibliographic Reference	Zhou, M.; Li, F.; Lu, W.; Wu, J.; Pei, S.; Efficiency of Neuromuscular Electrical Stimulation and Transcutaneous Nerve Stimulation on Hemiplegic Shoulder Pain: A Randomized Controlled Trial; Archives of Physical Medicine & Rehabilitation; 2018; vol. 99 (no. 9); 1730-1739

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	ChiCTR-TRC-13004272
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Hospital rehabilitation centre
Study dates	February 2014 to July 2016
Sources of funding	Research fund of the Baoshan district committee of science and technology, Shanghai, China
Inclusion criteria	The inclusion criteria were; hemiplegia in a unilateral limb and pain in the hemiplegic shoulder post stoke, a stable condition and suitability for physical training, mini-mental state examination score >24 points and being able to understand the requirements of test and training.
Exclusion criteria	Exclusion criteria were; a history of shoulder pain prior to stroke, an unstable medical condition or uncontrolled systemic disease, quadriplegia, those demanding pacemakers, administering any non steroidal anti-inflammatory drugs for shoulder pain prior to the study; and disturbance of awareness, severe visual and cognitive impairment
Stratification - Type of spasticity	Focal spasticity

Recruitment / selection of participants	184 HSP patients aged 18-80 years were recruited in the first rehabilitation hospital of Shanghai, China. All patients were diagnosed with first stroke.
Intervention(s)	NMES (15hx and pulse 200ns,dual channel stimulators, rehabilitation kit) was applied to the supraspinatus and deltoids in the NMES group. the surface electrode was place on the target muscle belly where the minimal current could induce a visible muscle contraction. During stimulation therapy, the stimulator completed a cycle every 30 seconds consisting of 5 seconds to ramp up, 10 seconds at maximum stimulation, 5 seconds to ramp down and 10 seconds of no stimulation. The 4-week treatment consisted of 20 sessions, each session composed of 1 hour of stimulation per day. TENS (100hx and pulse width 100ns, rehabilitation kit) was used in the same area; the amplitude was adjusted to cause minimal discomfort without any discernible muscle contraction. A total of 20 sessions of 1-hour stimulation were conducted daily for 4 weeks, consecutively. Patients in all groups underwent a standardised rehabilitation programme, which was delivered by occupational therapists and physiotherapists.
Subgroup 1: Severity of spasticity (as stated by category or as measured by modified Ashworth scale [MAS])	Mild (or MAS 1)
Subgroup 2: Time period after stroke when trial starts	Subacute (7 days - 6 months)
Subgroup 3: Acupuncture/dry needling	not applicable

Subgroup 4: For focal and multifocal spasticity only, area affected	Upper limb (including shoulder girdle)
Population subgroups	NR
Comparator	Patients in the control underwent a standardised rehabilitation programme without any stimulation, which was delivered by occupational therapists and physiotherapists.
Number of participants	90
Duration of follow-up	Baseline, 2, 4, and 8 weeks after treatment, respectively
Indirectness	NR
Additional comments	NR

Study arms

Transcutaneous electrical nerve stimulation (TENS) (N = 36)
TENS + conventional rehabilitation programme

Neuromuscular electrical nerve stimulation (NMES) (N = 36)
NMES + conventional rehabilitation programme

Usual care (N = 18)
Conventional rehabilitation only

Characteristics

Study-level characteristics

Characteristic	Study (N = 90)
Ethnicity Nominal	NR
Comorbidities Nominal	NR

Arm-level characteristics

Characteristic	Transcutaneous electrical nerve stimulation (TENS) (N = 36)	Neuromuscular electrical nerve stimulation (NMES) (N = 36)	Usual care (N = 18)
% Female Nominal	18.75	33.33	16.67
Mean age (SD) Mean (SD)	58.5 (9.07)	59.35 (10.78)	63.78 (11.17)
Severity of spasticity adductors Mean (SD)	0.28 (0.52)	0.19 (0.65)	0.22 (0.65)
Internal rotators Mean (SD)	0.94 (1.27)	0.77 (1.06)	0.94 (1.11)

Characteristic	Transcutaneous electrical nerve stimulation (TENS) (N = 36)	Neuromuscular electrical nerve stimulation (NMES) (N = 36)	Usual care (N = 18)
Time period after stroke days Mean (SD)	1008 (103.32)	73.61 (53.4)	105.89 (142.8)
Type of spasticity Nominal	NR	NR	NR

Outcomes

Study timepoints

- Baseline
- 8 week

NMES vs TENS vs control at 8 weeks

Outcome	Transcutaneous electrical nerve stimulation (TENS), Baseline, N = 32	Transcutaneous electrical nerve stimulation (TENS), 8 week, N = 36	Neuromuscular electrical nerve stimulation (NMES), Baseline, N = 31	Neuromuscular electrical nerve stimulation (NMES), 8 week, N = 36	Usual care, Baseline, N = 18	Usual care, 8 week, N = 18
Spasticity outcome measures (Modified ashworth scale, adductors/internal rotators) Scale range: 0-6. Change scores. The study reports the values for adductors	0.61 (1.03)	0.16 (4.73)	0.48 (3.08)	0.24 (3.05)	0.58 (0.98)	0 (1.22)

Outcome	Transcutaneous electrical nerve stimulation (TENS), Baseline, N = 32	Transcutaneous electrical nerve stimulation (TENS), 8 week, N = 36	Neuromuscular electrical nerve stimulation (NMES), Baseline, N = 31	Neuromuscular electrical nerve stimulation (NMES), 8 week, N = 36	Usual care, Baseline, N = 18	Usual care, 8 week, N = 18
and internal rotators separately as means and standard errors, that were converted to means and standard deviations and then combined to get an overall value for spasticity. Reported TENS adductors = 0.21 (0.69). Reported TENS internal rotators = 0.11 (0.88). Reported NMES adductors = 0.00 (0.00). Reported NMES internal rotators = 0.48 (0.93). Reported control adductors = 0.00 (0.00). Reported control internal rotators = 0.00 (0.41). Mean (SD)						
Physical function - upper limb (Fugl Meyer Assessment) Scale range. 0-66. Change scores. Converted from mean (SE). Mean (SD)	19.97 (20.09)	5.46 (57.12)	11 (10.58)	4.86 (29.3)	5.31 (19.07)	5.31 (44.1)
Pain (numeric rating scale) Scale range: 0-10. Change score. Converted from mean (SE). Mean (SD)	4.41 (1.24)	-1.57 (7.74)	4.23 (1.28)	-2.24 (5.2)	3.72 (1.02)	-1.23 (3.5)

Outcome	Transcutaneous electrical nerve stimulation (TENS), Baseline, N = 32	Transcutaneous electrical nerve stimulation (TENS), 8 week, N = 36	Neuromuscular electrical nerve stimulation (NMES), Baseline, N = 31	Neuromuscular electrical nerve stimulation (NMES), 8 week, N = 36	Usual care, Baseline, N = 18	Usual care, 8 week, N = 18
Activities of daily living - Barthel Index Scale range: 0-100. Change scores. Converted from mean (SE). Mean (SD)	37.5 (19.39)	14.82 (108.78)	46.13 (11.08)	11.67 (37.2)	39.44 (19.17)	13.08 (45.4)
Stroke-specific Patient-Reported Outcome Measures - Stroke-Specific Quality of Life (SS-QOL) Scale range: 49-245. Change scores. Converted from mean (SE). Mean (SD)	130 (31.07)	12.68 (116.22)	137.55 (17.97)	17.81 (98.1)	132.61 (31.9)	10.77 (53.3)
Discontinuation no reasons cited No of events	n = NA ; % = NA	n = 8 ; % = 30.7	n = NA ; % = NA	n = 15 ; % = 41.6	n = NA ; % = NA	n = 5 ; % = 27.7

1 Spasticity outcome measures (Modified ashworth scale, adductors/internal rotators) - Polarity - Higher values are better
2 Physical function - upper limb (Fugl Meyer Assessment) - Polarity - Higher values are better
3 Pain (numeric rating scale) - Polarity - Lower values are better
4 Activities of daily living - Barthel Index - Polarity - Higher values are better
5 Stroke-specific Patient-Reported Outcome Measures - Stroke-Specific Quality of Life (SS-QOL) - Polarity - Higher values are better
6 Discontinuation - Polarity - Lower values are better
7 Final values

8

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

NMESvsTENSvscontrolat8weeks-Discontinuation-NoOfEvents-TENS + conventional rehabilitation-NMES + conventional rehabilitation-Control group-t8

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

NMESvsTENSvscontrolat8weeks-Stroke-specificPatient-ReportedOutcomeMeasures-o Stroke-SpecificQualityofLife(SS-QOL)-MeanSD-TENS + conventional rehabilitation-NMES + conventional rehabilitation-Control group-t8

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to rate of missingness and pt reported outcome with no blinding)*
Overall bias and Directness	Overall Directness	Directly applicable

NMESvsTENSvscontrolat8weeks-Activitiesofdailyliving-BarthelIndex-MeanSD-TENS + conventional rehabilitation-NMES + conventional rehabilitation-Control group-t8

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

NMESvsTENSvscontrolat8weeks-Pain-numericratingscale-MeanSD-TENS + conventional rehabilitation-NMES + conventional rehabilitation-Control group-t8

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to rate of missingness and pt reported outcome with no blinding)*
Overall bias and Directness	Overall Directness	Directly applicable

NMESvsTENSvscontrolat8weeks-Physicalfunction-FuglMeyerassessment-MeanSD-TENS + conventional rehabilitation-NMES + conventional rehabilitation-Control group-t8

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

NMESvsTENSvscontrolat8weeks-Spastcityoutcome-Modifiedashworthscale-adductors-MeanSD-TENS + conventional rehabilitation-NMES + conventional rehabilitation-Control group-t8

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

1

2

Appendix E – Forest plots

Focal spasticity

Tizanidine compared to placebo

Figure 3: Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, change score) at ≤6 months

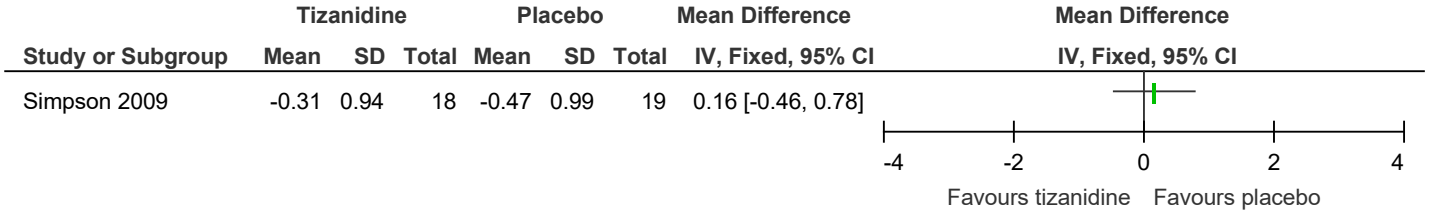
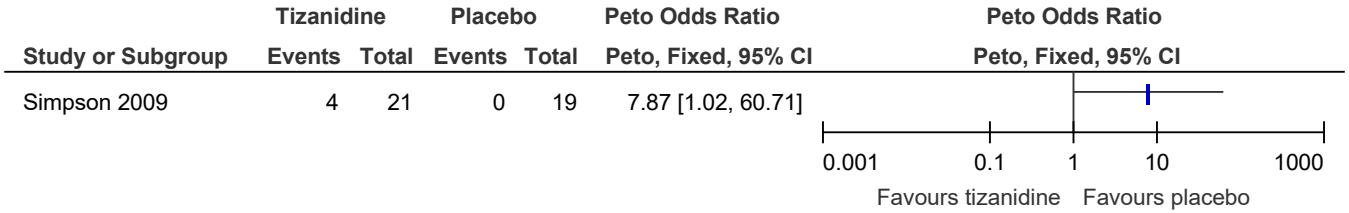


Figure 4: Withdrawal due to adverse events at ≤6 months



Onabotulinum toxin A (BOTOX) compared to tizanidine

Figure 5: Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, change scores) at ≤6 months

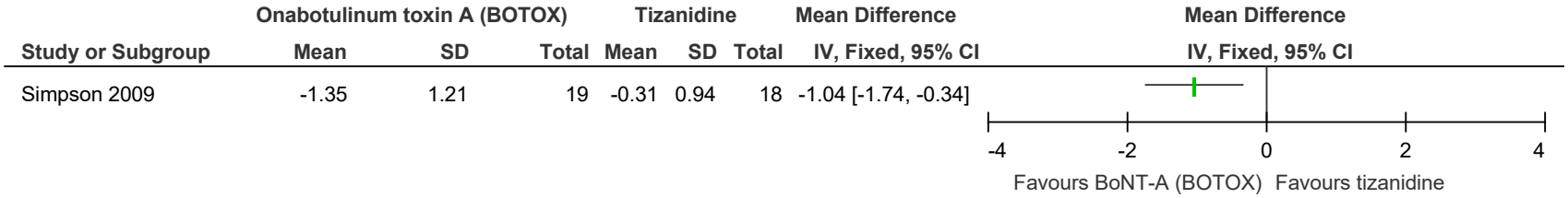
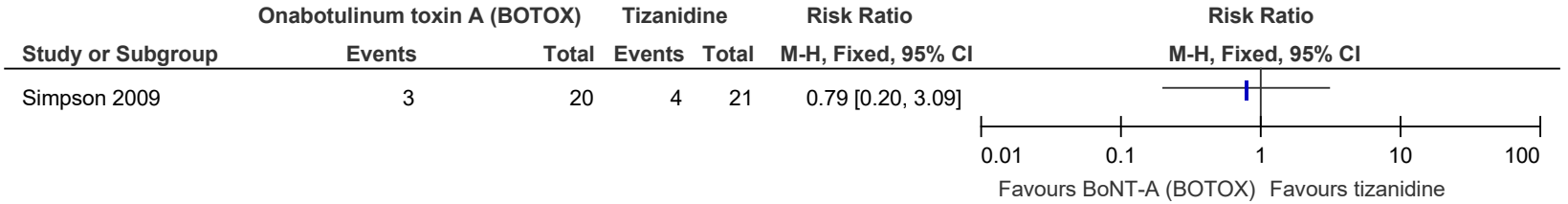


Figure 6: Withdrawal due to adverse events at ≤6 months



Onabotulinum toxin A (BOTOX) compared to placebo

Figure 7: Person/participant generic health-related quality of life (EQ-5D, 0-1, higher values are better, final value) at ≤6 months

	Onabotulinum toxin A (BOTOX)			Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Wallace 2020	-0.01	0.1058	14	0.043	0.1058	14	-0.05 [-0.13, 0.03]	

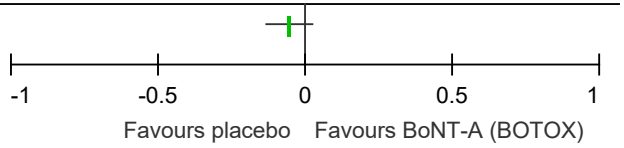


Figure 8: Spasticity outcome measures (Modified Ashworth scale, Resistance to passive movement (REPAS) [different scale ranges], lower values are better, change scores) at ≤6 months

	Onabotulinum toxin A (BOTOX)			Placebo				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Brashear 2002	-0.92	1.19	64	-0.67	1.14	62	14.8%	-0.21 [-0.56, 0.14]	
Kaji 2010a	-0.56	0.69	58	-0.4	0.58	62	14.8%	-0.25 [-0.61, 0.11]	
Kaji 2010b	-0.62	0.79	72	-0.19	0.5	37	14.5%	-0.60 [-1.01, -0.20]	
Kerzoncuf 2020	-0.74	1.01	19	-0.17	0.89	21	12.9%	-0.59 [-1.22, 0.05]	
Simpson 2009	-1.32	0.89	19	-0.47	0.99	19	12.7%	-0.88 [-1.55, -0.21]	
Ward 2014	-4.3	5.513	62	-1.7	4.725	62	14.8%	-0.50 [-0.86, -0.15]	
Wein 2018	-0.81	0.87	223	0.61	0.84	227	15.5%	-1.66 [-1.87, -1.44]	
Total (95% CI)			**517**			**490**	**100.0%**	**-0.68 [-1.20, -0.15]**	

Heterogeneity: Tau² = 0.46; Chi² = 83.01, df = 6 (P < 0.00001); I² = 93%

Test for overall effect: Z = 2.50 (P = 0.01)

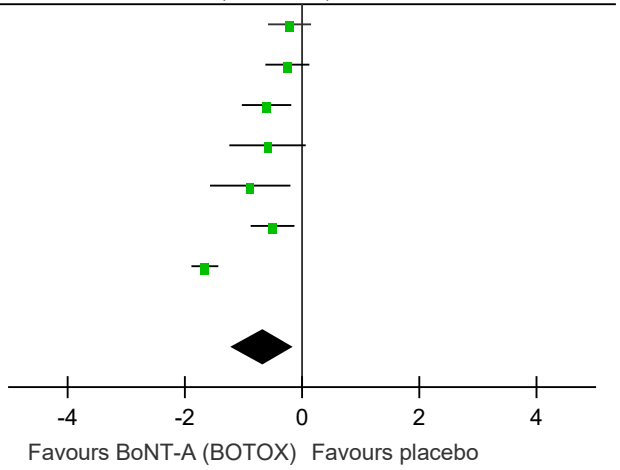


Figure 9: Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, final values) at ≤6 months

	Onabotulinum toxin A (BOTOX)			Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Tan 2021	2.42	0.56	18	2.64	0.81	18	-0.22 [-0.67, 0.23]	

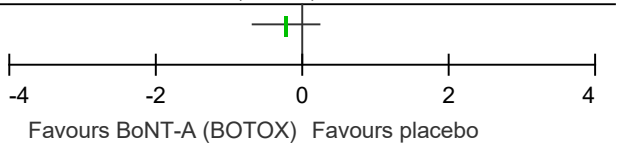


Figure 10: Physical function - upper limb (ARAT, FMA-UE [different scale ranges, higher values are better, final values) at ≤6 months

	Onabotulinum toxin A (BOTOX)			Placebo			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Lindsay 2021	15.3	21.6	40	12.4	20.7	43	57.0%	0.14 [-0.30, 0.57]	
Tan 2021	29.67	12.46	18	23.94	10.06	18	24.0%	0.49 [-0.17, 1.16]	
Wallace 2020	29.23	9.76	14	25.57	10.38	14	19.0%	0.35 [-0.39, 1.10]	
Total (95% CI)			**72**			**75**	**100.0%**	**0.26 [-0.06, 0.59]**	

Heterogeneity: Chi² = 0.86, df = 2 (P = 0.65); I² = 0%

Test for overall effect: Z = 1.58 (P = 0.11)

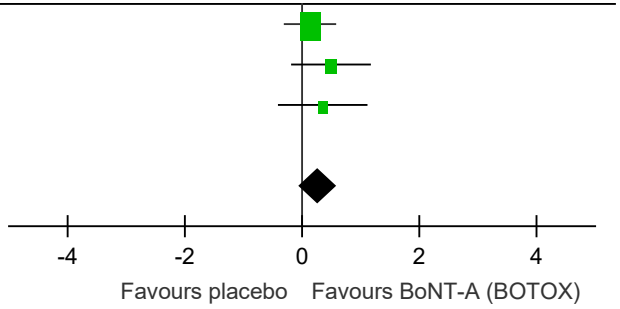


Figure 11: Physical function - upper limb (ARAT, 0-57, higher values are better, change score) at ≤6 months

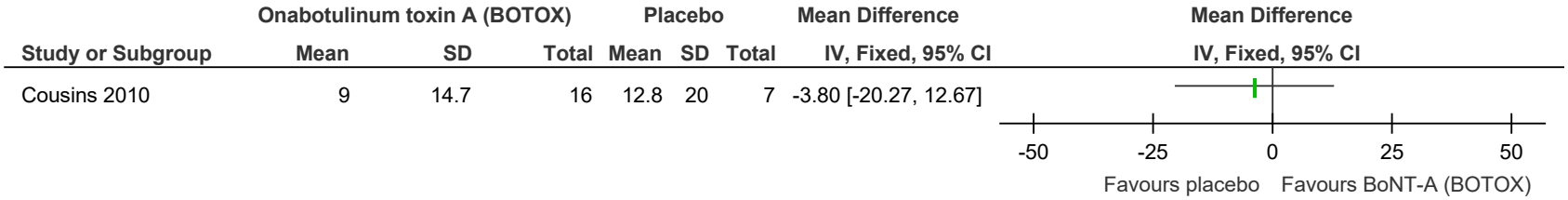


Figure 12: Physical function - lower limb (FMA-LE, 0-34, higher values are better, final value) at ≤6 months

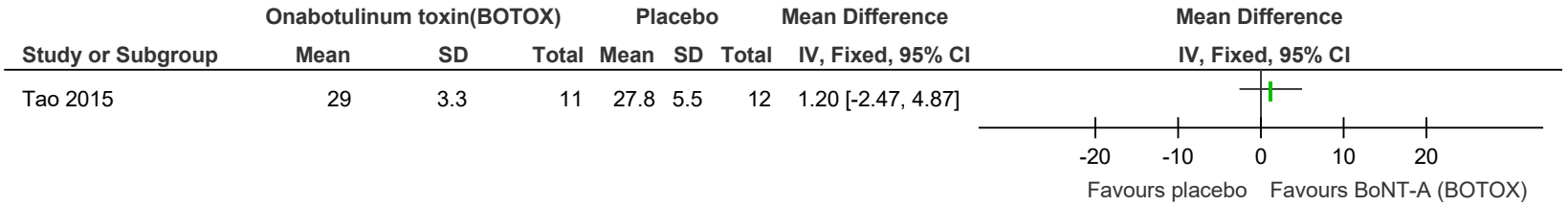


Figure 13: Pain (VAS, NRS, 0-10, lower values are better, change score and final value) at ≤6 months

	Onabotulinum toxin A (BOTOX)			Placebo				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
Esquenazi 2019	-0.8	2.3	233	-1.1	2.38	235	56.8%	0.30 [-0.12, 0.72]	
Tan 2021	4.22	1.7	18	5.17	1.34	18	43.2%	-0.95 [-1.95, 0.05]	
Total (95% CI)			**251**			**253**	**100.0%**	**-0.24 [-1.45, 0.97]**	

Heterogeneity: Tau² = 0.63; Chi² = 5.09, df = 1 (P = 0.02); I² = 80%

Test for overall effect: Z = 0.39 (P = 0.70)

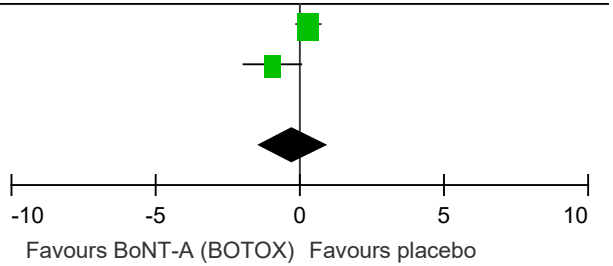


Figure 14: Activities of daily living (Disability assessment scale, 0-3, lower values are better, change scores) at ≤6 months

	Onabotulinum toxin A (BOTOX)			Placebo				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
Brashear 2002	-0.88	0.96	64	-0.46	0.83	62	35.1%	-0.42 [-0.73, -0.11]	
Kaji 2010b	-0.66	0.67	72	-0.2	0.53	37	64.9%	-0.46 [-0.69, -0.23]	
Total (95% CI)			**136**			**99**	**100.0%**	**-0.45 [-0.63, -0.26]**	

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%

Test for overall effect: Z = 4.71 (P < 0.00001)

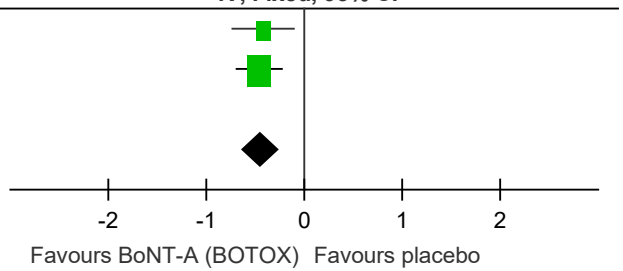


Figure 15: Activities of daily living (Barthel index, 0-100, higher values are better, final value) at ≤6 months

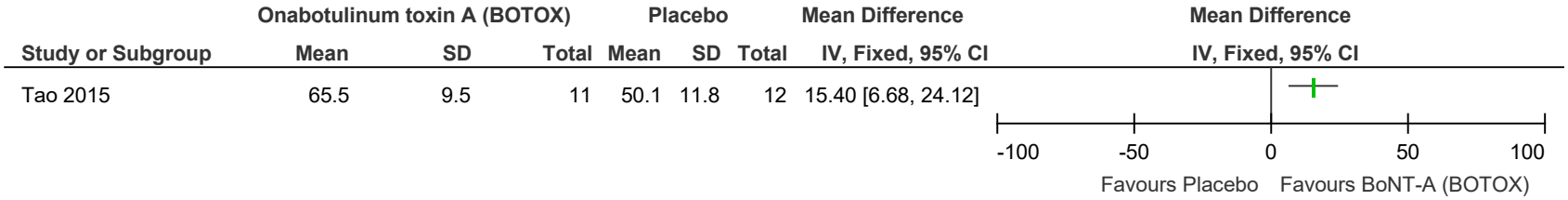


Figure 16: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Upper extremity, 0-100, higher values are better, final value) at ≤6 months

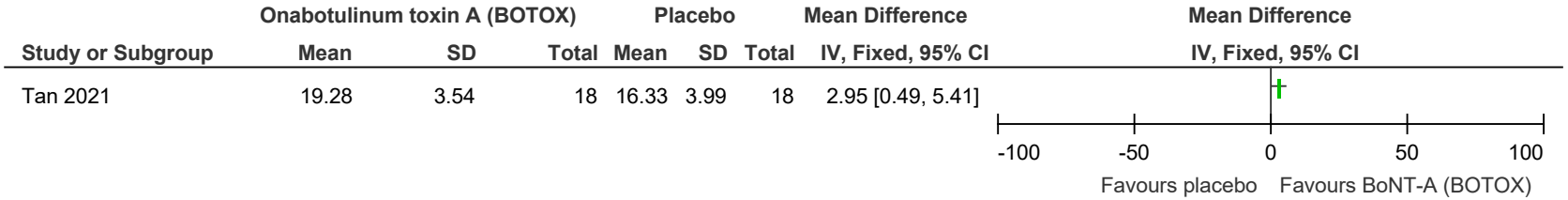


Figure 17: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Energy, 0-100, higher values are better, final value) at ≤6 months

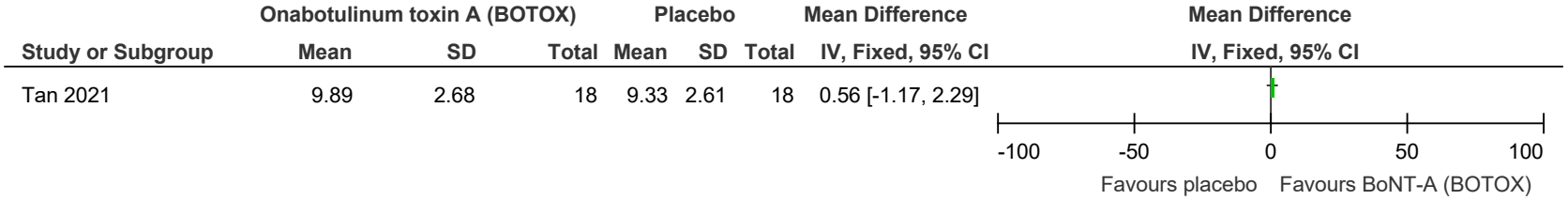


Figure 18: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Family, 0-100, higher values are better, final value) at ≤6 months

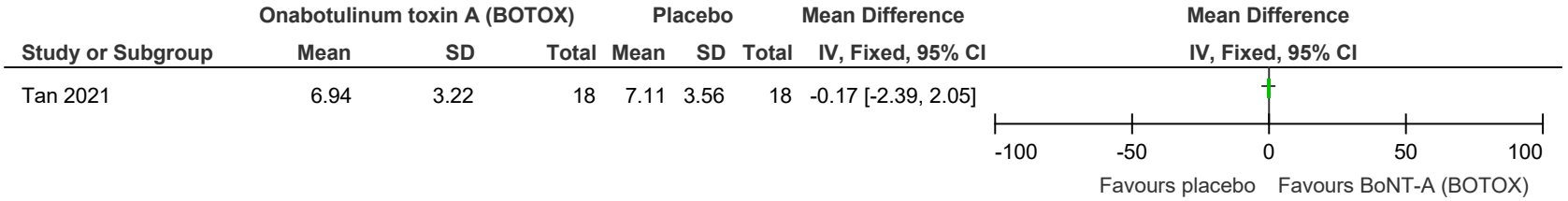


Figure 19: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Language, 0-100, higher values are better, final value) at ≤6 months

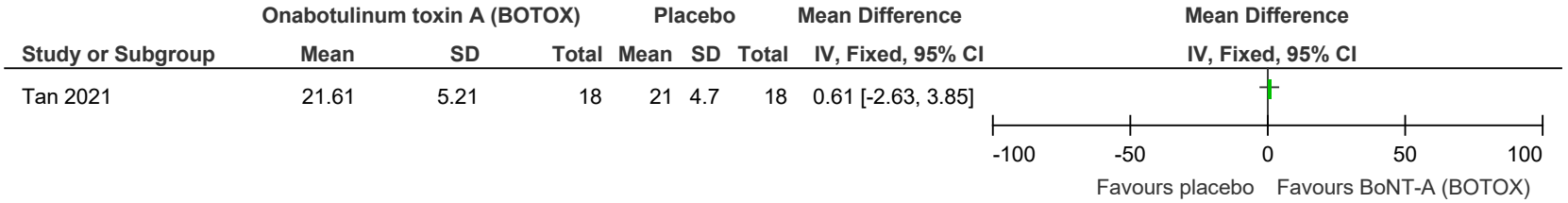


Figure 20: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Mobility, 0-100, higher values are better, final value) at ≤6 months

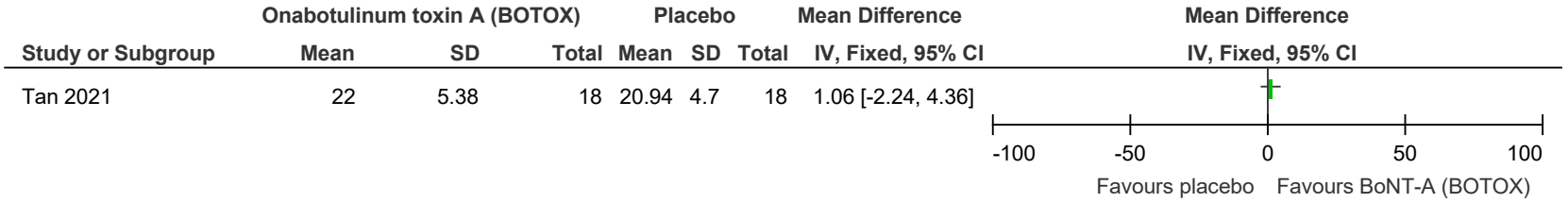


Figure 21: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Mood, 0-100, higher values are better, final value) at ≤6 months

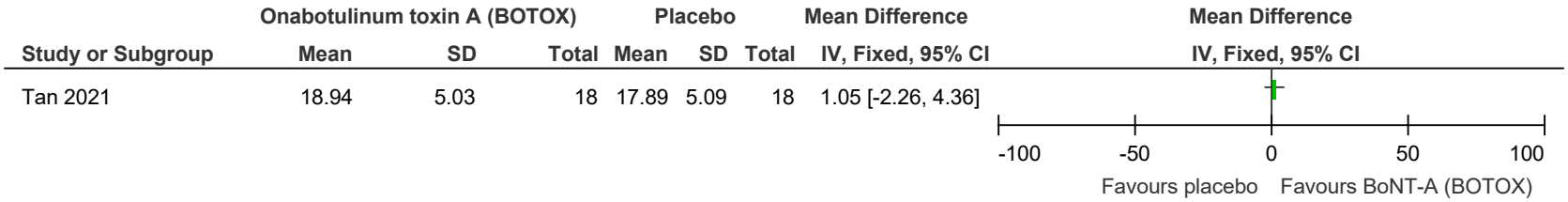


Figure 22: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Personality, 0-100, higher values are better, final value) at ≤6 months

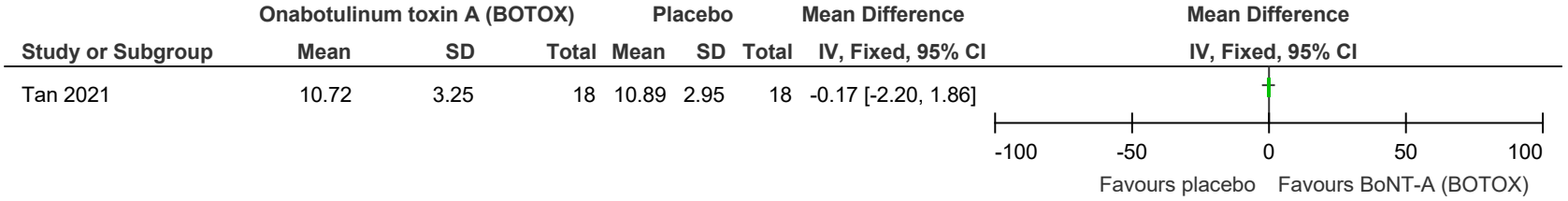


Figure 23: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Social roles, 0-100, higher values are better, final value) at ≤6 months

	Onabotulinum toxin A (BOTOX)			Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Tan 2021	8.78	1.63	18	8.94	1.55	18	-0.16 [-1.20, 0.88]	

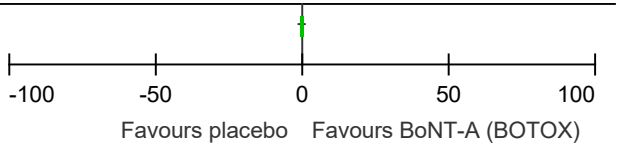


Figure 24: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Vision, 0-100, higher values are better, final value) at ≤6 months

	Onabotulinum toxin A (BOTOX)			Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Tan 2021	13.83	1.2	18	13.94	1.06	18	-0.11 [-0.85, 0.63]	

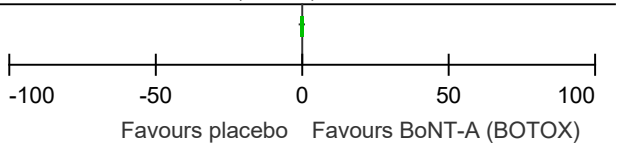


Figure 25: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Work, 0-100, higher values are better, final value) at ≤6 months

	Onabotulinum toxin A (BOTOX)			Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Tan 2021	8.28	3	18	7.78	2.88	18	0.50 [-1.42, 2.42]	

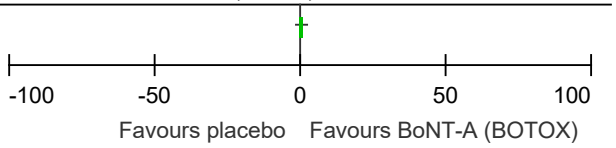


Figure 26: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Self-care, 0-100, higher values are better, final value) at ≤6 months

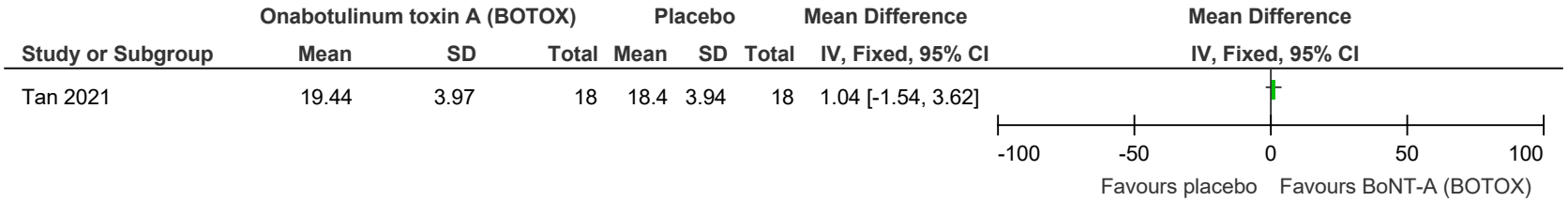


Figure 27: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Thinking, 0-100, higher values are better, final value) at ≤6 months

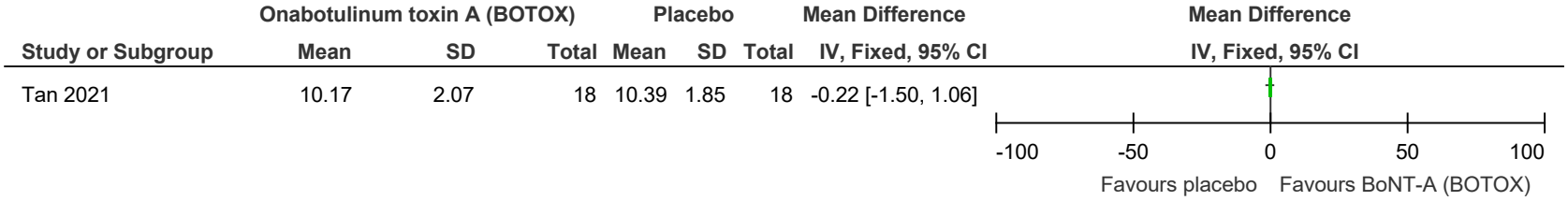


Figure 28: Withdrawal due to adverse events at ≤6 months

	Onabotulinum toxin A (BOTOX)		Placebo			Risk Difference
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Childers 2004	0	31	0	18	2.0%	0.00 [-0.08, 0.08]
Cousins 2010	2	19	5	11	1.2%	-0.35 [-0.67, -0.02]
Esquenazi 2019	5	233	2	235	20.9%	0.01 [-0.01, 0.03]
Kaji 2010a	3	58	0	62	5.4%	0.05 [-0.01, 0.12]
Kaji 2010b	3	72	1	37	4.4%	0.01 [-0.06, 0.08]
Lindsay 2021	9	49	5	48	4.3%	0.08 [-0.06, 0.22]
Marciniak 2012	0	10	2	11	0.9%	-0.18 [-0.44, 0.08]
Patel 2020	10	233	8	235	20.9%	0.01 [-0.03, 0.04]
Simpson 2009	3	20	0	19	1.7%	0.15 [-0.02, 0.32]
Tan 2021	0	18	0	18	1.6%	0.00 [-0.10, 0.10]
Tao 2015	0	11	0	12	1.0%	0.00 [-0.15, 0.15]
Wallace 2020	0	14	0	14	1.3%	0.00 [-0.13, 0.13]
Ward 2014	0	139	0	135	12.2%	0.00 [-0.01, 0.01]
Wein 2018	10	233	8	235	20.9%	0.01 [-0.03, 0.04]
Wolf 2012	4	12	1	13	1.1%	0.26 [-0.05, 0.56]
Total (95% CI)		**1152**		**1103**	**100.0%**	**0.01 [-0.00, 0.03]**
Total events	49		32			

Heterogeneity: Chi² = 17.49, df = 14 (P = 0.23); I² = 20%

Test for overall effect: Z = 1.59 (P = 0.11)

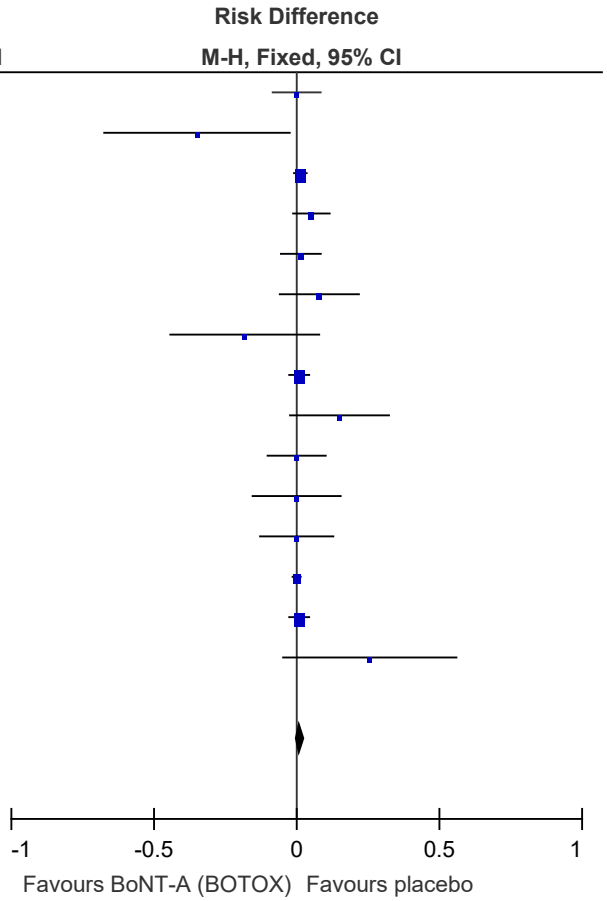
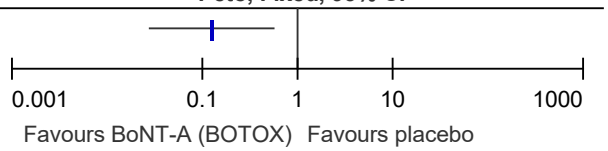


Figure 29: Withdrawal due to adverse events at >6 months

	Onabotulinum toxin A (BOTOX)		Placebo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Ward 2014	0	139	7	135	0.13 [0.03, 0.56]	



Onabotulinum toxin A (BOTOX) compared to usual care

Figure 30: Spasticity outcome measures (Clinical spasticity influx, Tardieu scale [different scale ranges] lower values are better, final value) at ≤6 months

	Onaobotulinum toxin (BOTOX)			Usual care			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Ding 2015	5.92	1.2	33	10.12	1.56	35	50.1%	-2.97 [-3.67, -2.27]	
Lannin 2018	2.3	0.7	12	2.2	0.8	14	49.9%	0.13 [-0.64, 0.90]	
Total (95% CI)			**45**			**49**	**100.0%**	**-1.43 [-4.46, 1.61]**	

Heterogeneity: Tau² = 4.66; Chi² = 33.97, df = 1 (P < 0.00001); I² = 97%

Test for overall effect: Z = 0.92 (P = 0.36)

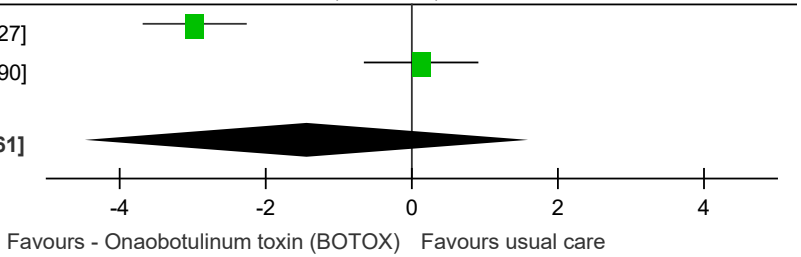


Figure 31: Physical function - lower limb (6 minute walk test, m/s, lower values are better, final value) at ≤6 months

	Onaobotulinum toxin (BOTOX)			Usual care			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Lannin 2018	0.27	0.23	12	0.35	0.6	14	-0.08 [-0.42, 0.26]

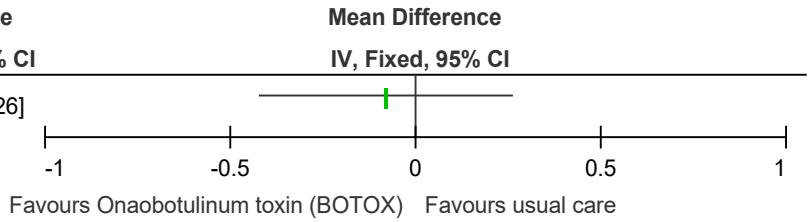


Figure 32: Physical function - lower limb (Fugl-meyer assessment, 0-34, higher values are better, final value) at ≤6 months

	Onabotulinum toxin A (BOTOX)			Placebo			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Ding 2015	17.61	3.98	33	7.65	1.07	35	9.96 [8.56, 11.36]

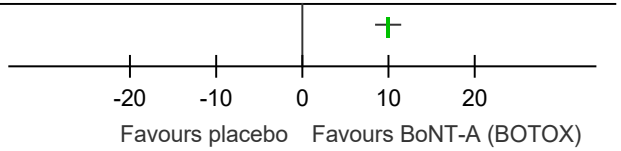
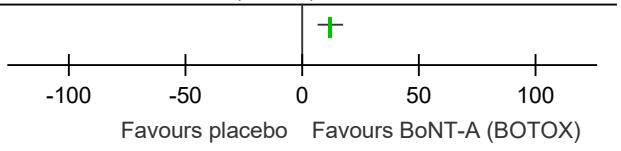


Figure 33: Activities of daily living (FIM, 18-126, higher values are better, final values) at ≤6 months

	Onabotulinum toxin A (BOTOX)			Placebo			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Ding 2015	72.4	10.8	33	60.3	10.5	35	12.10 [7.03, 17.17]



Abobotulinum toxin A (Dysport) compared to tizanidine

Figure 34: Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, final value) at ≤6 months

	Abobotulinum toxin A (Dysport)			Tizanidine			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Yazdchi 2013	1.68	0.47	34	2.32	0.56	34	-0.64 [-0.89, -0.39]

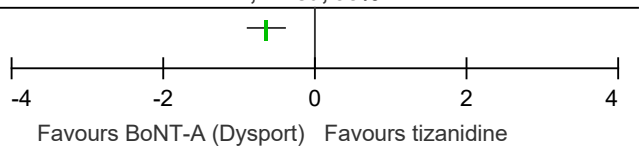


Figure 35: Physical function - upper limb (ARAT, 0-57, higher values are better, final value) at ≤6 months

	Abobotulinum toxin A (Dysport)			Tizanidine			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Yazdchi 2013	10.79	4.57	34	11.35	5.85	34	-0.56 [-3.06, 1.94]

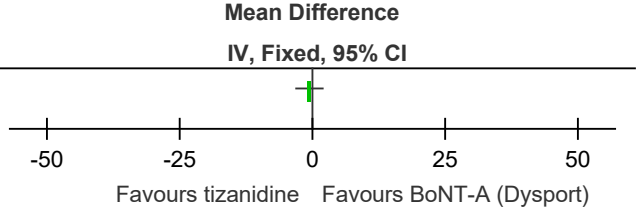
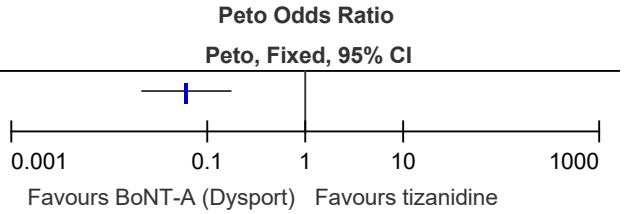


Figure 36: Withdrawal due to adverse events at ≤6 months

	Abobotulinum toxin A (Dysport)		Tizanidine		Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Peto, Fixed, 95% CI
Yazdchi 2013	0	34	20	34	0.06 [0.02, 0.17]



Abobotulinum toxin A (Dysport) compared to neuromuscular electrical stimulation (NMES)

Figure 37: Spasticity outcome measures (Modified Ashworth scale, 0-5, lower values are better, final value) at ≤6 months

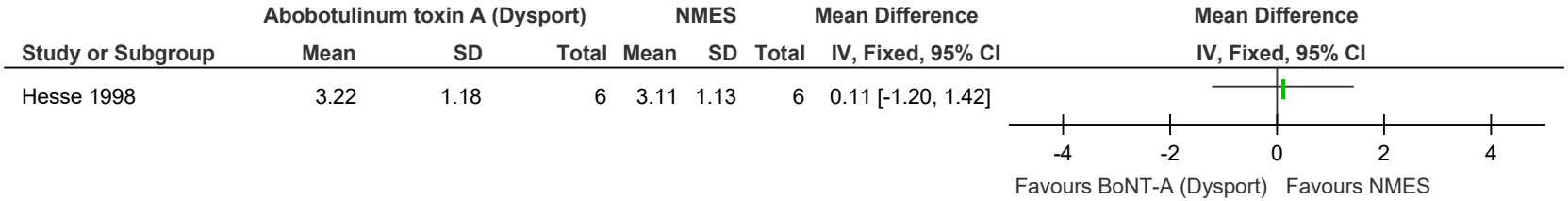
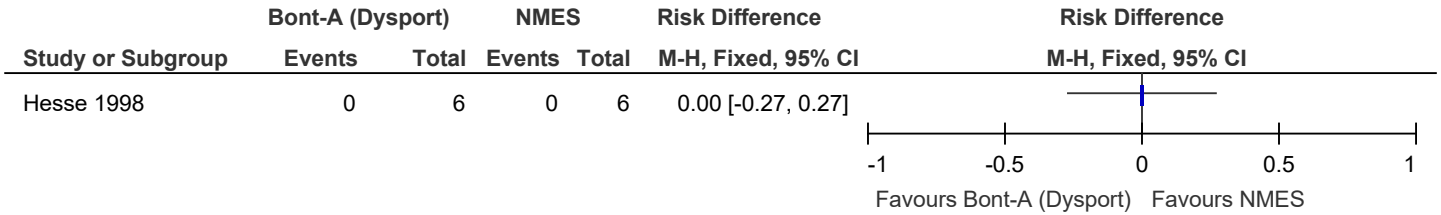


Figure 38: Withdrawal due to adverse events at ≤6 months



Abobotulinum toxin A (Dysport) compared to placebo

Figure 39: Person/participant generic health-related quality of life (AQOL, 0-1, higher values are better, change score) at ≤6 months

	Abobotulinum toxin A (Dysport)			Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
McCrory 2009	0.03	0.15	54	0.06	0.13	42	-0.03 [-0.09, 0.03]	

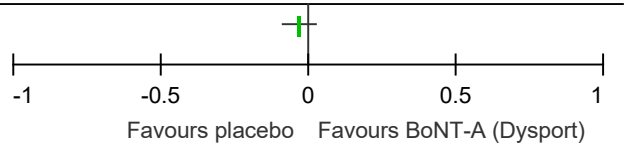


Figure 40: Spasticity outcome measures (Modified Ashworth scale, ROC analysis [different scale ranges], lower values are better, change scores) at ≤6 months

	Abobotulinum toxin A (Dysport)			Placebo			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bakheit 2000	-15.9	14.9	63	-5.3	15.1	19	21.2%	-0.70 [-1.23, -0.18]	
Gracies 2015	-1.3	1.1	159	-0.3	0.6	79	30.5%	-1.03 [-1.32, -0.75]	
McCrory 2009	-1.8	1.6	54	-0.2	1.2	42	24.6%	-1.10 [-1.54, -0.67]	
Simpson 1996	0.25	0.6	37	0.45	0.86	37	23.7%	-0.27 [-0.72, 0.19]	
Total (95% CI)			**313**			**177**	**100.0%**	**-0.80 [-1.17, -0.43]**	

Heterogeneity: Tau² = 0.09; Chi² = 9.43, df = 3 (P = 0.02); I² = 68%

Test for overall effect: Z = 4.26 (P < 0.0001)

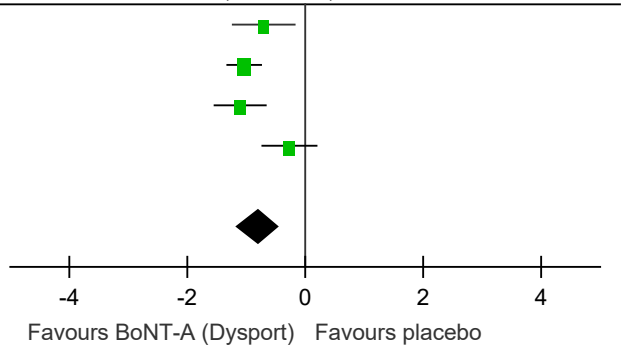


Figure 41: Spasticity outcome measures (Modified Ashworth scale [different scale ranges] lower values are better, final value) at ≤6 months

	Abobotulinum toxin A (Dysport)			Placebo				Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
Hesse 1998	3.22	1.18	6	3.17	9.95	6	21.0%	0.01 [-1.13, 1.14]
Prazeres 2018	1.3	1.22	20	1.5	0.92	20	35.0%	-0.18 [-0.80, 0.44]
Rosales 2012	0.96	0.77	79	1.73	0.77	81	44.0%	-1.00 [-1.32, -0.67]
Total (95% CI)			**105**			**107**	**100.0%**	**-0.50 [-1.19, 0.19]**

Heterogeneity: Tau² = 0.25; Chi² = 7.06, df = 2 (P = 0.03); I² = 72%

Test for overall effect: Z = 1.43 (P = 0.15)

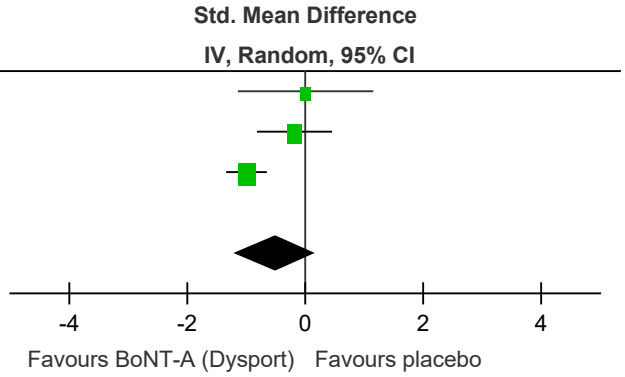


Figure 42: Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, final value) at >6 months

	Abobotulinum toxin A (Dysport)			Placebo			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
Prazeres 2018	1.4	1.04	20	1.9	0.67	20	-0.50 [-1.04, 0.04]

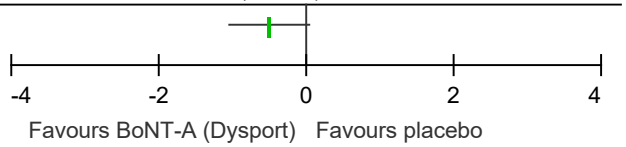


Figure 43: Physical function - upper limb (Rivermead motor assessment arm, scale range unclear, lower values are better, change score) at ≤6 months

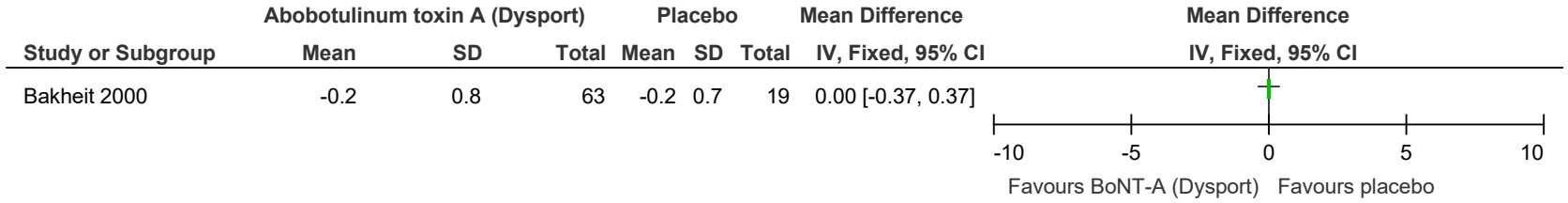


Figure 44: Physical function - lower limb (2 min walk test, meters, higher values are better, final value) at ≤6 months

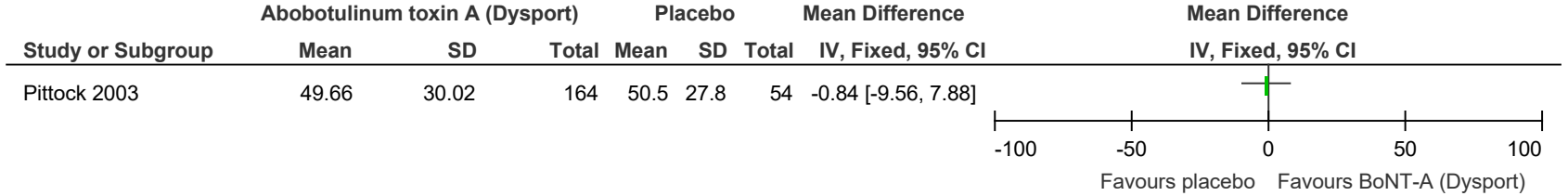


Figure 45: Pain (VAS, Global pain scale, 0-100, lower values are better, change score) at ≤6 months

	Abobotulinum toxin A (Dysport)			Placebo		Mean Difference	Mean Difference
Study or Subgroup	**Mean Difference**	**SE**	**Total**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
McCrory 2009	-10.1	8.31	54	42	14.1%	-10.10 [-26.39, 6.19]	
Rosales 2012	-7.15	3.3725	80	83	85.9%	-7.15 [-13.76, -0.54]	
Total (95% CI)			**134**	**125**	**100.0%**	**-7.57 [-13.69, -1.44]**	

Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%

Test for overall effect: Z = 2.42 (P = 0.02)

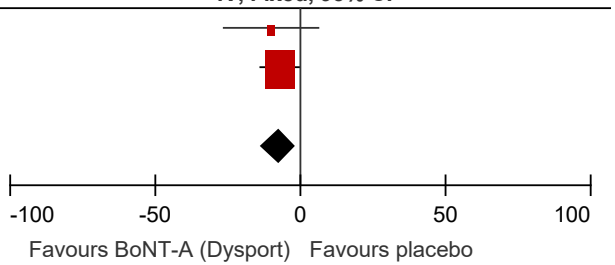


Figure 46: Activities of daily living (Barthel index, disability assessment scale [different scale ranges], higher values are better, change scores) at ≤6 months

	Abobotulinum toxin A (Dysport)			Placebo		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	**Std. Mean Difference**	**SE**	**Total**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
Bakheit 2000	-0.2659	0.2626	63	19	20.0%	-0.27 [-0.78, 0.25]	
Gracies 2015	0.2595	0.1382	159	79	42.3%	0.26 [-0.01, 0.53]	
Rosales 2012	0	0.1567	80	83	37.7%	0.00 [-0.31, 0.31]	
Total (95% CI)			**302**	**181**	**100.0%**	**0.06 [-0.21, 0.33]**	

Heterogeneity: Tau² = 0.03; Chi² = 3.67, df = 2 (P = 0.16); I² = 46%

Test for overall effect: Z = 0.41 (P = 0.68)

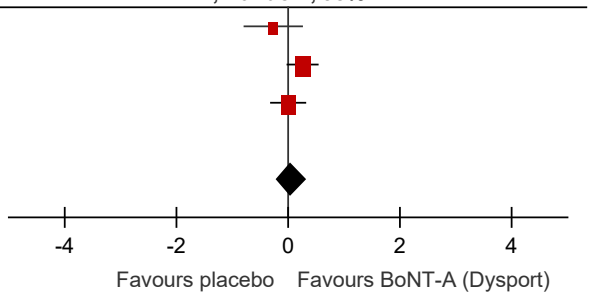


Figure 47: Stroke outcome - Modified Rankin scale (Modified Rankin scale, 0-6, higher values are better, change score) at ≤6 months

Study or Subgroup	Mean Difference	SE	Abobotulinum toxin A (Dysport) Total	Placebo Total	Mean Difference IV, Fixed, 95% CI
Rosales 2012	0.09	0.1173	80	83	0.09 [-0.14, 0.32]

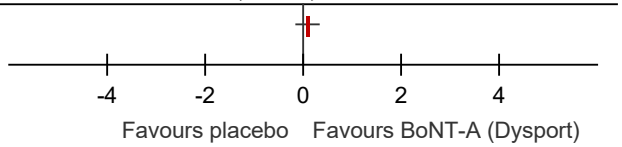
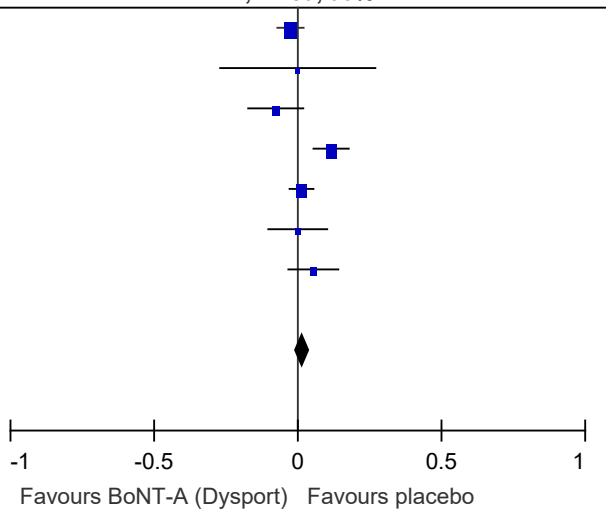


Figure 48: Withdrawal due to adverse events at ≤6 months

Study or Subgroup	Abobotulinum toxin A (Dysport) Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Gracies 2015	2	159	3	79	27.8%	-0.03 [-0.07, 0.02]
Hesse 1998	0	6	0	6	1.6%	0.00 [-0.27, 0.27]
McCrory 2009	1	54	4	42	12.4%	-0.08 [-0.17, 0.02]
Pittock 2003	24	179	1	55	22.1%	0.12 [0.05, 0.18]
Rosales 2012	2	80	1	83	21.4%	0.01 [-0.03, 0.05]
Rosales 2018	0	28	0	14	4.9%	0.00 [-0.10, 0.10]
Simpson 1996	2	37	0	37	9.7%	0.05 [-0.03, 0.14]
Total (95% CI)		**543**		**316**	**100.0%**	**0.02 [-0.01, 0.04]**
Total events	31		9			

Heterogeneity: Chi² = 17.91, df = 6 (P = 0.006); I² = 67%

Test for overall effect: Z = 1.27 (P = 0.20)



Abobotulinum toxin A (Dysport) compared to usual care

Figure 49: Person/participant generic health-related quality of life (EQ5D, -0.11-1, higher values are better, final value) at ≤6 months

	Abobotulinum toxin A (Dysport)			Usual care			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Shaw 2010	0.35	0.29	150	0.32	0.3	162	0.03 [-0.04, 0.10]	

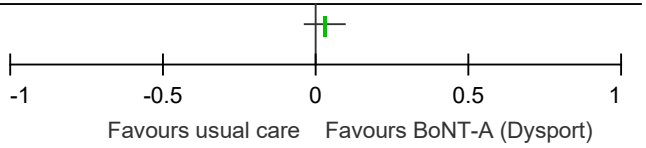


Figure 50: Person/participant generic health-related quality of life (EQ5D, -0.11-1, higher values are better, final value) at >6 months

	Abobotulinum toxin A (Dysport)			Usual care			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Shaw 2010	0.32	0.29	88	0.27	0.31	86	0.05 [-0.04, 0.14]	

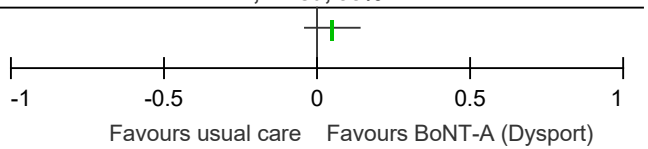


Figure 51: Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, final value) at ≤6 months

	Abobotulinum toxin A (Dysport)			Usual care			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Shaw 2010	-0.3	0.6465	163	-0.1	1.2438	151	-0.20 [-0.42, 0.02]	

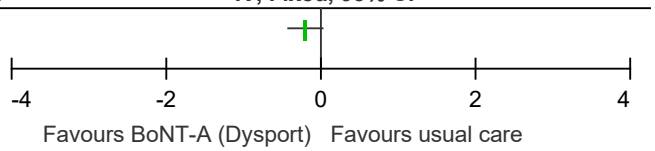


Figure 52: Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, final value) at >6 months

	Abobotulinum toxin A (Dysport)			Usual care			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Shaw 2010	-0.3	0.9657	92	-0.2	1.4885	97	-0.10 [-0.46, 0.26]	

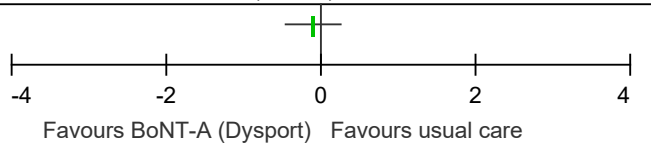


Figure 53: Physical function - upper limb (ARAT, 0-57, higher values are better, final values) at ≤6 months

	Abobotulinum toxin A (Dysport)			Usual care			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Shaw 2010	12.5	14.8702	163	11.4	13.6819	151	1.10 [-2.06, 4.26]	

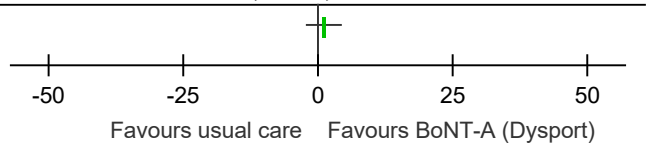


Figure 54: Physical function - upper limb (ARAT, 0-57, higher values are better, final value) at >6 months

	Abobotulinum toxin A (Dysport)			Usual care			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Shaw 2010	13.6	14.4862	92	11.9	14.3889	97	1.70 [-2.42, 5.82]	

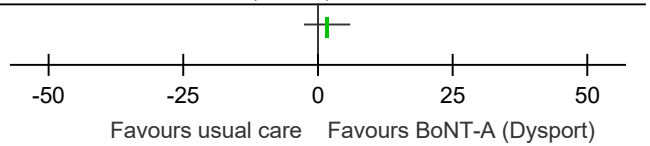


Figure 55: Pain (VAS, 0-10, lower values are better, final value) at ≤6 months

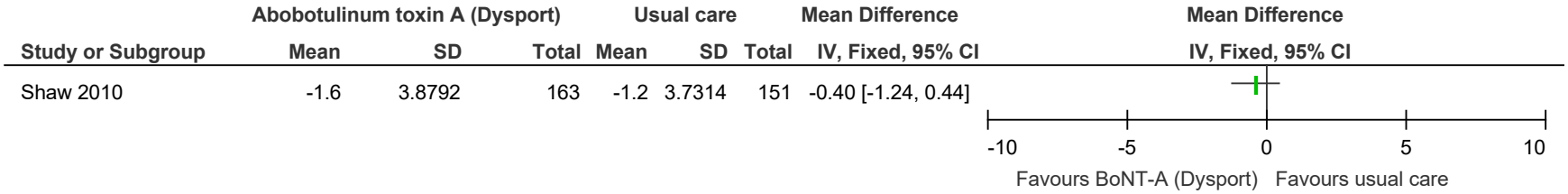


Figure 56: Pain (VAS, 0-10, lower values are better, final value) at >6 months

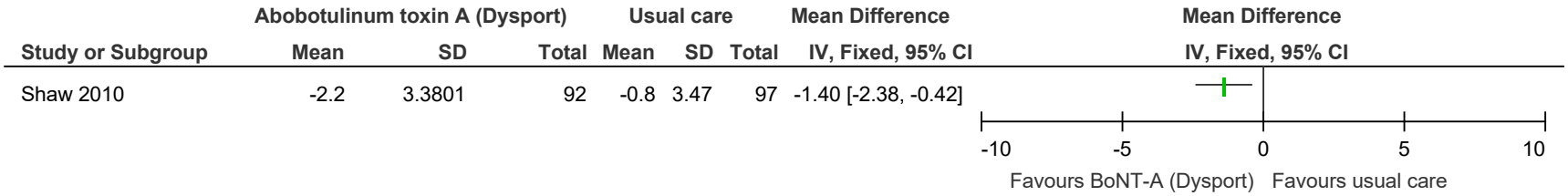


Figure 57: Activities of daily living (Barthel index, 0-100, higher values are better, final value) at ≤6 months

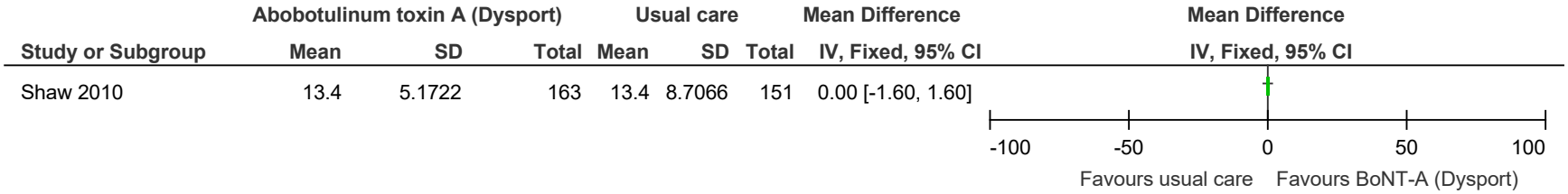


Figure 58: Activities of daily living (Barthel index, 0-100, higher values are better, final value) at >6 months

	Abobotulinum toxin A (Dysport)			Usual care			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Shaw 2010	13.4	4.8287	92	13.7	4.4655	97	-0.30 [-1.63, 1.03]	

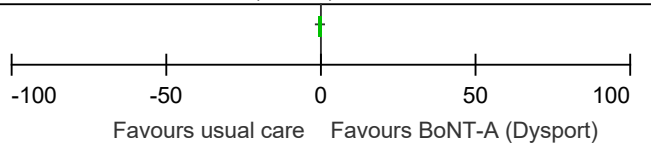


Figure 59: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Strength, 0-100, higher values are better, final values) at ≤6 months

	Abobotulinum toxin A (Dysport)			Usual care			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Shaw 2010	32.1	21.982	163	31.2	24.8761	151	0.90 [-4.31, 6.11]	

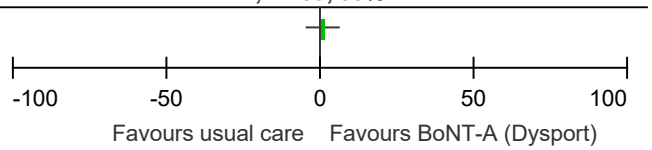


Figure 60: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Memory, 0-100, higher values are better, final values) at ≤6 months

	Abobotulinum toxin A (Dysport)			Usual care			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Shaw 2010	75.1	22.63	163	73.6	29.85	151	1.50 [-4.39, 7.39]	

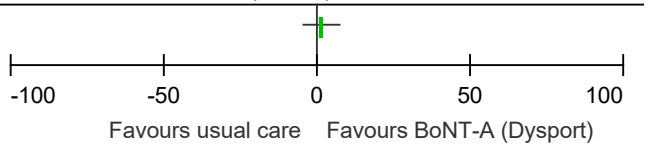


Figure 61: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Emotion, 0-100, higher values are better, final values) at ≤6 months

	Abobotulinum toxin A (Dysport)			Usual care			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Shaw 2010	63.9	17.4563	163	67.3	17.41	151	-3.40 [-7.26, 0.46]	

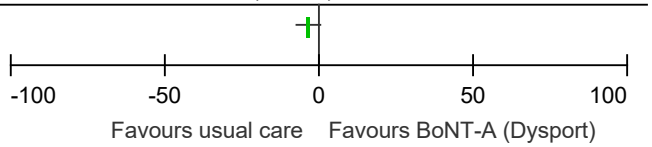


Figure 62: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Communication, 0-100, higher values are better, final values) at ≤6 months

	Abobotulinum toxin A (Dysport)			Usual care			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Shaw 2010	79.5	25.8612	163	76.4	28.6075	151	3.10 [-2.95, 9.15]	

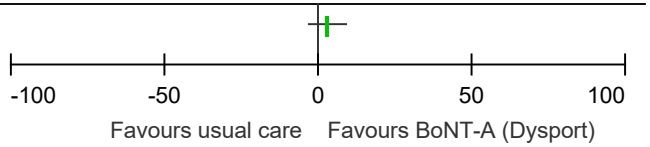


Figure 63: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - ADL, 0-100, higher values are better, final values) at ≤6 months

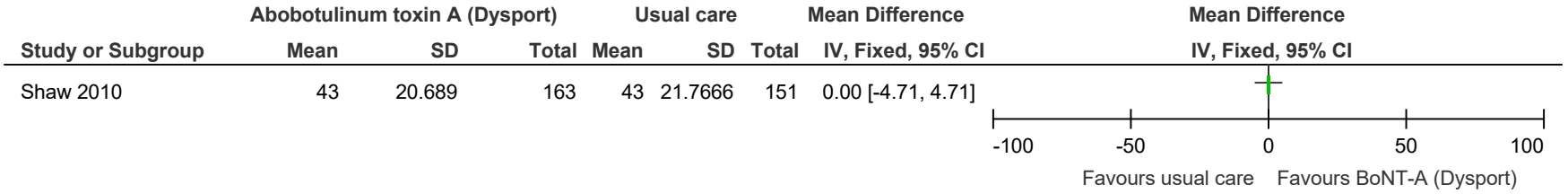


Figure 64: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Mobility, 0-100, higher values are better, final values) at ≤6 months

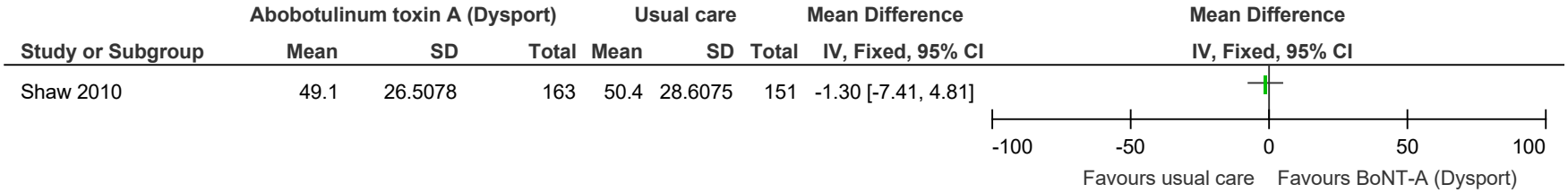


Figure 65: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Hand function, 0-100, higher values are better, final values) at ≤6 months

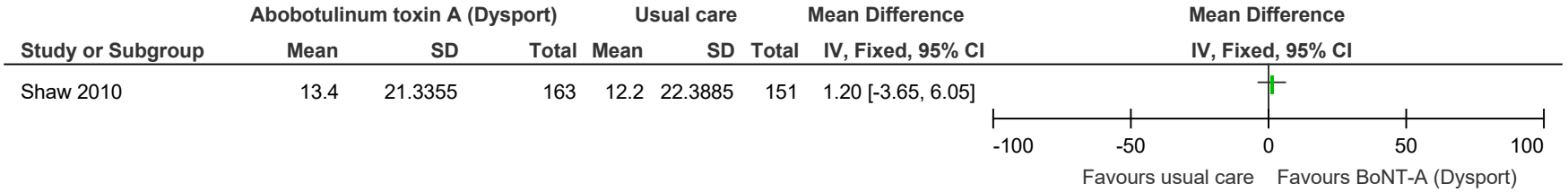


Figure 66: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Participation/handicap, 0-100, higher values are better, final values) at ≤6 months

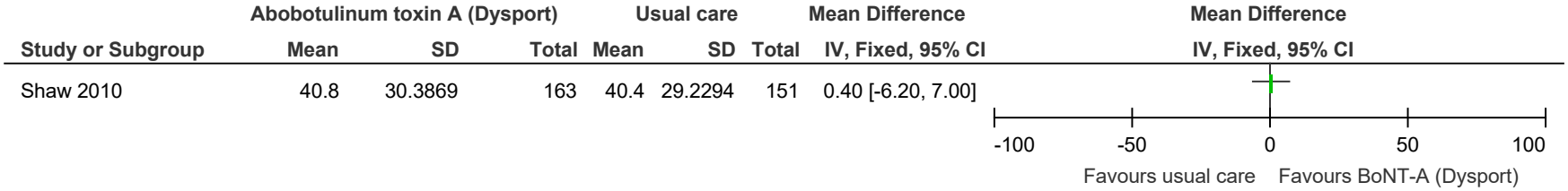


Figure 67: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Physical domains, 0-100, higher values are better, final values) at ≤6 months

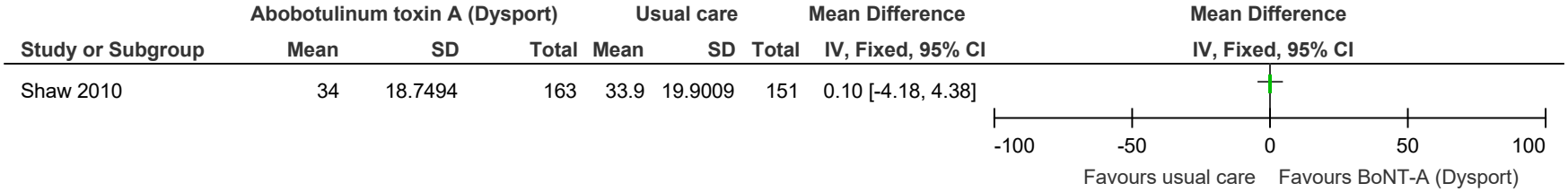


Figure 68: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Stroke recovery, 0-100, higher values are better, final values) at ≤6 months

	Abobotulinum toxin A (Dysport)			Usual care			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Shaw 2010	43.5	20.689	163	43.8	22.3885	151	-0.30 [-5.08, 4.48]	

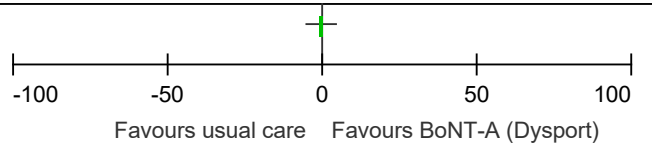


Figure 69: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Strength, 0-100, higher values are better, final values) at >6 months

	Abobotulinum toxin A (Dysport)			Usual care			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Shaw 2010	31.5	27.1543	92	29.7	26.1199	97	1.80 [-5.80, 9.40]	

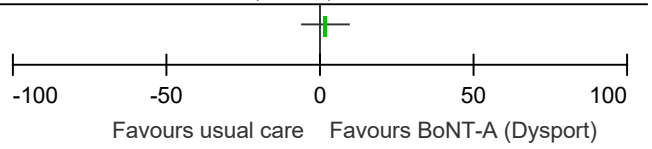


Figure 70: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Memory, 0-100, higher values are better, final values) at >6 months

	Abobotulinum toxin A (Dysport)			Usual care			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Shaw 2010	75	30.3869	92	71.1	32.9608	97	3.90 [-5.13, 12.93]	

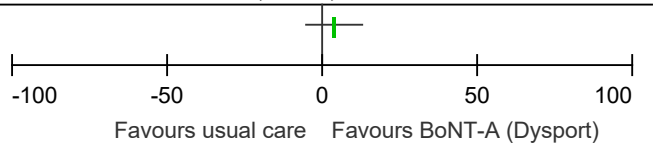


Figure 71: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Emotion, 0-100, higher values are better, final values) at >6 months

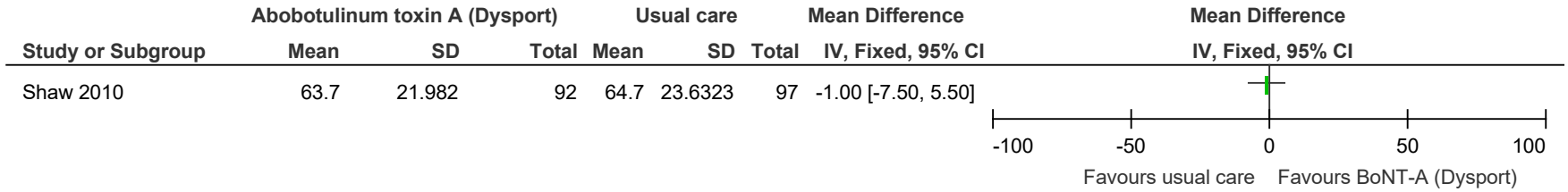


Figure 72: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Communication, 0-100, higher values are better, final values) at >6 months

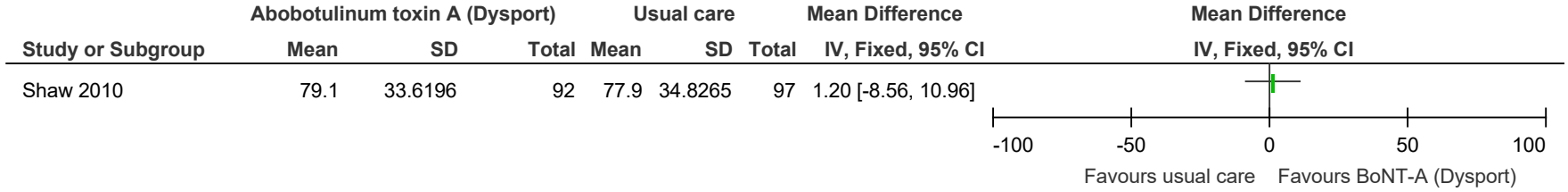


Figure 73: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - ADL, 0-100, higher values are better, final values) at >6 months

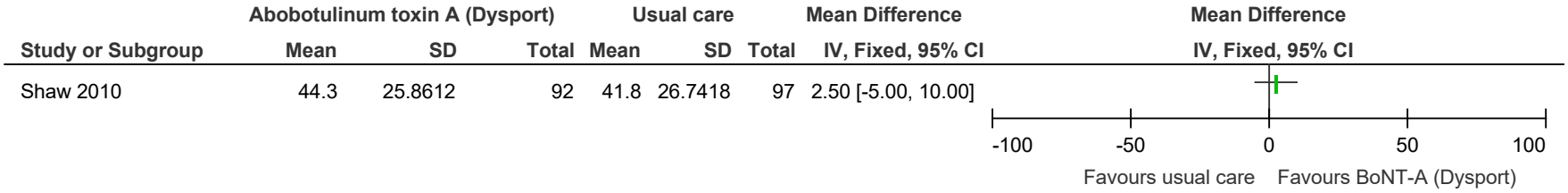


Figure 74: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Mobility, 0-100, higher values are better, final values) at >6 months

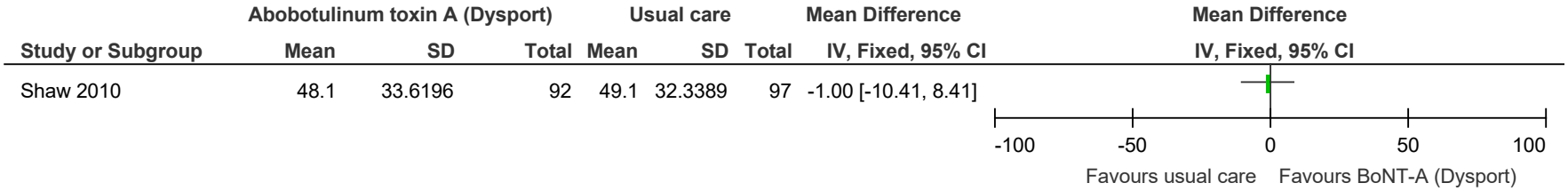


Figure 75: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Hand function, 0-100, higher values are better, final values) at >6 months

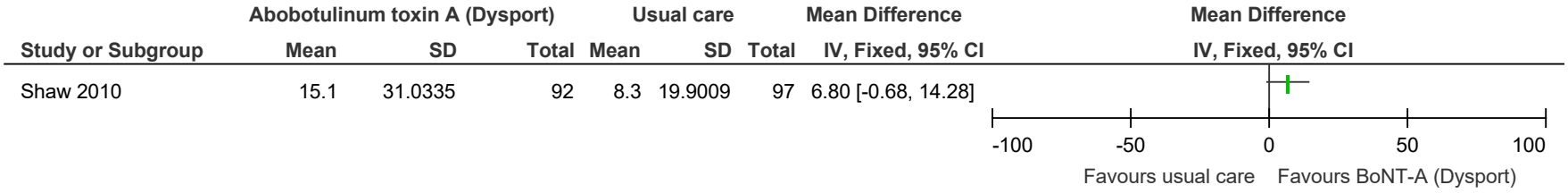


Figure 76: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Participation/handicap, 0-100, higher values are better, final values) at >6 months

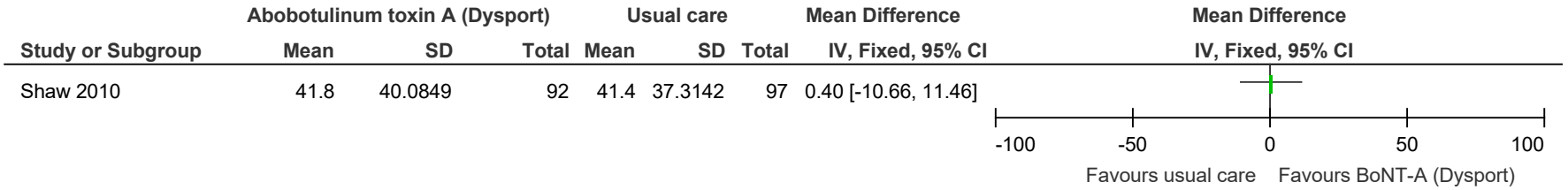


Figure 77: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Physical domains, 0-100, higher values are better, final values) at >6 months

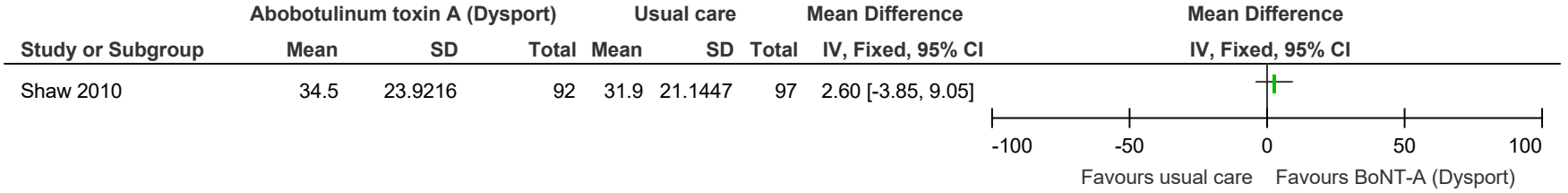
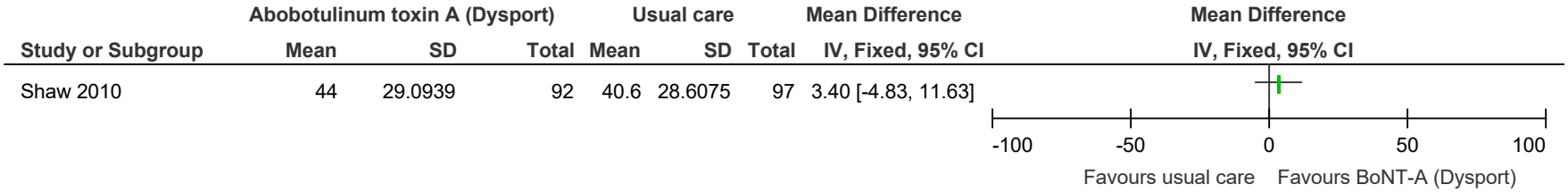


Figure 78: Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Stroke recovery, 0-100, higher values are better, final values) at >6 months



Incobotulinum toxin A (Xeomin) compared to oral baclofen

Figure 79: Person/participant generic health-related quality of life (Romanian version of the general instrument 15D, 0-1, higher values are better, final value) at ≤6 months

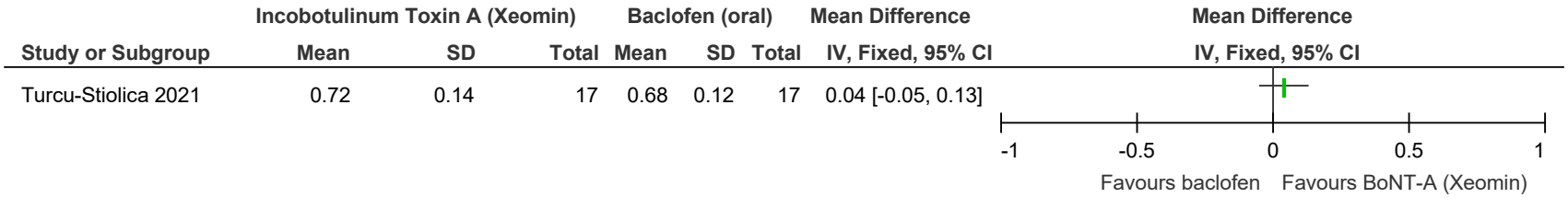


Figure 80: Spasticity outcome measures (Tardieu scale, 0-4, lower values are better, final value) at ≤6 months

	Incobotulinum Toxin A (Xeomin)			Baclofen (oral)			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Turcu-Stiolica 2021	2.18	0.81	17	2.21	0.64	17	-0.03 [-0.52, 0.46]	

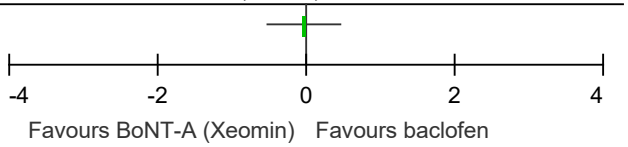


Figure 81: Physical function - upper limb (muscle strength, 0-5, higher values are better, final value) at ≤6 months

	Incobotulinum Toxin A (Xeomin)			Baclofen (oral)			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Turcu-Stiolica 2021	3	0.1	17	2.74	0.75	17	0.26 [-0.10, 0.62]	

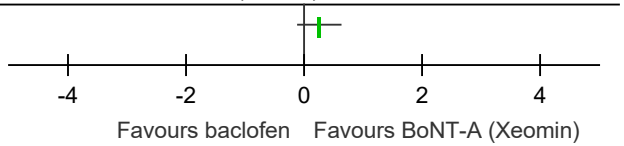
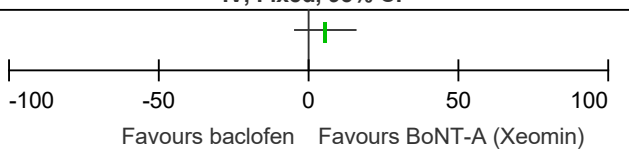


Figure 82: Activities of daily living (Barthel Index, 0-100, higher values are better, final value) at ≤6 months

	Incobotulinum Toxin A (Xeomin)			Baclofen (oral)			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Turcu-Stiolica 2021	52.94	11.6	17	47.35	17.81	17	5.59 [-4.51, 15.69]	



Incobotulinum toxin A (Xeomin) compared to placebo

Figure 83: Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, change scores) at ≤6 months

	Incobotulinum toxin A (Xeomin)			Placebo				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
Elovic 2016	-0.9	0.06	171	-0.5	0.08	88	50.1%	-0.40 [-0.42, -0.38]
Masakado 2022	-0.6	0.1	104	-0.4	0.1	104	49.9%	-0.20 [-0.23, -0.17]
Total (95% CI)			**275**			**192**	**100.0%**	**-0.30 [-0.50, -0.10]**

Heterogeneity: Tau² = 0.02; Chi² = 139.82, df = 1 (P < 0.00001); I² = 99%

Test for overall effect: Z = 3.00 (P = 0.003)

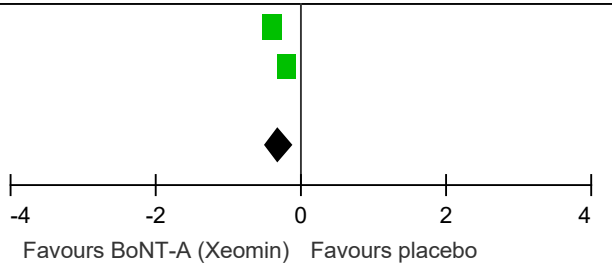


Figure 84: Physical function - lower limb (10 meter walk test, seconds, lower values are better, change score) at ≤6 months

	Incobotulinum toxin A (Xeomin)			Placebo			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
Masakado 2022	-1.2	10.4766	56	0.7	10.8444	60	-1.90 [-5.78, 1.98]

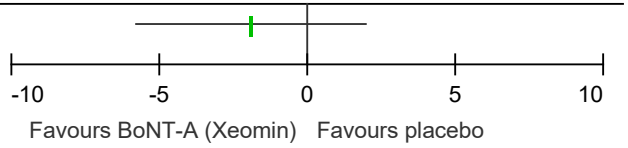


Figure 85: Pain (Ankle pain score, scale range unclear, lower values are better, change score) at ≤6 months

	Incobotulinum toxin A (Xeomin)			Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Masakado 2022	-0.6	2.0396	104	-0.5	2.0396	104	-0.10 [-0.65, 0.45]	

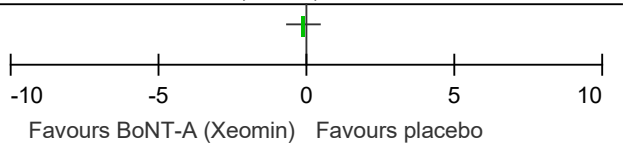


Figure 86: Withdrawal due to adverse events at ≤6 months

	Incobotulinum toxin A (Xeomin)		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Kanovsky 2009	1	73	1	75	11.8%	1.03 [0.07, 16.12]	
Masakado 2020	2	67	4	33	64.2%	0.25 [0.05, 1.28]	
Masakado 2022	1	104	2	104	24.0%	0.50 [0.05, 5.43]	
Total (95% CI)		**244**		**212**	**100.0%**	**0.40 [0.12, 1.29]**	
Total events	4		7				

Heterogeneity: Chi² = 0.82, df = 2 (P = 0.66); I² = 0%

Test for overall effect: Z = 1.54 (P = 0.12)

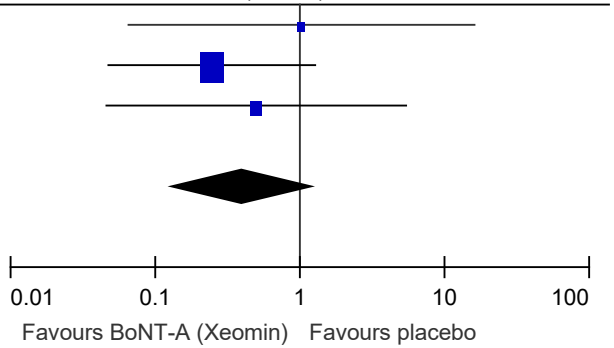
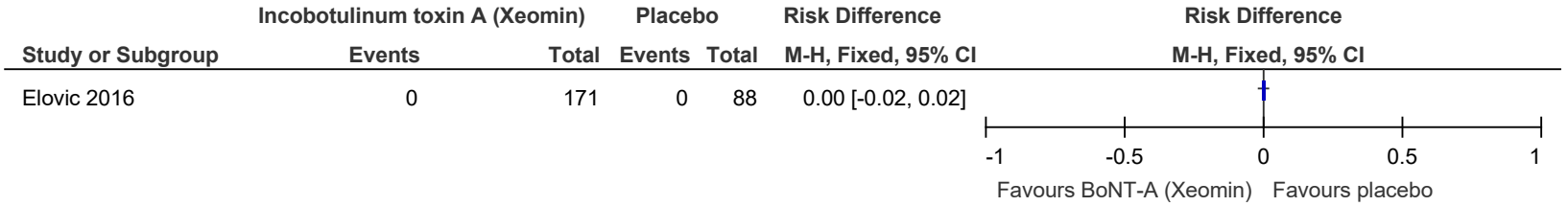


Figure 87: Withdrawal due to adverse events at >6 months



Incobotulinum toxin A (Xeomin) compared to usual care

Figure 88: Spasticity outcome measures (Modified Ashworth scale, 0-5, lower values are better, change score and final value) at ≤6 months

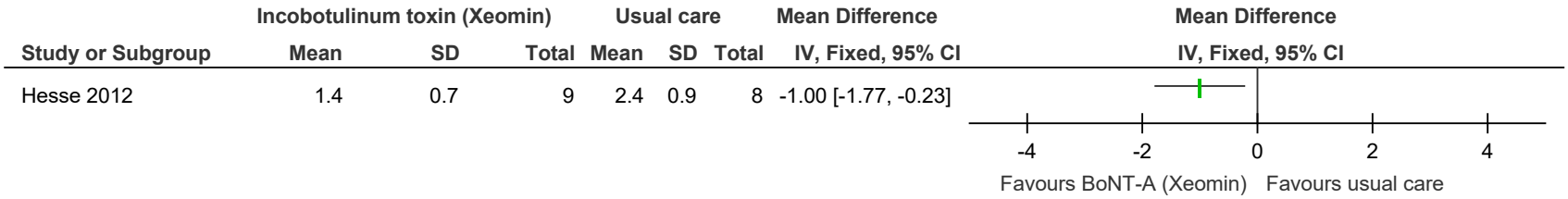


Figure 89: Physical function - upper limb (Fugl-Meyer score, 0-66, higher values are better, final value) at ≤6 months

	Incobotulinum toxin (Xeomin)			Usual care			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Hesse 2012	13.1	4.9	9	12.8	5.8	8	0.30 [-4.84, 5.44]	

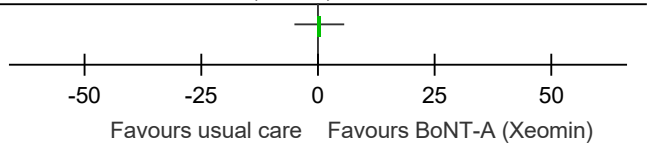


Figure 90: Activities of daily living (disability scale, 0-24, lower values are better, final value) at ≤6 months

	Incobotulinum toxin (Xeomin)			Usual care			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Hesse 2012	5.7	3.2	9	10.9	4.4	8	-5.20 [-8.90, -1.50]	

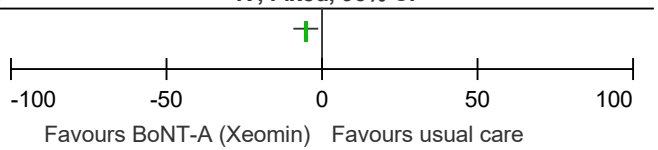
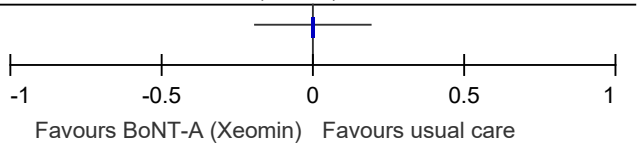


Figure 91: Withdrawal due to adverse events at ≤6 months

	Incobotulinum toxin (Xeomin)		Usual care		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Hesse 2012	0	9	0	9	0.00 [-0.19, 0.19]	



Functional electrical stimulation compared to placebo

Figure 92: Spasticity outcome measures (Composite spasticity scale, 0-100, lower values are better, final value) at ≤6 months

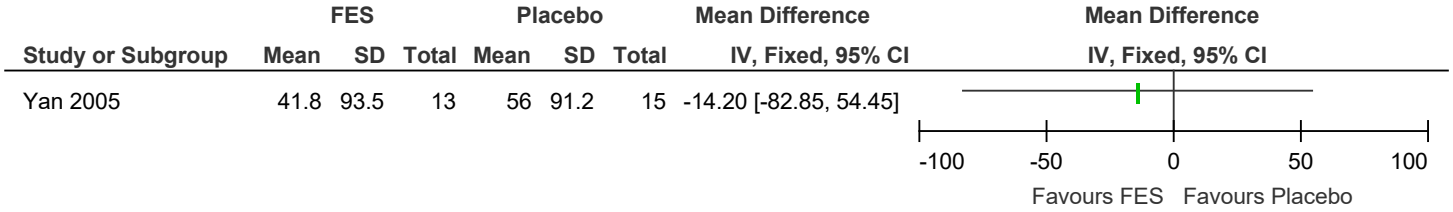


Figure 93: Physical function - lower limb (Timed up and go, seconds, lower values are better, final value) at ≤6 months

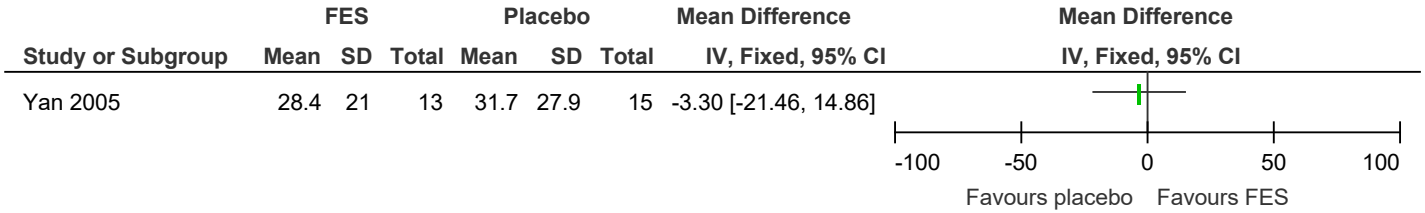


Figure 94: Physical function - lower limb (walking speed, m/s, higher values are better, change score) at ≤6 months

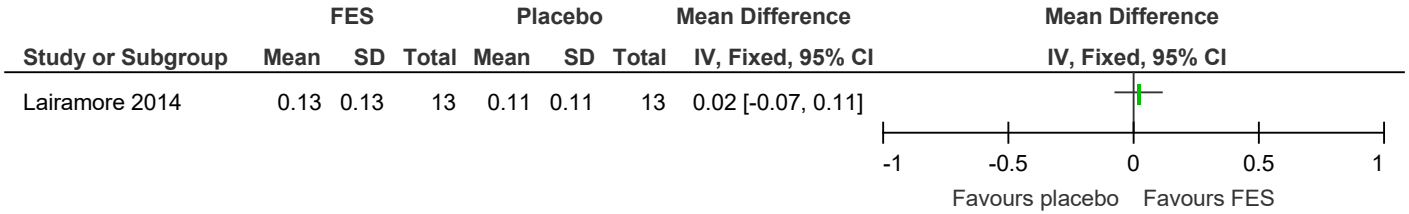


Figure 95: Activities of daily living (FIM, 1-7, higher values are better, final value) at ≤6 months

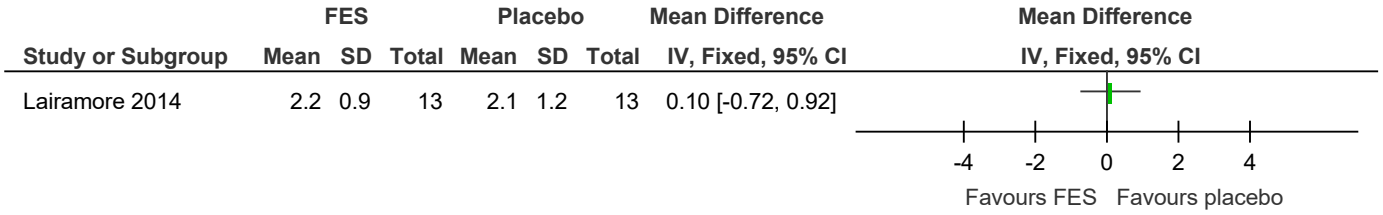
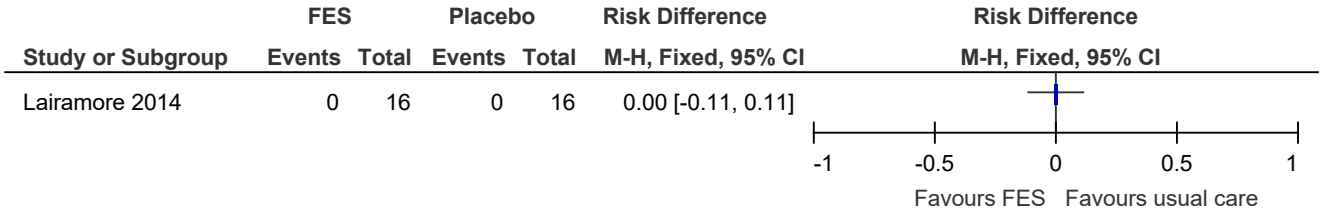


Figure 96: Withdrawal due to adverse events at ≤6 months



Functional electrical stimulation compared to usual care

Figure 97: Spasticity outcome measures (Modified Ashworth scale, Composite spasticity scale [different scale ranges], lower values are better, final values) at ≤6 months

	FES			Usual care				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Sabut 2010	1.8	0.64	27	2.1	0.64	24	52.6%	-0.46 [-1.02, 0.10]
You 2014	10.9	1.8	19	13.1	0.6	18	47.4%	-1.59 [-2.34, -0.84]
Total (95% CI)			**46**			**42**	**100.0%**	**-0.99 [-2.10, 0.11]**

Heterogeneity: Tau² = 0.52; Chi² = 5.57, df = 1 (P = 0.02); I² = 82%

Test for overall effect: Z = 1.77 (P = 0.08)

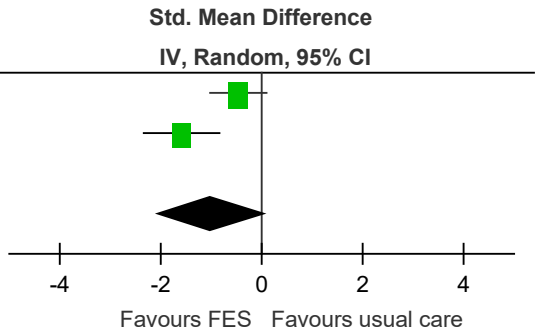


Figure 98: Spasticity outcome measures (Composite spasticity scale, %, 0-100, lower values are better, change score) at ≤6 months

	FES			Usual care			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Yan 2005	41.8	93.5	13	78.6	64.7	13	-36.80 [-98.61, 25.01]

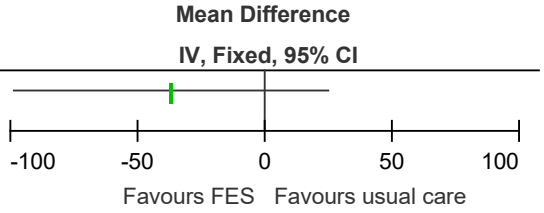


Figure 99: Physical function - upper limb (Rivermead motor assessment hand, 0-13, higher values are better, final value) at ≤6 months

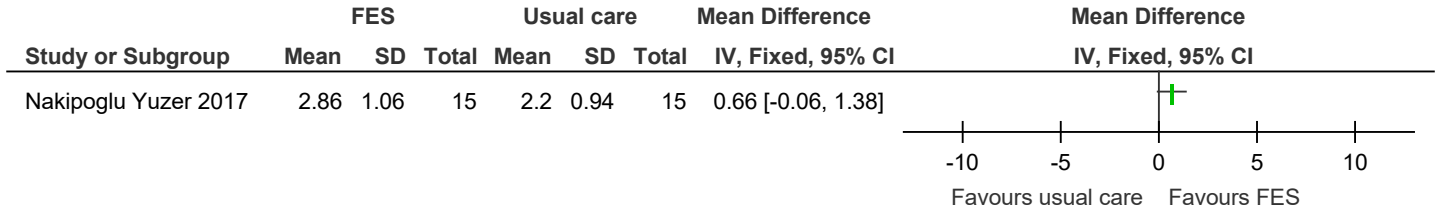


Figure 100: Physical function - lower limb (Berg Balance Scale, FMA-LE [different scale ranges], higher values are better, final values) at ≤6 months

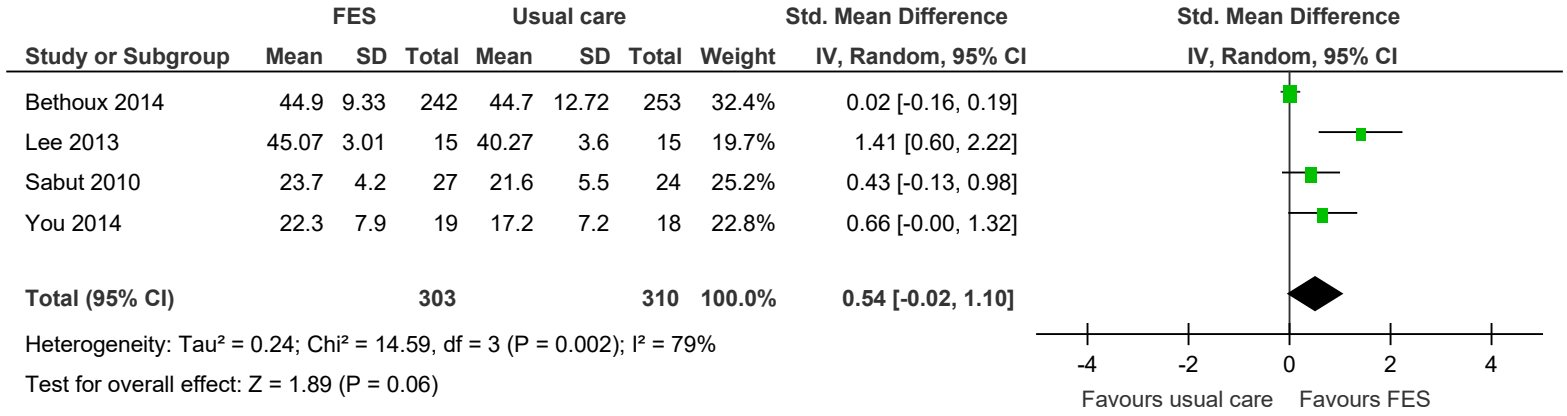


Figure 101: Physical function - lower limb (6 min walk, meters, higher values are better, final value) at ≤6 months

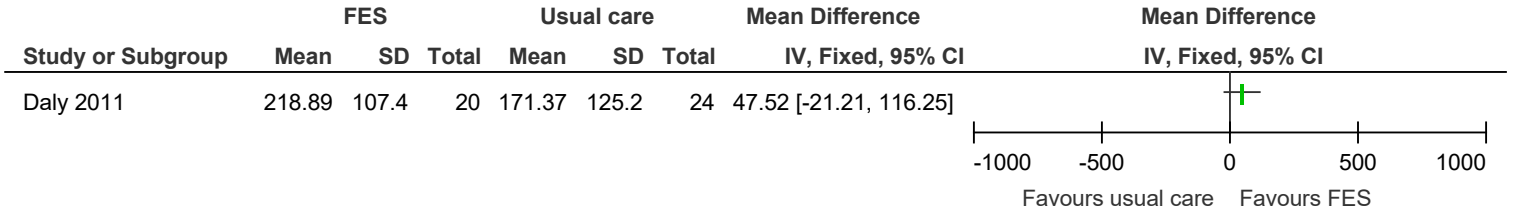


Figure 102: Physical function - lower limb (timed up and go, seconds, lower values are better, final value) at ≤6 months

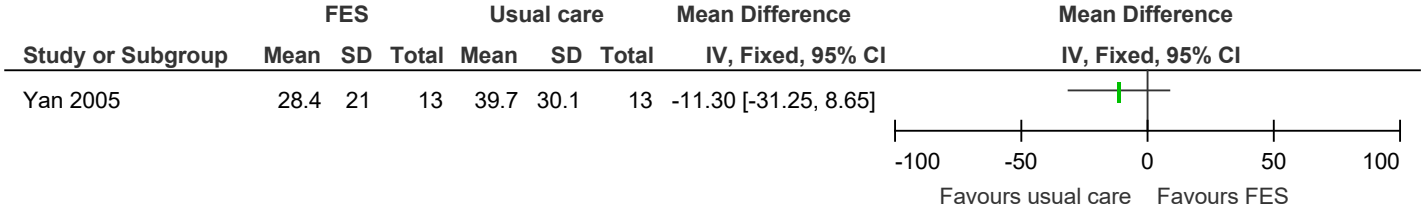


Figure 103: Activities of daily living (Barthel index, 0-100, higher values are better, final values) at ≤6 months

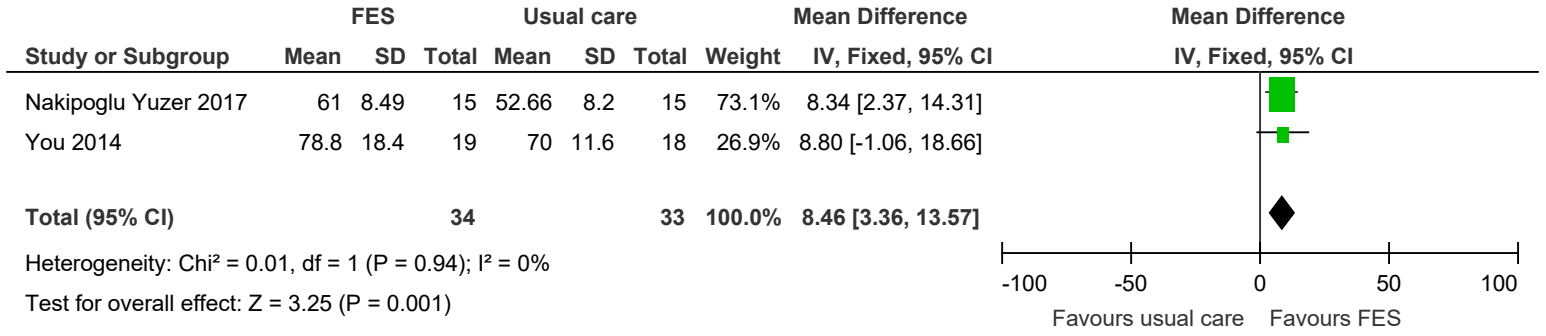


Figure 104: Stroke-specific Patient-Reported Outcome Measures (Stroke-Specific Quality of Life, 49-245, higher values are better, final values) at ≤6 months

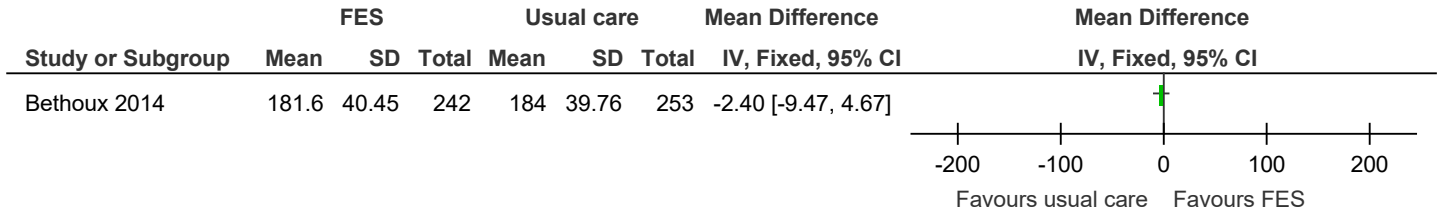
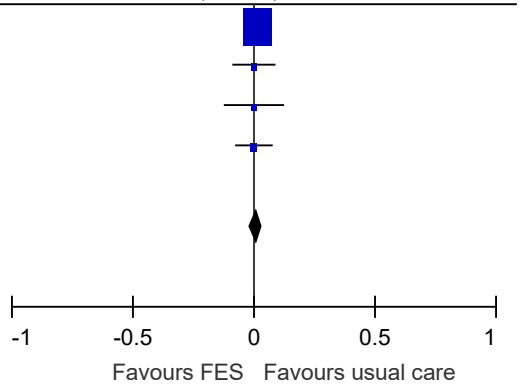


Figure 105: Withdrawal due to adverse events at ≤6 months

Study or Subgroup	FES Events	FES Total	Usual care Events	Usual care Total	Weight	Risk Difference M-H, Fixed, 95% CI
Bethoux 2014	9	242	6	253	79.9%	0.01 [-0.02, 0.04]
Daly 2011	0	20	0	24	7.0%	0.00 [-0.09, 0.09]
Lee 2013	0	15	0	15	4.8%	0.00 [-0.12, 0.12]
Sabut 2010	0	27	0	24	8.2%	0.00 [-0.07, 0.07]
Total (95% CI)		**304**		**316**	**100.0%**	**0.01 [-0.02, 0.04]**
Total events	9		6			

Heterogeneity: Chi² = 0.20, df = 3 (P = 0.98); I² = 0%

Test for overall effect: Z = 0.79 (P = 0.43)



Neuromuscular electrical stimulation compared to transcutaneous electrical nerve stimulation

Figure 106: Spasticity outcome measures measure (modified Ashworth scale, 0-6, lower values are better, change score) at ≤6 months

Study or Subgroup	NMES Mean	NMES SD	NMES Total	TENS Mean	TENS SD	TENS Total	Mean Difference IV, Fixed, 95% CI
Zhou 2018	0.24	3.05	36	0.16	0.43	36	0.08 [-0.93, 1.09]

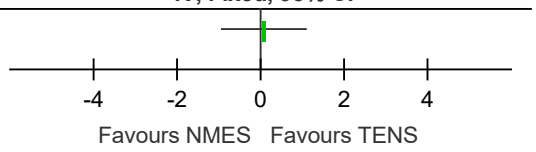


Figure 107: Physical function - upper limb (Fugl-meyer- Upper limb, 0-66, higher values are better, change score) at ≤6 months

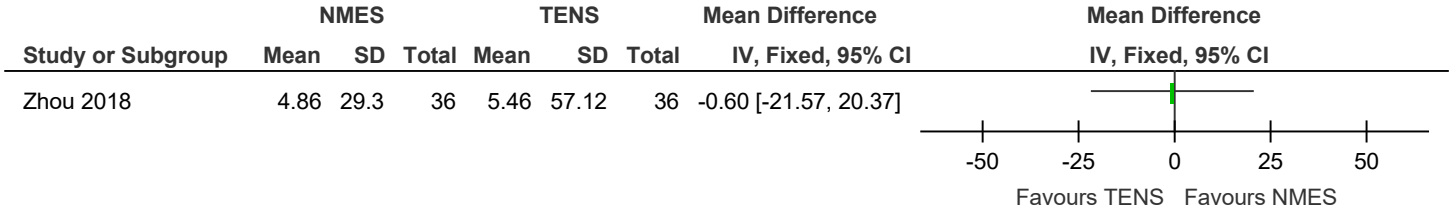


Figure 108: Pain (Numeric rating scale, 0-10, lower values are better, change score) at ≤6 months

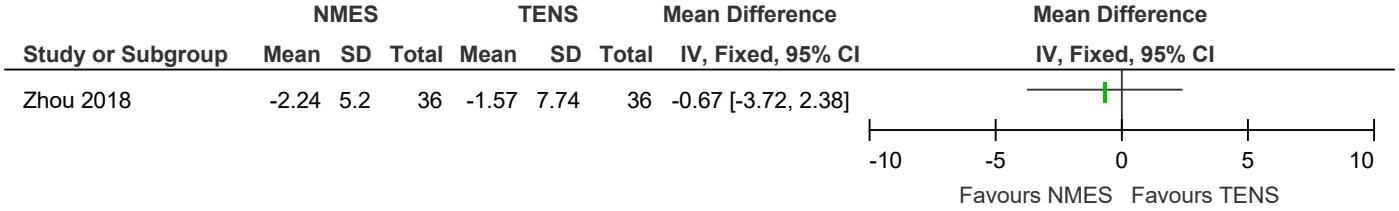


Figure 109: Activities of daily living (Barthel index, 0-100, higher values are better, change score) at ≤6 months

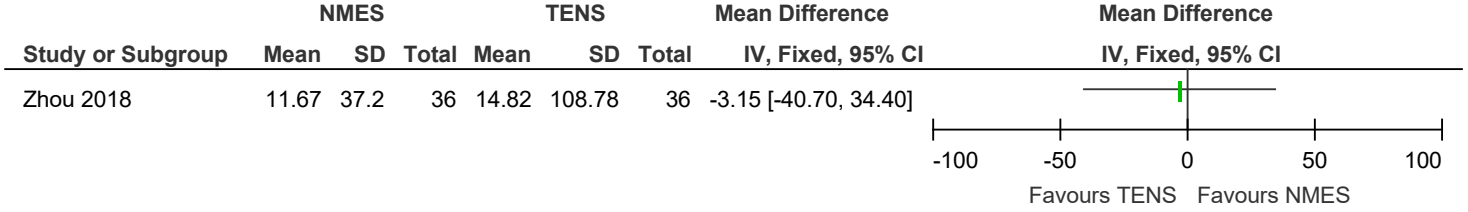


Figure 110: Stroke-specific Patient-Reported Outcome Measures (SS-QOL, 49-245, higher values are better, change score) at ≤6 months

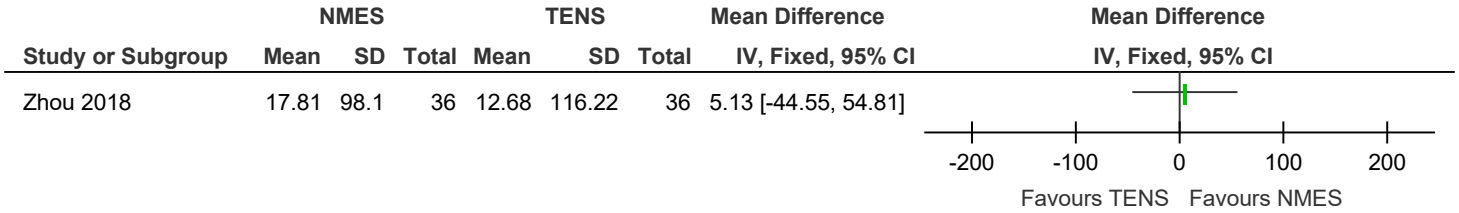
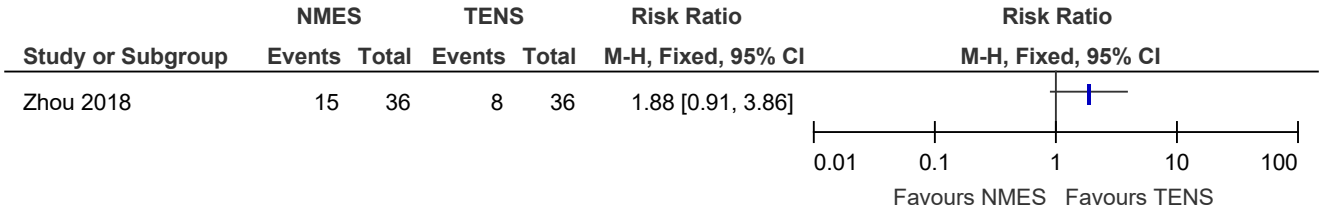


Figure 111: Withdrawal due to adverse events at ≤6 months



Neuromuscular electrical stimulation compared to placebo

Figure 112: Spasticity outcome measures (Modified Ashworth scale, Leeds adult/arm spasticity impact scale [different scale ranges], lower values are better, final values) at ≤6 months

	NMES			Placebo				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Boyaci 2013	1.24	0.96	20	1.05	1.12	10	25.6%	0.18 [-0.58, 0.94]
De Jong 2013	-68.6	17.6	17	-66.7	20.7	22	36.9%	-0.10 [-0.73, 0.54]
Lee 2015	0.62	0.69	20	0.69	0.78	19	37.5%	-0.09 [-0.72, 0.54]
Total (95% CI)			**57**			**51**	**100.0%**	**-0.02 [-0.41, 0.36]**

Heterogeneity: Chi² = 0.38, df = 2 (P = 0.83); I² = 0%

Test for overall effect: Z = 0.12 (P = 0.90)

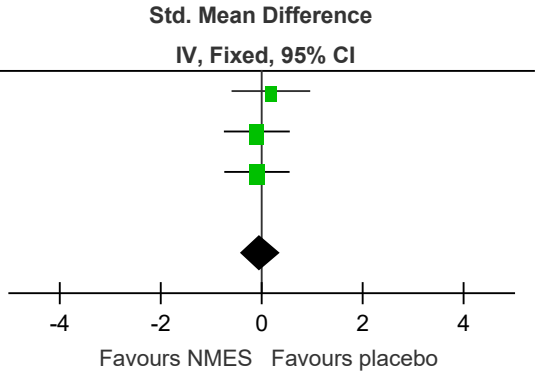


Figure 113: Physical function - upper limb (Fugl Meyer Assessment - Upper Extremity, 0-66, higher values are better, final values) at ≤6 months

	NMES			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Boyaci 2013	38.54	15.48	20	34.7	20.17	10	10.8%	3.84 [-10.38, 18.06]
De Jong 2013	21.6	16.1	17	21.7	16.1	22	21.0%	-0.10 [-10.29, 10.09]
Lee 2015	32.9	8.75	20	29.21	9.25	19	68.2%	3.69 [-1.97, 9.35]
Total (95% CI)			**57**			**51**	**100.0%**	**2.91 [-1.76, 7.58]**

Heterogeneity: Chi² = 0.42, df = 2 (P = 0.81); I² = 0%

Test for overall effect: Z = 1.22 (P = 0.22)

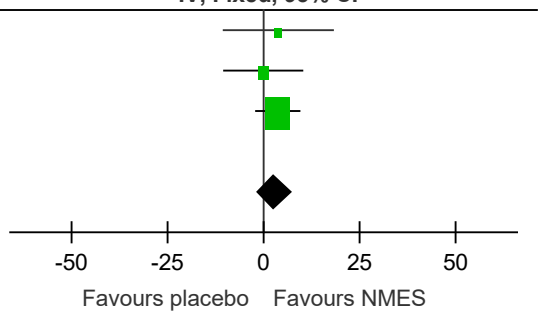


Figure 114: Pain (Visual analogue scale, 0-10, lower values are better, final value) at ≤6 months

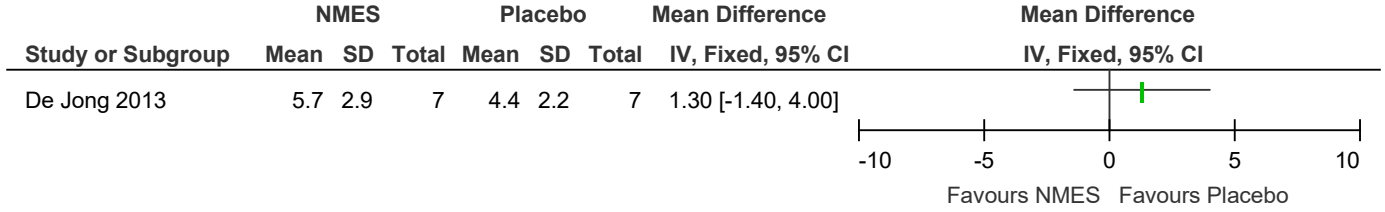


Figure 115: Activities of daily living (Functional Independence Measure Self-Care subscale, 0-100, higher values are better, final value) at ≤6 months

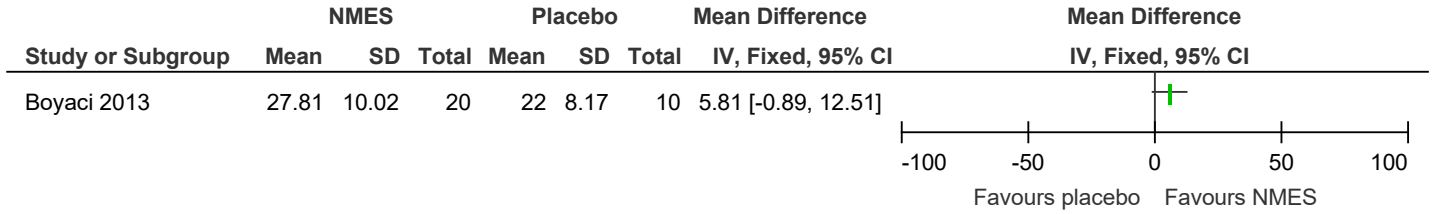


Figure 116: Stroke-specific Patient-Reported Outcome Measures (Stroke impact scale, 0-100, higher values are better, final value) at ≤6 months

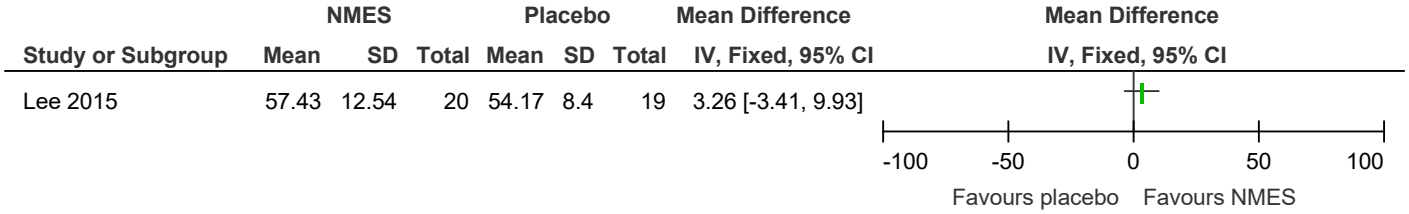


Figure 117: Additional health care contacts (prescription of spasticity medication) at ≤6 months

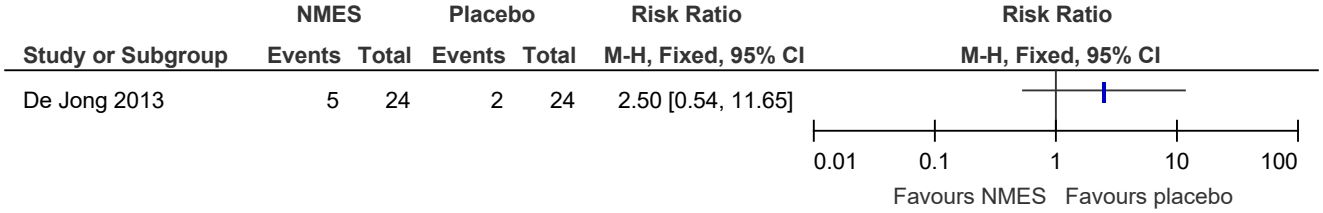


Figure 118: Additional health care contacts (prescription of pain medication) at ≤6 months

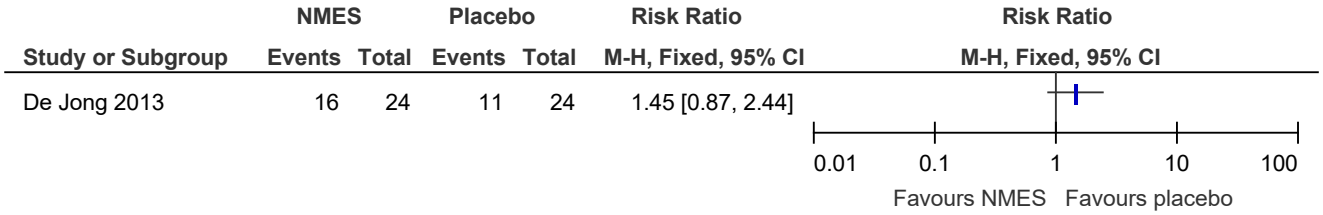


Figure 119: Hospitalisation at ≤6 months

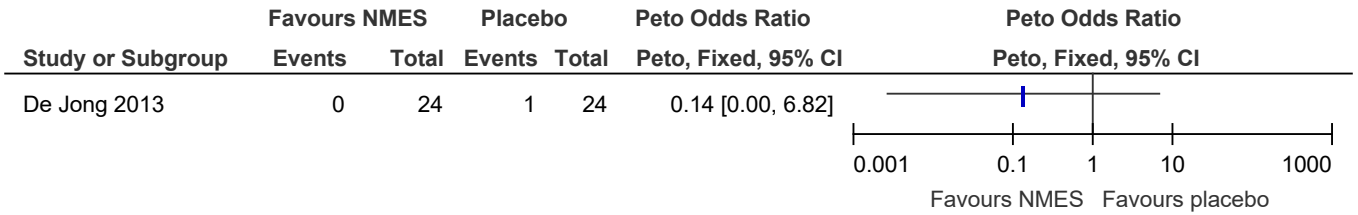
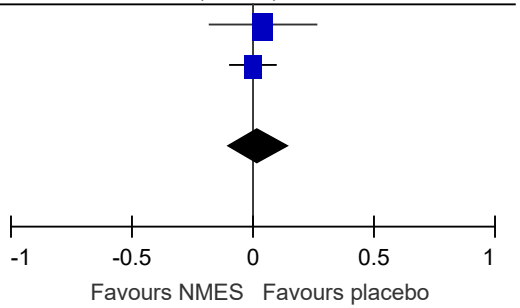


Figure 120: Withdrawal due to adverse events at ≤6 months

	NMES		Placebo			Risk Difference	Risk Difference
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
De Jong 2013	5	24	4	24	55.2%	0.04 [-0.18, 0.26]	
Lee 2015	0	20	0	19	44.8%	0.00 [-0.09, 0.09]	
Total (95% CI)		**44**		**43**	**100.0%**	**0.02 [-0.11, 0.15]**	
Total events	5		4				

Heterogeneity: Chi² = 0.25, df = 1 (P = 0.61); I² = 0%

Test for overall effect: Z = 0.35 (P = 0.73)



Neuromuscular electrical stimulation compared to usual care

Figure 121: Spasticity outcome measures (modified Ashworth scale [different scale ranges], lower values are better, change score) at ≤6 months

	NMES			Usual care				Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
Bakhtiary 2008	-1.6	0.5	20	-1.1	0.31	20	33.2%	-1.18 [-1.85, -0.50]
Mesci 2009	-1.2	0.5	20	-0.15	0.6	20	32.3%	-1.86 [-2.62, -1.11]
Zhou 2018	0.24	3.05	36	0	1.22	18	34.4%	0.09 [-0.48, 0.66]
Total (95% CI)			**76**			**58**	**100.0%**	**-0.96 [-2.12, 0.20]**

Heterogeneity: Tau² = 0.93; Chi² = 18.35, df = 2 (P = 0.0001); I² = 89%

Test for overall effect: Z = 1.63 (P = 0.10)

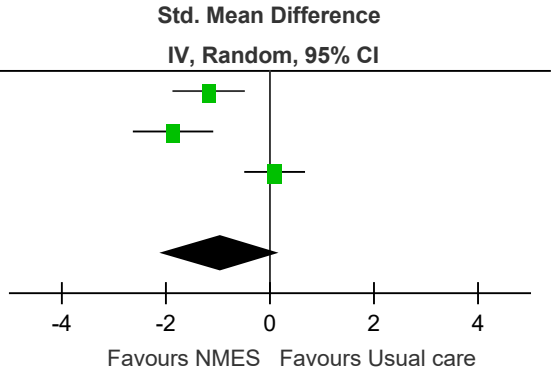


Figure 122: Spasticity outcome measures (modified Ashworth scale, composite spasticity scale [different scale ranges], lower values are better, final values) at ≤6 months

	NMES			Usual care				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Hu 2015	0.8	0.55	11	0.8	0.54	15	10.1%	0.00 [-0.78, 0.78]
Huang 2020	0.54	0.7	15	1.19	1.03	15	11.1%	-0.72 [-1.46, 0.02]
Lin 2011	1.67	0.52	19	1.86	0.38	18	14.3%	-0.41 [-1.06, 0.25]
Sentandreu-Mano 2021	1.01	0.79	41	1.28	0.76	20	21.0%	-0.34 [-0.88, 0.20]
Wang 2016	9.48	1.43	50	9.81	0.98	16	19.1%	-0.24 [-0.81, 0.32]
Yang 2018	1.61	0.32	17	1.5	0.1	8	8.5%	0.39 [-0.46, 1.24]
Yun 2011	0.7	0.5	20	0.7	0.5	20	15.9%	0.00 [-0.62, 0.62]
Total (95% CI)			**173**			**112**	**100.0%**	**-0.22 [-0.47, 0.02]**

Heterogeneity: Chi² = 5.03, df = 6 (P = 0.54); I² = 0%

Test for overall effect: Z = 1.77 (P = 0.08)

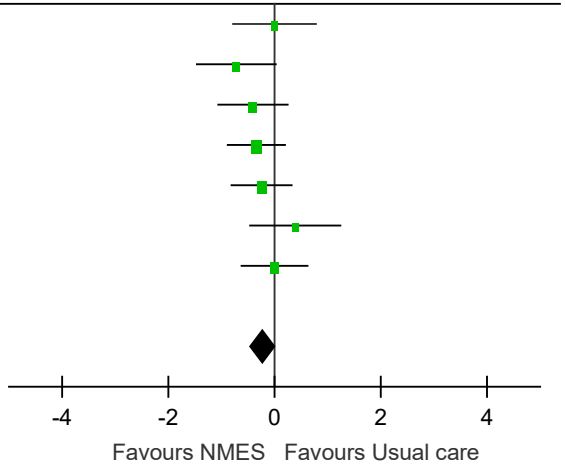


Figure 123: Physical function - upper limb (Fugl-meyer UE, 0-66, higher values are better, change scores) at ≤6 months

	NMES			Usual care			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Zhou 2018	4.86	29.3	36	5.31	44.1	18	-0.45 [-22.96, 22.06]

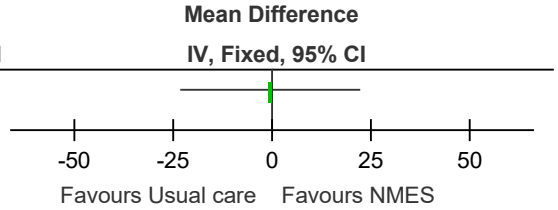


Figure 124: Physical function - upper limb (FMA shoulder/elbow, UE, FIM, Box and block test [different scale ranges], higher values are better, final values) at ≤6 months

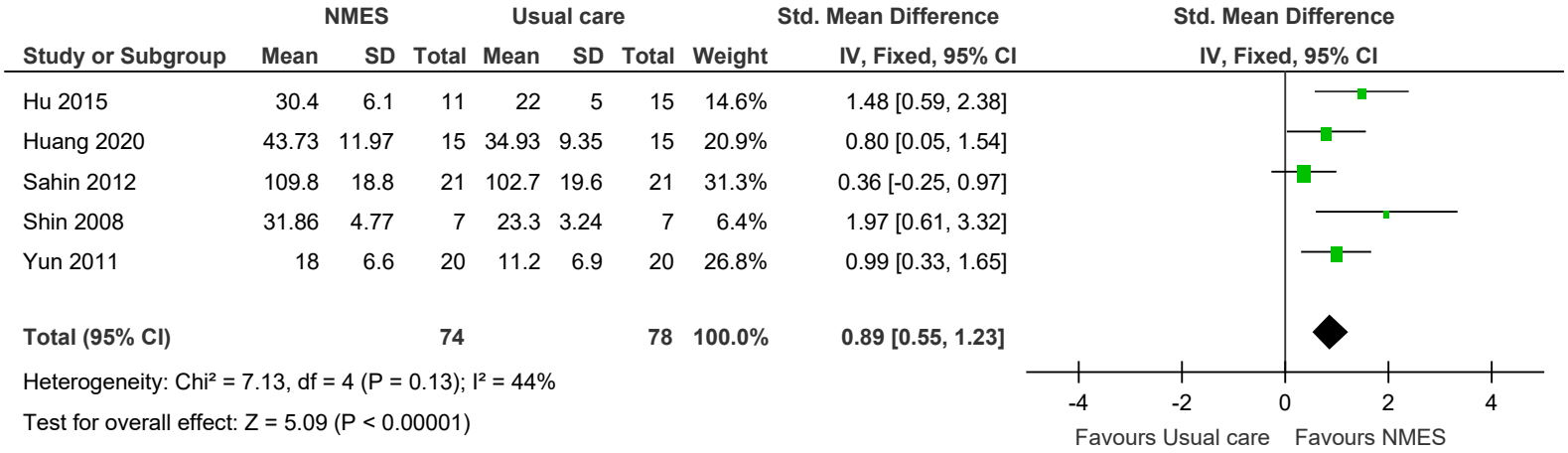


Figure 125: Physical function - lower limb (Rivermead motor assessment scale, 0-23, higher values are better, change score) at ≤6 months

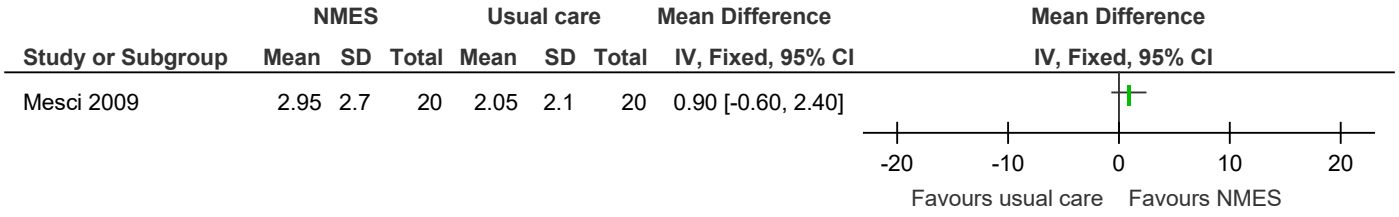


Figure 126: Physical function - lower limb (timed up and go, seconds, lower values are better, final value) at ≤6 months

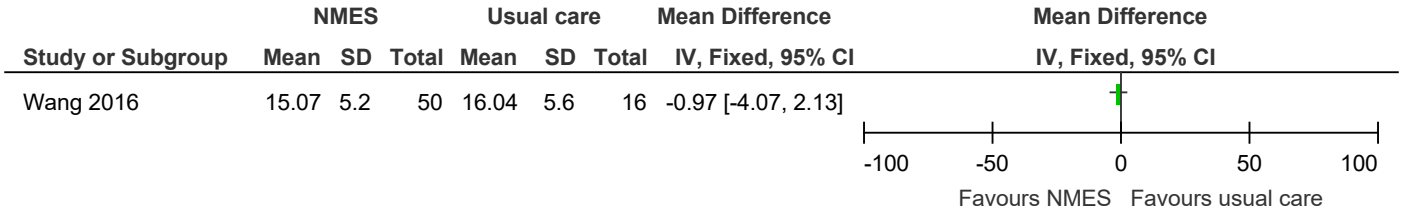


Figure 127: Physical function - lower limb (walking speed, m/s, higher values are better, final value) at ≤6 months

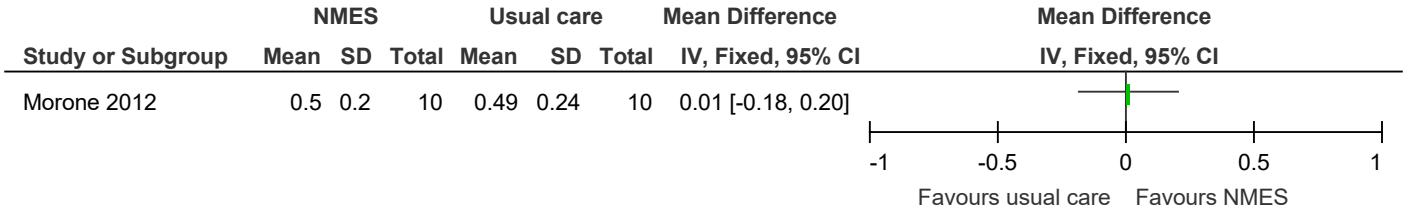


Figure 128: Pain (verbal rating scale, 0-5, lower values are better, final values) at ≤6 months

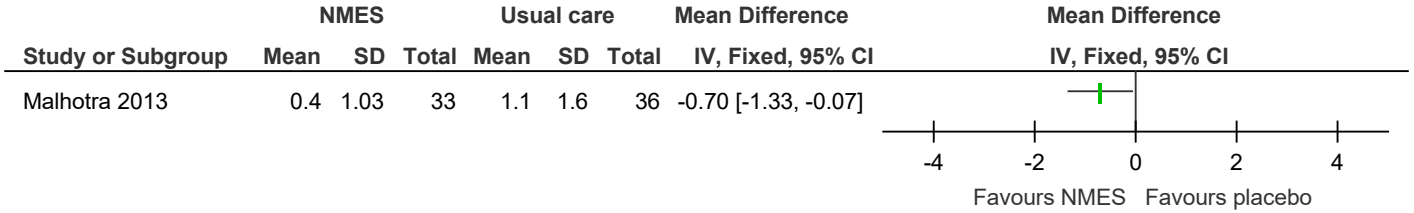


Figure 129: Activities of daily living (Barthel index, 0-100, higher values are better, change score) at ≤6 months

Study or Subgroup	NMES Mean	NMES SD	NMES Total	Usual care Mean	Usual care SD	Usual care Total	Mean Difference IV, Fixed, 95% CI
Zhou 2018	11.67	37.2	36	13.08	45.4	18	-1.41 [-25.65, 22.83]

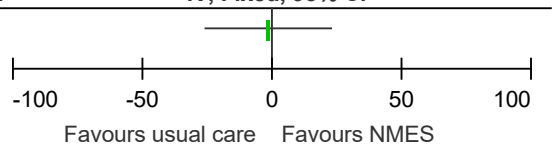


Figure 130: Activities of daily living (FIM, Barthel index [different scale ranges], higher values are better, final values) at ≤6 months

Study or Subgroup	NMES Mean	NMES SD	NMES Total	Usual care Mean	Usual care SD	Usual care Total	Weight	Std. Mean Difference IV, Random, 95% CI
Huang 2020	65.87	1.93	15	65.93	2.08	15	32.1%	-0.03 [-0.74, 0.69]
Lin 2011	79.2	5.2	19	66.1	11.3	18	31.7%	1.47 [0.74, 2.21]
Sentandreu-Mano 2021	71.83	15.88	41	64.5	19.66	20	36.2%	0.42 [-0.12, 0.96]
Total (95% CI)			**75**			**53**	**100.0%**	**0.61 [-0.19, 1.41]**

Heterogeneity: Tau² = 0.38; Chi² = 8.74, df = 2 (P = 0.01); I² = 77%

Test for overall effect: Z = 1.50 (P = 0.13)

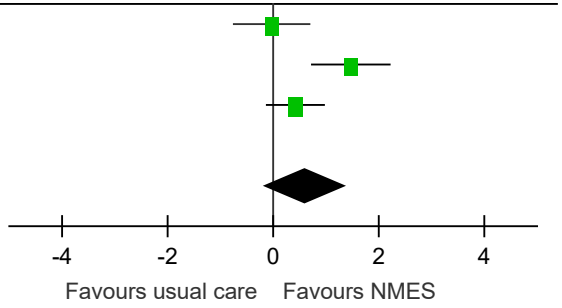


Figure 131: Stroke-specific Patient-Reported Outcome Measures (SS-QOL, 49-245, higher values are better, change score) at ≤6 months

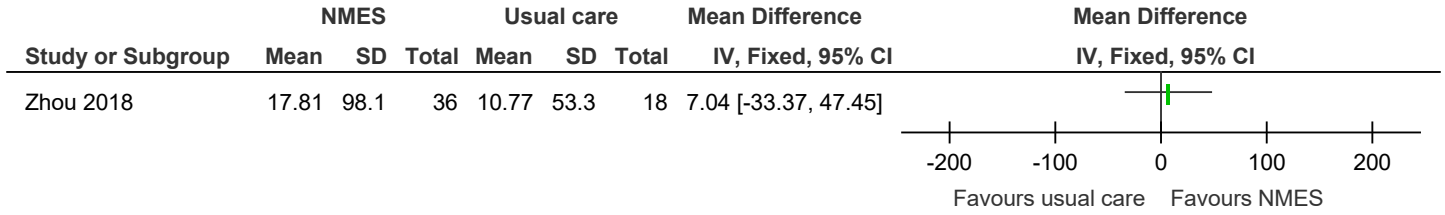
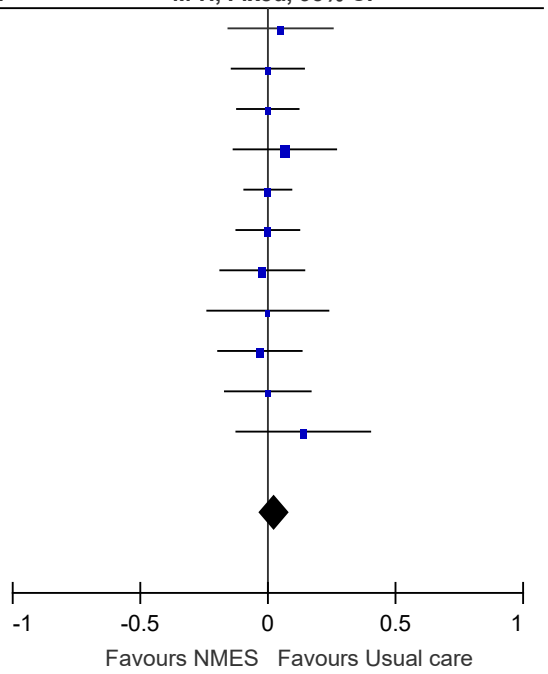


Figure 132: Withdrawal due to adverse events at ≤6 months

	NMES		Usual care			Risk Difference	Risk Difference
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Bakhtiary 2008	3	20	2	20	8.6%	0.05 [-0.15, 0.25]	
Hu 2015	0	11	0	15	5.4%	0.00 [-0.14, 0.14]	
Huang 2020	0	15	0	15	6.4%	0.00 [-0.12, 0.12]	
Malhotra 2013	19	45	16	45	19.3%	0.07 [-0.13, 0.27]	
Mesci 2009	0	20	0	20	8.6%	0.00 [-0.09, 0.09]	
Sahin 2012	1	22	1	22	9.4%	0.00 [-0.12, 0.12]	
Sentandreu-Mano 2021	5	46	3	23	13.1%	-0.02 [-0.19, 0.14]	
Shin 2008	0	7	0	7	3.0%	0.00 [-0.24, 0.24]	
Wang 2016	4	50	2	18	11.3%	-0.03 [-0.19, 0.13]	
Yang 2018	0	17	0	8	4.7%	0.00 [-0.17, 0.17]	
Zhou 2018	15	36	5	18	10.3%	0.14 [-0.12, 0.40]	
Total (95% CI)		**289**		**211**	**100.0%**	**0.03 [-0.04, 0.09]**	
Total events	47		29				

Heterogeneity: Chi² = 2.56, df = 10 (P = 0.99); I² = 0%

Test for overall effect: Z = 0.79 (P = 0.43)



Transcutaneous electrical nerve stimulation compared to placebo

Figure 133: Spasticity outcome measures (Composite spasticity score. 0-16, lower values are better, final value and change score) at ≤6 months

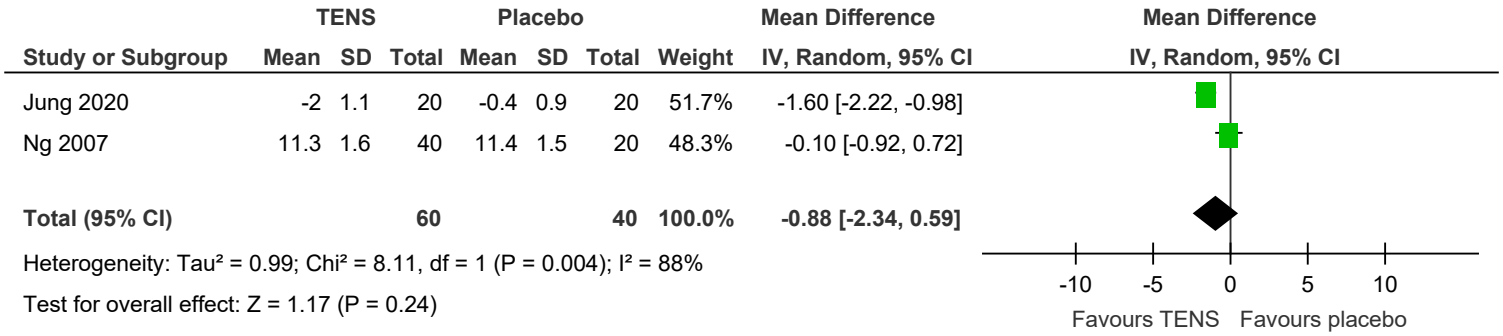


Figure 134: Spasticity outcome measures (Modified Ashworth Scale, 0-5, lower values are better, final values and change scores) at ≤6 months

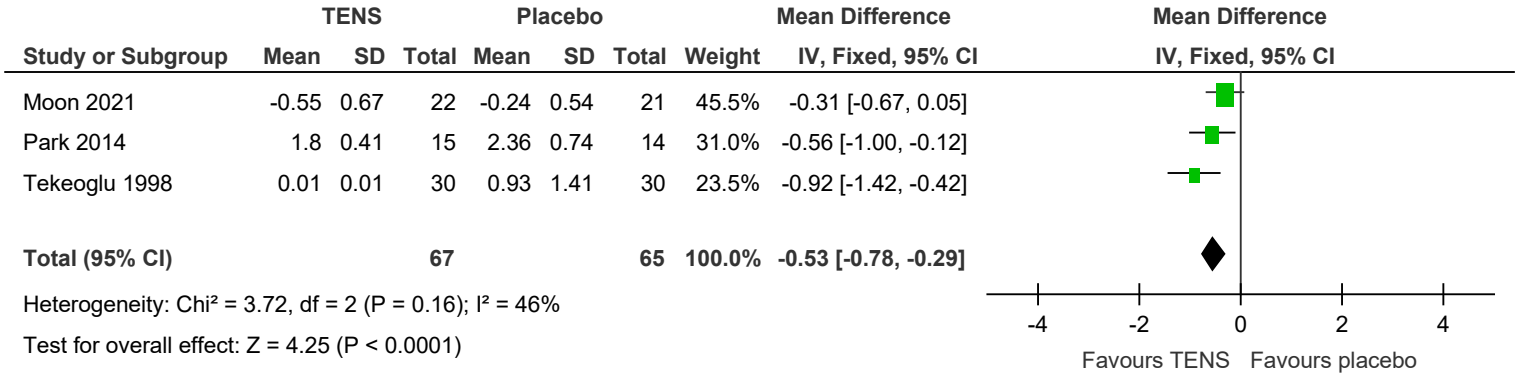


Figure 135: Physical function - lower limb (Timed up and go, seconds, lower values are better, final values) at ≤6 months

	TENS			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Ng 2009	21.4	10.6	51	27.8	22.8	23	34.2%	-6.40 [-16.16, 3.36]
Park 2014	21.84	9.28	15	24.61	11.61	14	41.1%	-2.77 [-10.45, 4.91]
Yan 2009	15.2	8.4	19	34.5	28.5	19	24.7%	-19.30 [-32.66, -5.94]
Total (95% CI)			**85**			**56**	**100.0%**	**-8.09 [-16.69, 0.50]**

Heterogeneity: Tau² = 31.46; Chi² = 4.43, df = 2 (P = 0.11); I² = 55%

Test for overall effect: Z = 1.85 (P = 0.07)

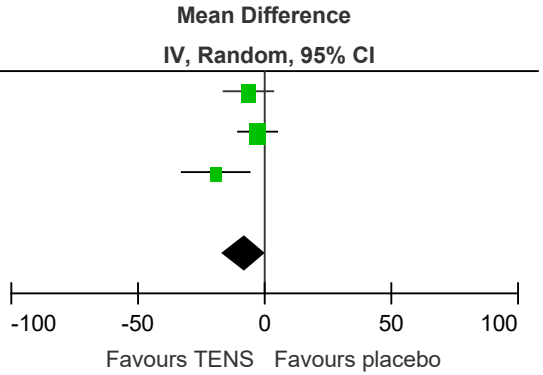


Figure 136: Physical function - lower limb (10m walk, seconds, lower values are better, change score) at ≤6 months

	TENS			Placebo			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Jung 2020	-5.3	1.4	20	-2.7	1.2	20	-2.60 [-3.41, -1.79]

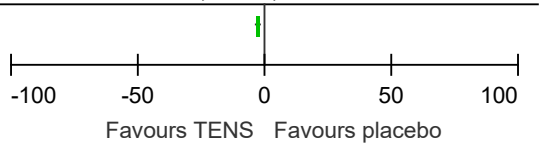


Figure 137: Activities of daily living (Barthel index, 0-100, higher values are better, change score and final value) at ≤6 months

	TENS			Placebo				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
Moon 2021	18.96	11.8	22	13.86	8.57	21	49.9%	5.10 [-1.04, 11.24]	
Tekeoglu 1998	80.4	10	30	60.4	13.3	30	50.1%	20.00 [14.05, 25.95]	
Total (95% CI)			**52**			**51**	**100.0%**	**12.57 [-2.03, 27.17]**	

Heterogeneity: Tau² = 101.48; Chi² = 11.65, df = 1 (P = 0.0006); I² = 91%

Test for overall effect: Z = 1.69 (P = 0.09)

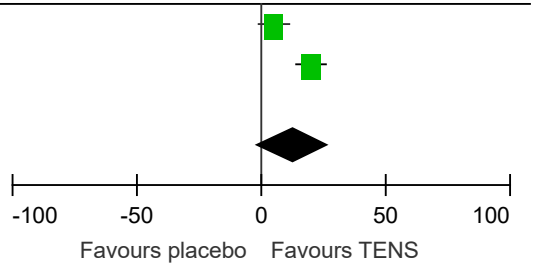
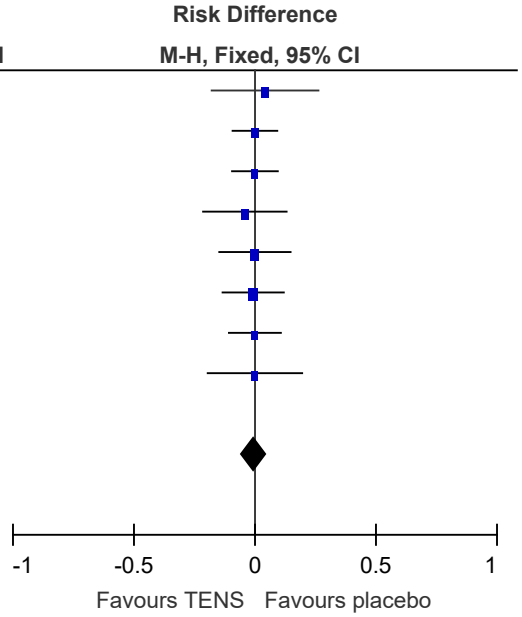


Figure 138: Withdrawal due to adverse events at ≤6 months

	TENS		Placebo			Risk Difference
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
De Jong 2013	5	24	4	24	12.8%	0.04 [-0.18, 0.26]
Jung 2020	0	20	0	20	10.7%	0.00 [-0.09, 0.09]
Lee 2015	0	20	0	19	10.4%	0.00 [-0.09, 0.09]
Moon 2021	2	24	3	24	12.8%	-0.04 [-0.21, 0.13]
Ng 2007	4	44	2	22	15.7%	0.00 [-0.15, 0.15]
Ng 2009	4	55	2	25	18.4%	-0.01 [-0.13, 0.12]
Park 2014	0	17	0	17	9.1%	0.00 [-0.11, 0.11]
Yan 2009	2	19	2	19	10.1%	0.00 [-0.20, 0.20]
Total (95% CI)		**223**		**170**	**100.0%**	**-0.00 [-0.06, 0.05]**
Total events	17		13			

Heterogeneity: Chi² = 0.37, df = 7 (P = 1.00); I² = 0%

Test for overall effect: Z = 0.05 (P = 0.96)



Transcutaneous electrical nerve stimulation compared to usual care

Figure 139: Spasticity outcome measures (Modified Ashworth scale, composite spasticity score, 0-4, lower values are better, change scores) at ≤6 months

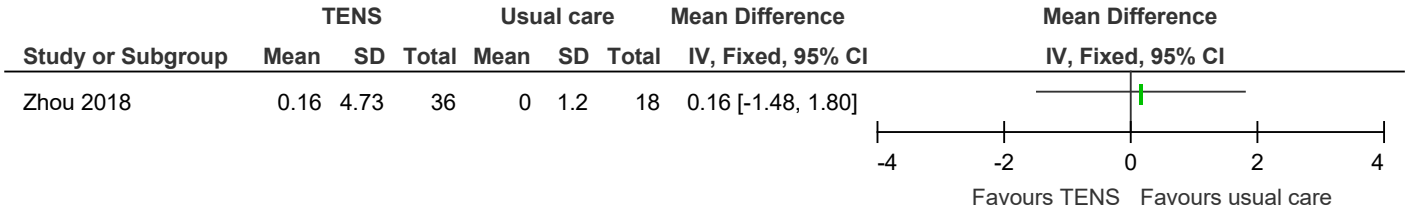


Figure 140: Spasticity outcome measures (modified Ashworth scale, composite spasticity scale [different scale ranges], lower values are better, final values) at ≤6 months

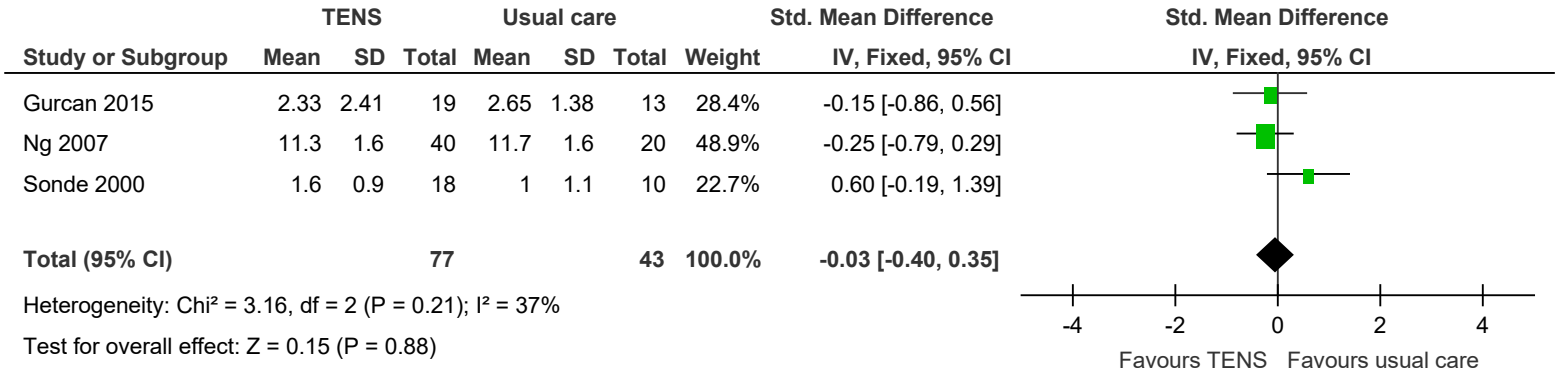


Figure 141: Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, final value) at >6 months

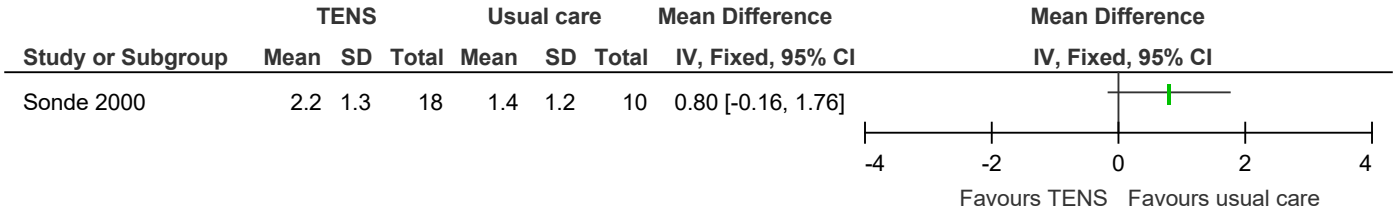


Figure 142: Physical function - upper limb (Fugl-meyer, 0-66, higher values are better, change score and final value) at ≤6 months

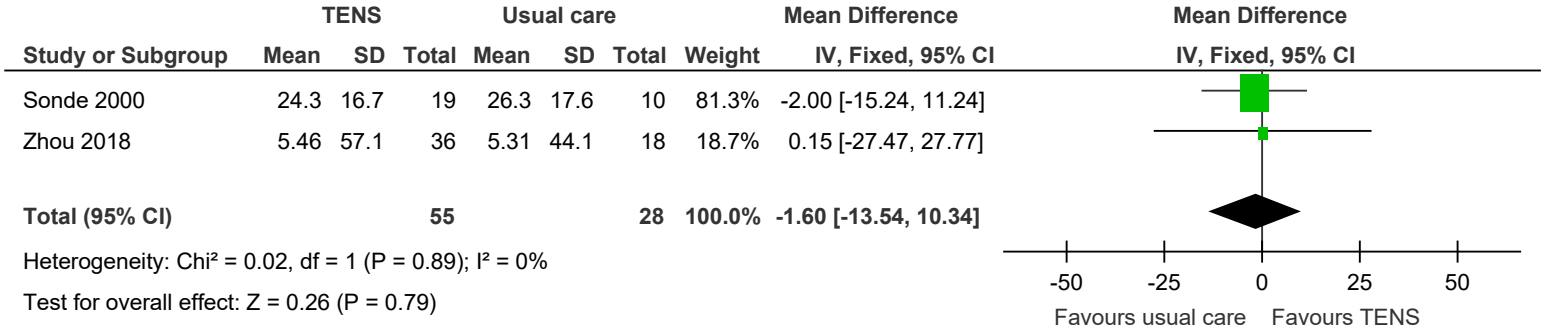


Figure 143: Physical function - upper limb (Fugl-meyer, 0-50, higher values are better, change score) at ≤6 months

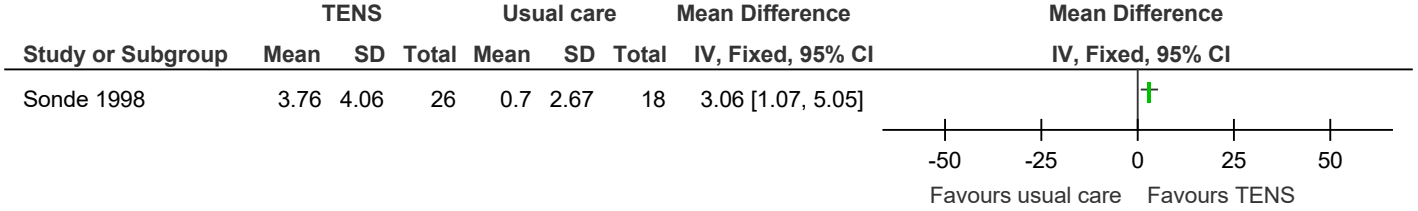


Figure 144: Physical function - upper limb (Fugl-meyer, 0-66, higher values are better, final value) at >6 months

	TENS			Usual care			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Sonde 2000	20.2	13.9	18	24.2	17.4	10	-4.00 [-16.55, 8.55]	

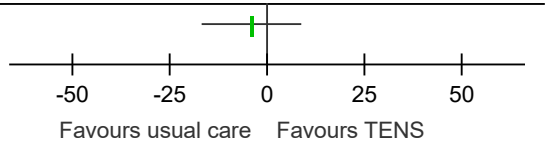


Figure 145: Physical function - lower limb (Timed up and go, seconds, lower values are better, final values) at ≤6 months

	TENS			Usual care				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Ng 2009	21.4	10.6	51	23.2	14.9	27	53.9%	-1.80 [-8.13, 4.53]	
Yan 2009	15.2	8.4	19	36.3	25.3	18	46.1%	-21.10 [-33.38, -8.82]	
Total (95% CI)			**70**			**45**	**100.0%**	**-10.70 [-29.56, 8.15]**	

Heterogeneity: Tau² = 161.40; Chi² = 7.49, df = 1 (P = 0.006); I² = 87%

Test for overall effect: Z = 1.11 (P = 0.27)

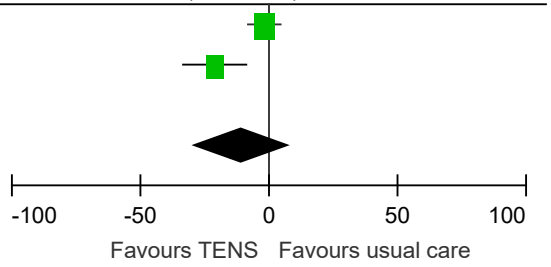


Figure 146: Physical function - lower limb (10m walking scale, seconds, lower values are better, final value) at ≤6 months

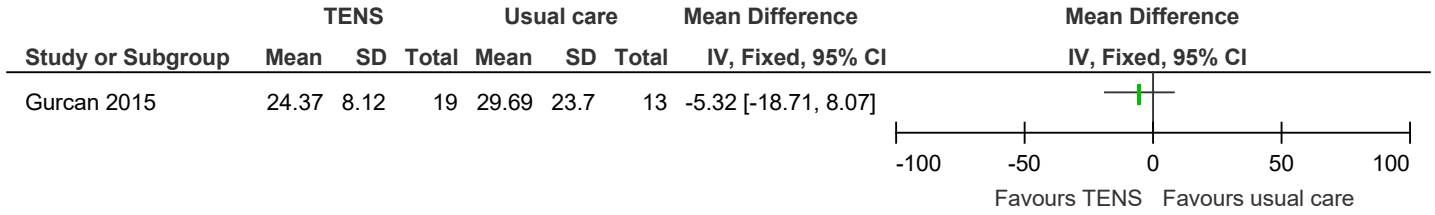


Figure 147: Pain (Numeric rating scale, 0-10, lower values are better, change score) at ≤6 months

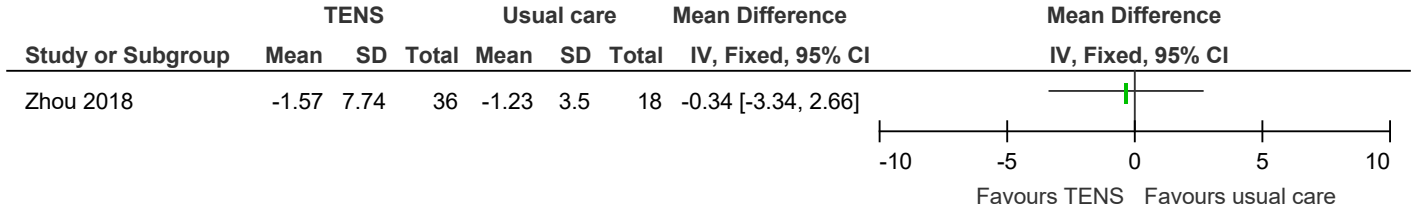


Figure 148: Activities of daily living (Barthel index 0-100, higher values are better, change score) at ≤6 months

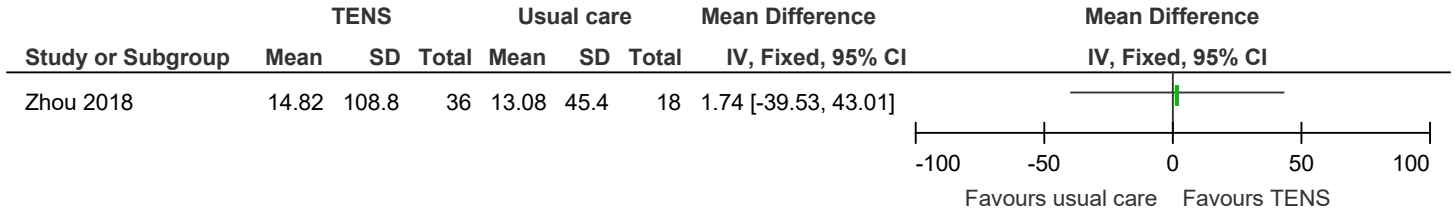


Figure 149: Activities of daily living (functional independence measure, Barthel index [different scale ranges], higher values are better, final values) at ≤6 months

	TENS			Usual care				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Gurcan 2015	86.1	21.62	19	89.53	28.13	13	54.7%	-0.14 [-0.84, 0.57]
Sonde 2000	81.9	13.3	18	79	10.7	10	45.3%	0.23 [-0.55, 1.00]
Total (95% CI)			**37**			**23**	**100.0%**	**0.03 [-0.49, 0.55]**

Heterogeneity: Chi² = 0.46, df = 1 (P = 0.50); I² = 0%

Test for overall effect: Z = 0.10 (P = 0.92)

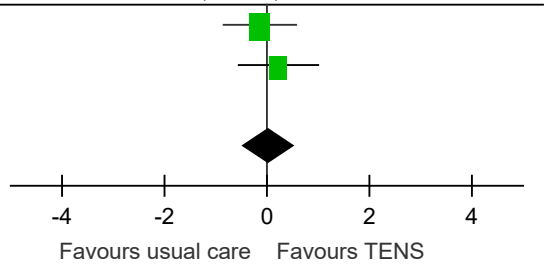


Figure 150: Activities of daily living (Barthel index, 0-100, higher values are better, final value) at >6 months

	TENS			Usual care			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Sonde 2000	78.1	16.6	18	66.5	22.4	10	11.60 [-4.26, 27.46]

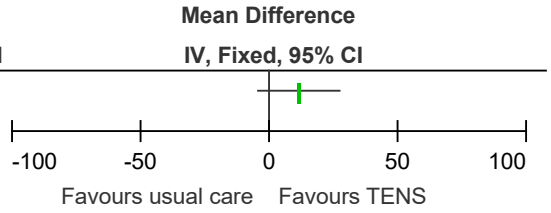


Figure 151: Stroke-specific Patient-Reported Outcome Measures (SS-QOL, 49-245, higher values are better, change score) at ≤6 months

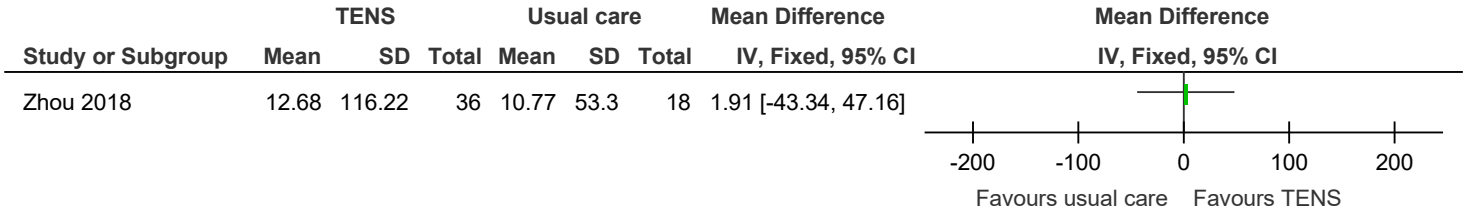


Figure 152: Withdrawal due to adverse events at ≤6 months

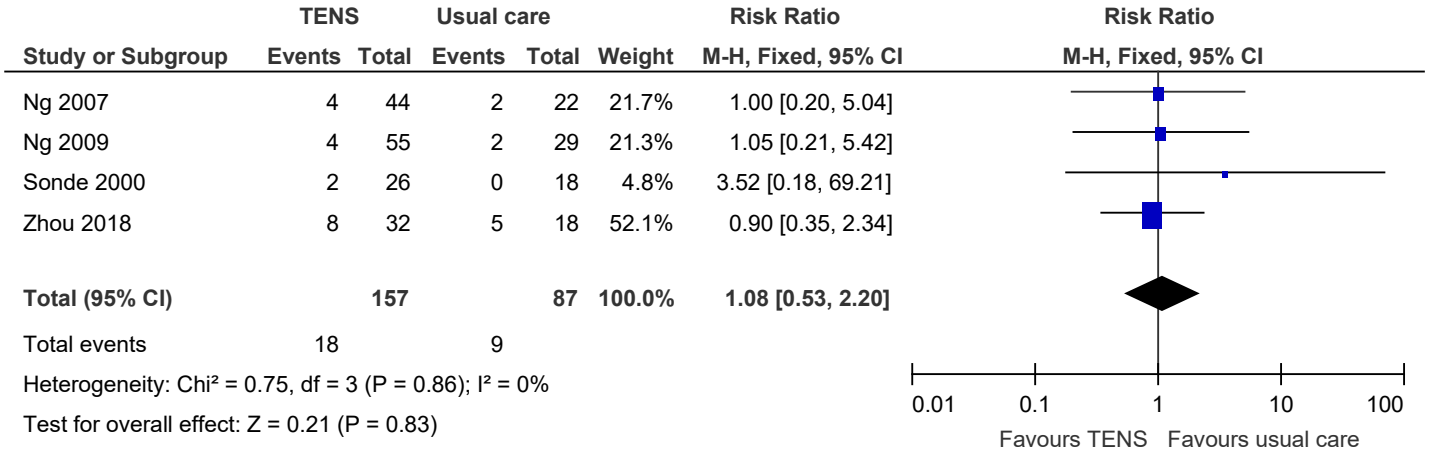
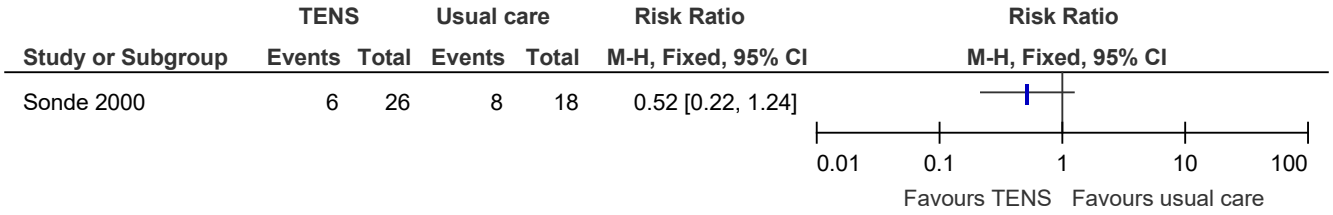


Figure 153: Withdrawal due to adverse events at >6 months



Acupuncture compared to placebo

Figure 154: Person/participant generic health-related quality of life (EQ-5D, -0.11-1, higher values are better, change score) at ≤6 months

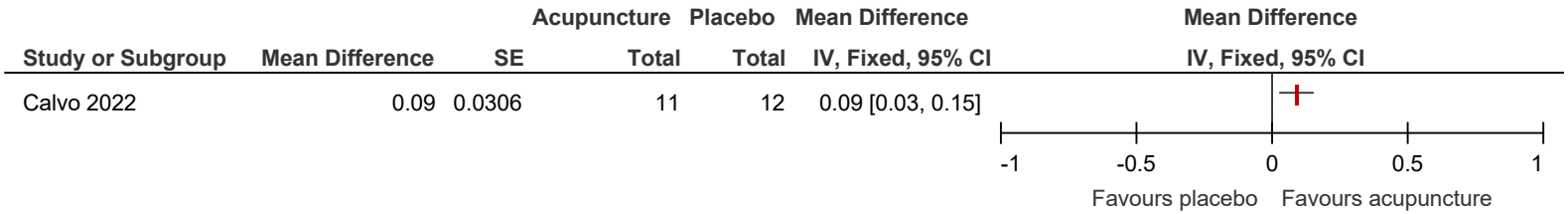


Figure 155: Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, final value) at ≤6 months

	Acupuncture			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Calvo 2022	-0.46	0.72	11	-0.25	0.55	12	53.6%	-0.21 [-0.74, 0.32]
Ghannadi 2020	1.33	0.89	12	2.33	0.78	12	46.4%	-1.00 [-1.67, -0.33]
Total (95% CI)			**23**			**24**	**100.0%**	**-0.58 [-1.35, 0.20]**

Heterogeneity: Tau² = 0.22; Chi² = 3.30, df = 1 (P = 0.07); I² = 70%

Test for overall effect: Z = 1.46 (P = 0.14)

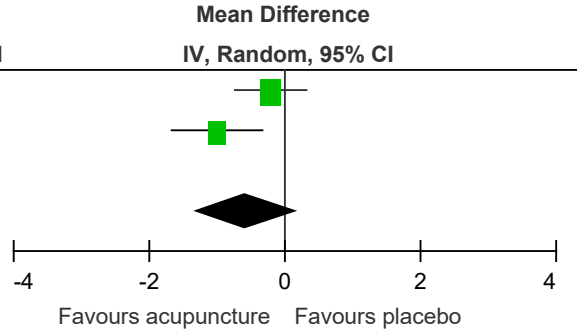


Figure 156: Physical function - upper limb (Fugl Meyer Assessment Upper Extremity, 0-66, higher values are better, change score) at ≤6 months

			Acupuncture	Placebo	Mean Difference
Study or Subgroup	Mean Difference	SE	Total	Total	IV, Fixed, 95% CI
Calvo 2022	4.18	2.3062	11	12	4.18 [-0.34, 8.70]

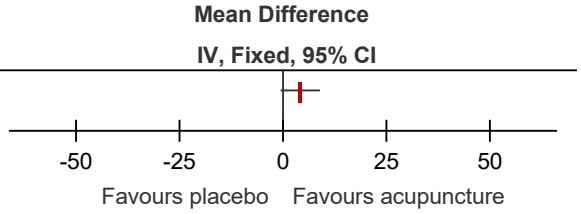


Figure 157: Physical function - upper limb (Box and block test, 0-150, higher values are better, final value) at ≤6 months

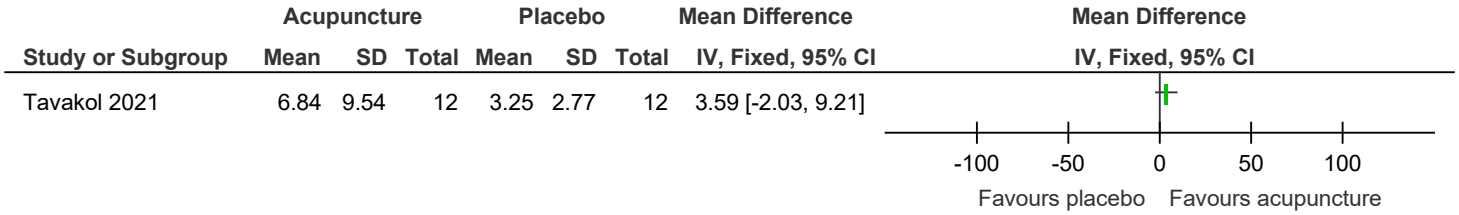


Figure 158: Physical function - lower limb (10m walk, seconds, lower values are better, final value) at ≤6 months

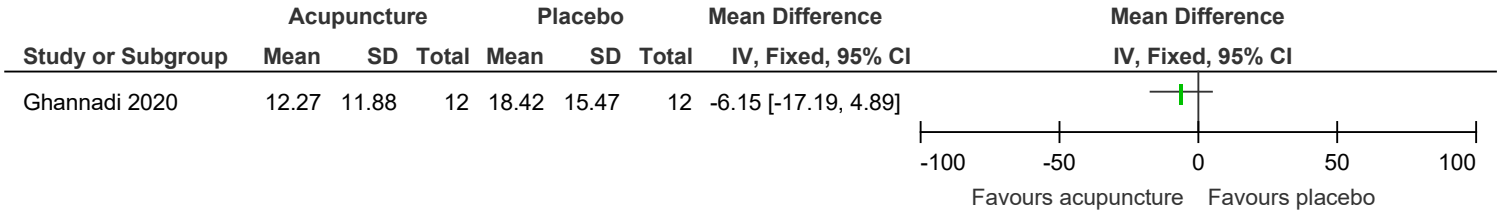


Figure 159: Activities of daily living (Barthel Index, 0-100, higher values are better, final values) at ≤6 months

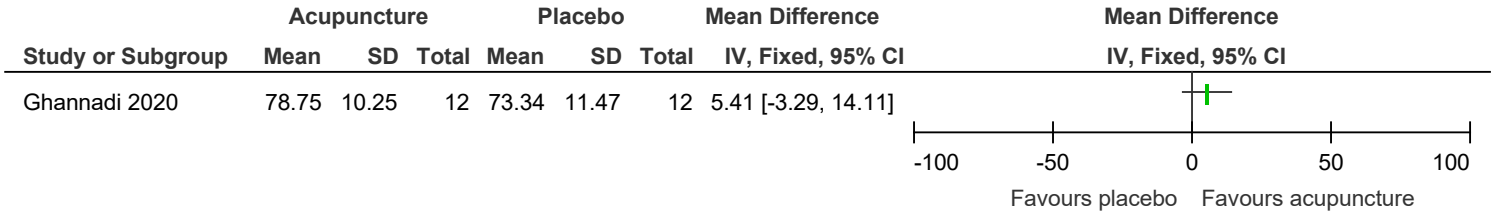
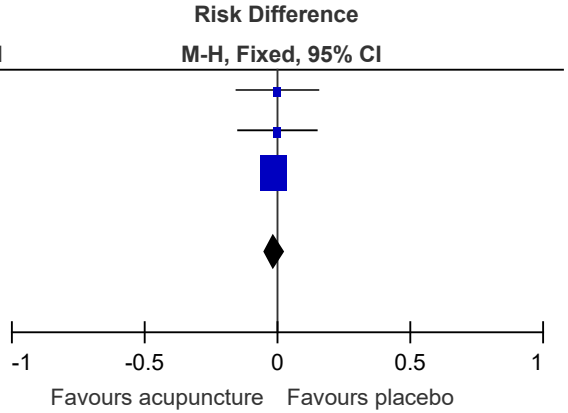


Figure 160: Withdrawal due to adverse events at ≤6 months

Study or Subgroup	Acupuncture Events	Acupuncture Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Calvo 2022	0	11	0	12	12.3%	0.00 [-0.15, 0.15]
Tavakol 2021	0	12	0	12	12.8%	0.00 [-0.15, 0.15]
Zhang 2021B	0	70	1	70	74.9%	-0.01 [-0.05, 0.02]
Total (95% CI)		**93**		**94**	**100.0%**	**-0.01 [-0.05, 0.03]**
Total events	0		1			

Heterogeneity: Chi² = 0.07, df = 2 (P = 0.96); I² = 0%

Test for overall effect: Z = 0.51 (P = 0.61)



Acupuncture compared to usual care

Figure 161: Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, final value) at ≤6 months

Study or Subgroup	Acupuncture Mean	Acupuncture SD	Acupuncture Total	Usual care Mean	Usual care SD	Usual care Total	Mean Difference IV, Fixed, 95% CI
Wang 2019	1.55	0.65	30	1.92	0.74	29	-0.37 [-0.73, -0.01]

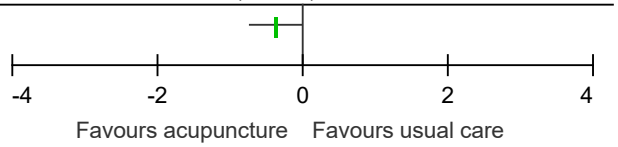


Figure 162: Physical function - lower limb (Fugl-Meyer lower extremity, 0-34, higher values are better, final value) at ≤6 months

	Acupuncture			Usual care			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Wang 2019	25.33	6.94	30	19.57	8.18	29	5.76 [1.88, 9.64]	

Figure 163: Activities of daily living (Barthel Index, 0-100, higher values are better, final value) at ≤6 months

	Acupuncture			Usual care			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Wang 2019	70.67	23	30	66.55	25.74	29	4.12 [-8.35, 16.59]	

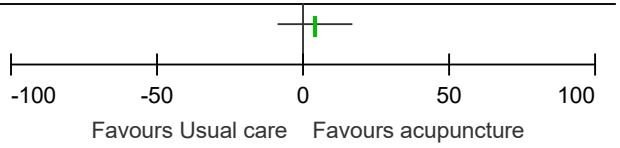
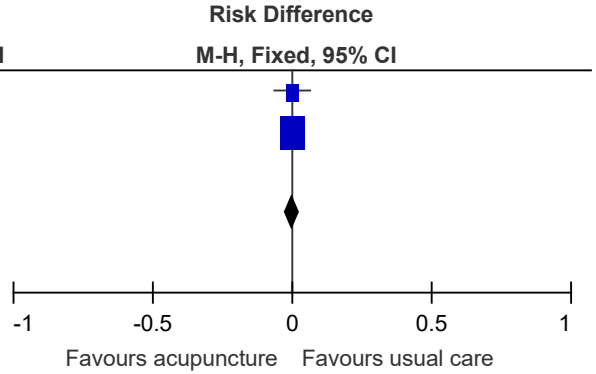


Figure 164: Withdrawal due to adverse events at ≤6 months

Study or Subgroup	Acupuncture Events	Acupuncture Total	Usual care Events	Usual care Total	Weight	Risk Difference M-H, Fixed, 95% CI
Wang 2019	0	30	0	29	29.6%	0.00 [-0.06, 0.06]
Zhang 2021B	0	70	0	70	70.4%	0.00 [-0.03, 0.03]
Total (95% CI)		**100**		**99**	**100.0%**	**0.00 [-0.03, 0.03]**
Total events	0		0			

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%

Test for overall effect: Z = 0.00 (P = 1.00)



Combination therapy: Abobotulinum toxin A (Dysport) and neuromuscular electrical stimulation (NMES) compared to abobotulinum toxin A (Dysport) alone

Figure 165: Spasticity outcome measures (Modified Ashworth scale, 0-5, lower values are better, final value) at ≤6 months

Study or Subgroup	Bont-A (Dysport) + NMES Mean	SD	Total	Bont-A (Dysport) alone Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Hesse 1998	2.44	0.66	6	3.22	1.18	6	-0.78 [-1.86, 0.30]

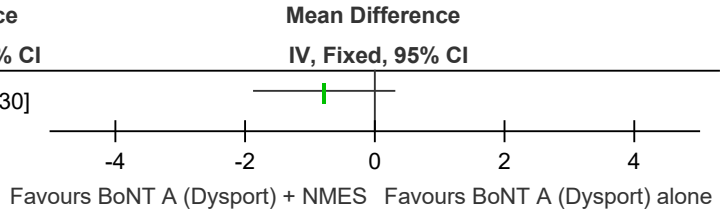
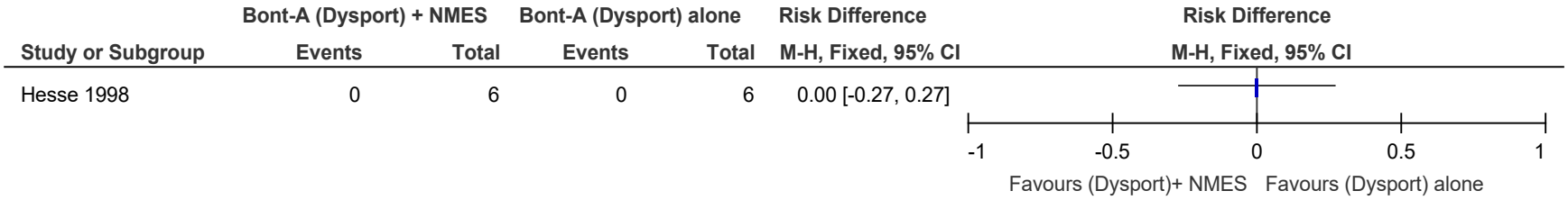


Figure 166: Withdrawal due to adverse events at ≤6 months



Combination therapy: Abobotulinum toxin A (Dysport) and neuromuscular electrical stimulation (NMES) compared to neuromuscular electrical stimulation (NMES) alone

Figure 167: Spasticity outcome measures (Modified Ashworth scale, 0-5, lower values are better, final value) at ≤6 months

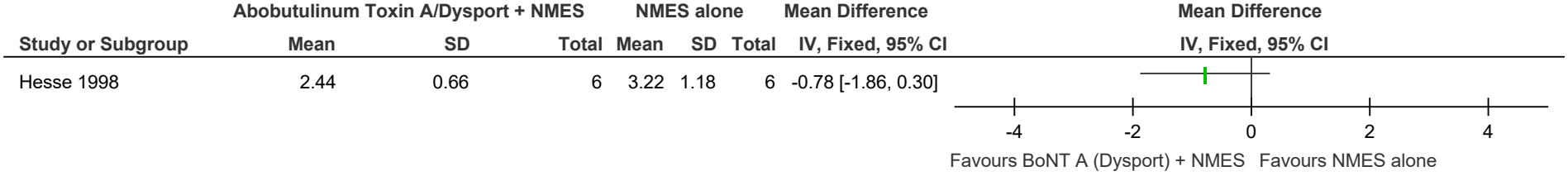
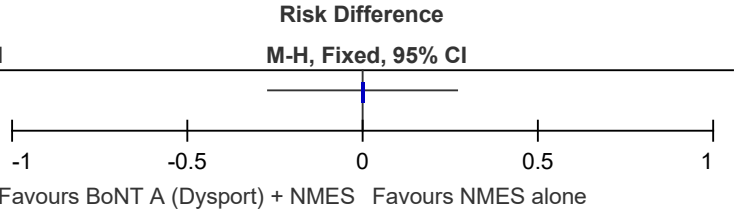


Figure 168: Withdrawal due to adverse events at ≤6 months

Study or Subgroup	Abobutulinum Toxin A/Dysport + NMES Events	Total	NMES alone Events	Total	Risk Difference M-H, Fixed, 95% CI
Hesse 1998	0	6	0	6	0.00 [-0.27, 0.27]



Combination therapy: Abobotulinum toxin A (Dysport) and transcutaneous electrical nerve stimulation (TENS) compared to placebo and transcutaneous electrical nerve stimulation

Figure 169: Spasticity outcome measures (Modified Ashworth scale, 0-5, lower values are better, final value) at ≤6 months

Study or Subgroup	Abobotulinum toxin A/Dysport + TENS Mean	SD	Total	Placebo + TENS Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Marco 2007	2.9	1.2	14	3.2	0.9	15	-0.30 [-1.08, 0.48]

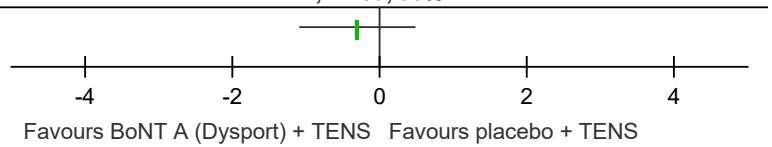


Figure 170: Pain (VAS, 0-100, lower values are better, final value) at ≤6 months

	Abobotulinum toxin A/Dysport + TENS			Placebo + TENS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Marco 2007	30.1	26.9	14	48.3	19.4	15	-18.20 [-35.37, -1.03]	

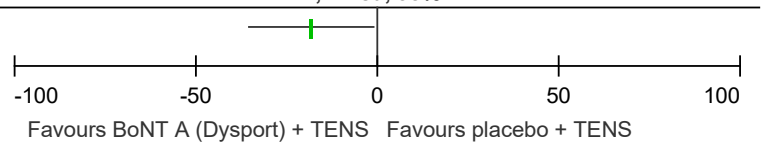
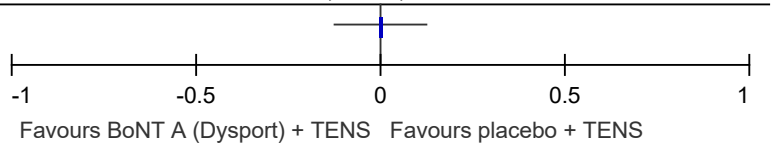


Figure 171: Withdrawal due to adverse events at ≤6 months

	Abobotulinum toxin A/Dysport + TENS		Placebo + TENS		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Marco 2007	0	14	0	15	0.00 [-0.12, 0.12]	



Combination therapy: Onabotulinum toxin A (BOTOX) and functional electrical stimulation compared to onabotulinum toxin A (BOTOX) only

Figure 172: Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, final value) at ≤6 months

	Onabotulinum toxin A (BOTOX) + FES			Onabotulinum toxin A (BOTOX)			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Ding 2017	2.26	0.58	41	2.88	0.6	39	-0.62 [-0.88, -0.36]

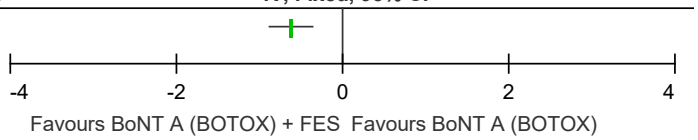


Figure 173: Physical function - lower limb (Fugl-meyer assessment, 0-34, higher values are better, final value) at ≤6 months

	Onabotulinum toxin A (BOTOX) + FES			Onabotulinum toxin A (BOTOX)			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Ding 2017	25.16	0.78	41	16.88	0.66	39	8.28 [7.96, 8.60]

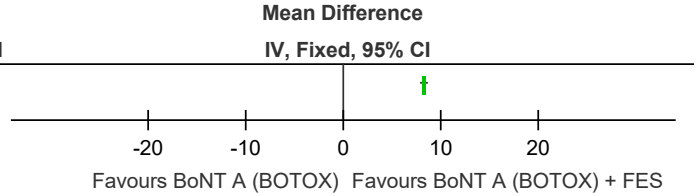
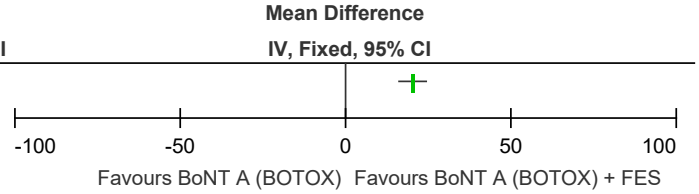


Figure 174: Activities of daily living (Barthel index, 0-100, higher values are better, final value) at ≤6 months

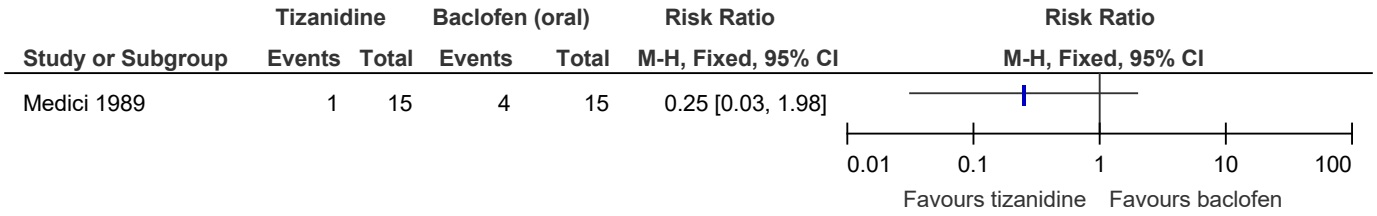
	Onabotulinum toxin A (BOTOX) + FES			Onabotulinum toxin A (BOTOX)			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Ding 2017	82.17	10.58	41	61.87	7.96	39	20.30 [16.21, 24.39]



Generalised spasticity

Tizanidine compared to oral baclofen

Figure 175: Withdrawal due to adverse events at >6 months



Intrathecal baclofen compared to usual care

Figure 176: Person/participant generic health-related quality of life (EQ-5D-3L, -0.11-1, higher values are better, change score) at ≤6 months

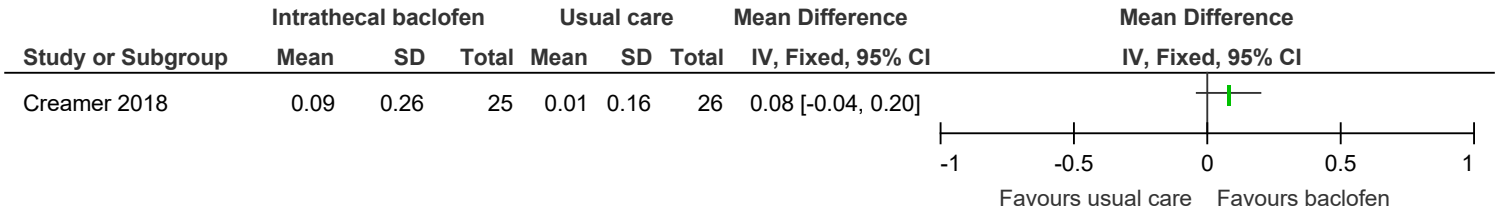


Figure 177: Spasticity outcome measures (Modified Ashworth Scale, 0-4, lower values are better, change score) at ≤6 months

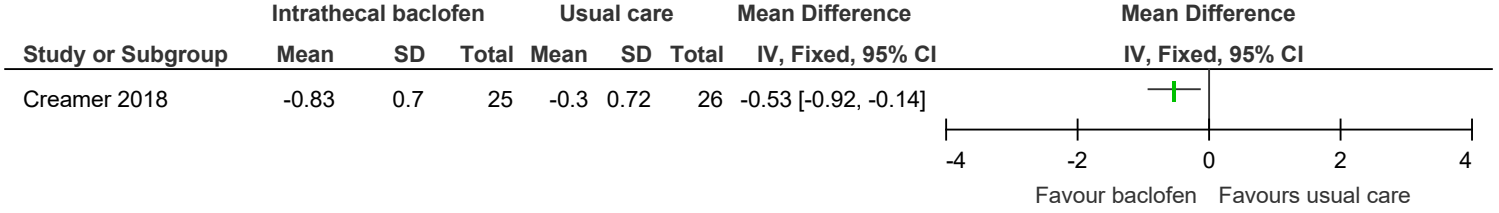


Figure 178: Pain (NRS, 0-10, lower values are better, change score) at ≤6 months

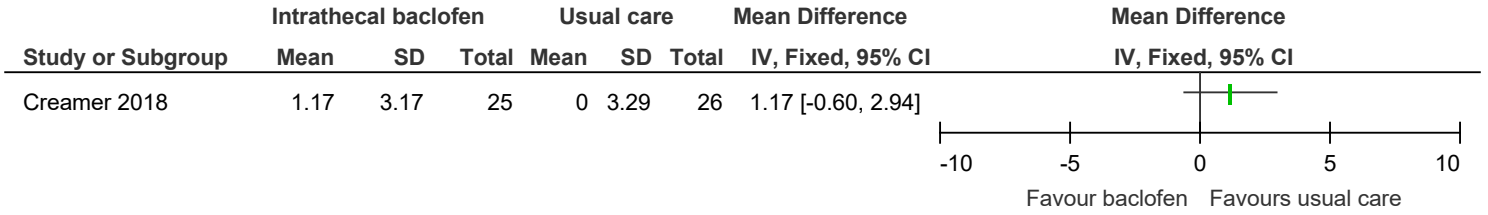


Figure 179: Activities of daily living (Functional Independence Measure total score, 18-126, high values are better, change score) at ≤6 months

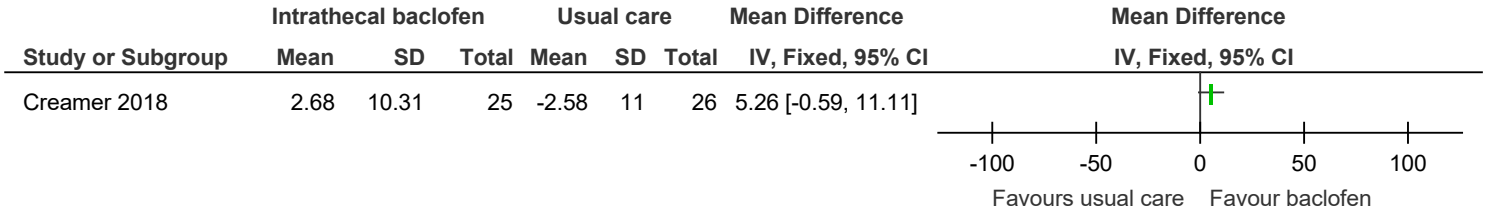


Figure 180: Stroke-specific Patient-Reported Outcome Measures (SS-QOL, 1-5, higher values are better, change score) at ≤6 months

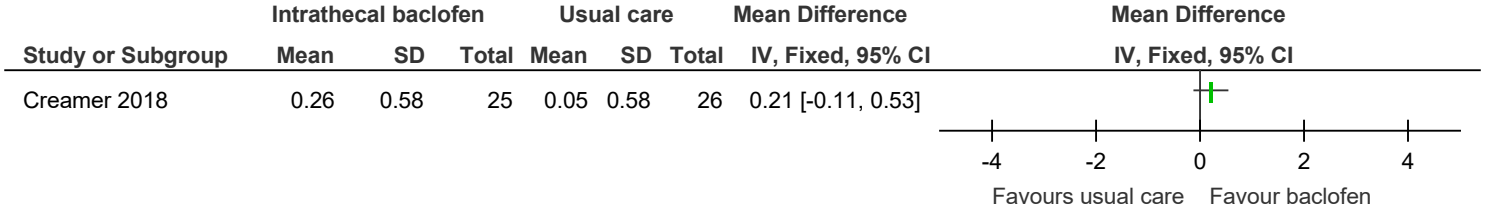
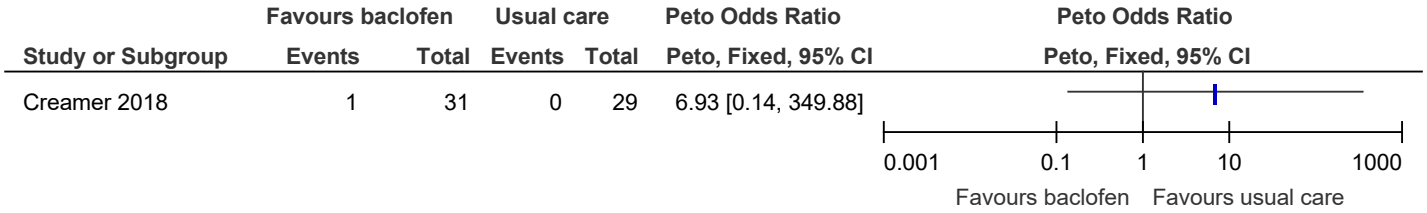


Figure 181: Withdrawal due to adverse events at ≤6 months



Acupuncture compared to placebo

Figure 182: Person/participant generic health-related quality of life (Nottingham health profile part 1, 0-100, higher values are better, change score) at ≤6 months

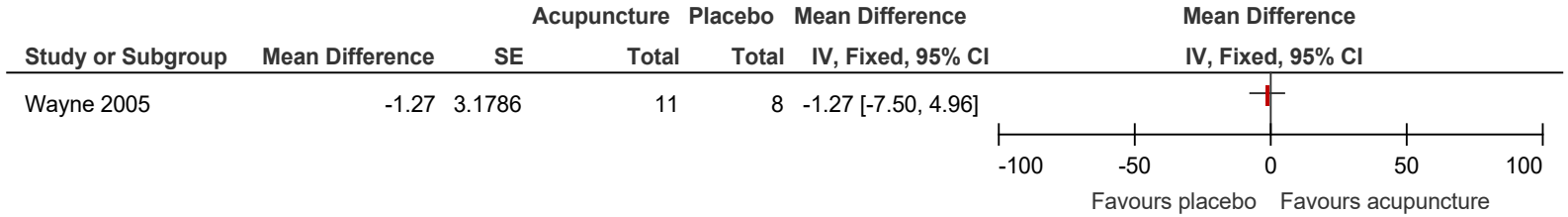


Figure 183: Spasticity outcome measures (Modified Ashworth scale, unclear scale range, lower values are better, change score) at ≤6 months

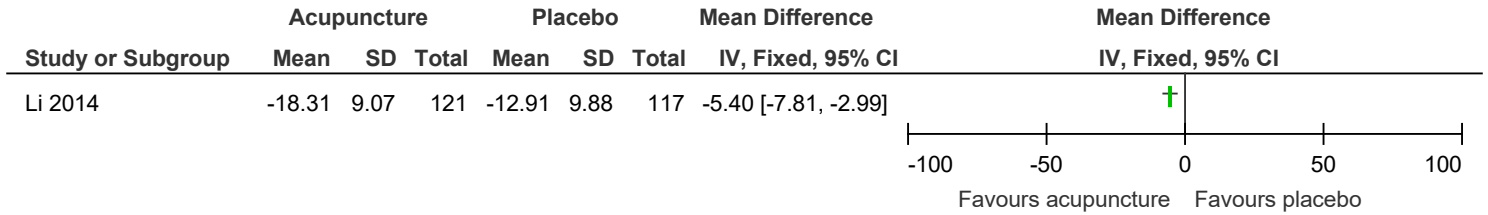


Figure 184: Spasticity outcome measures (Modified Ashworth scale wrist, 0-4, lower values are better, change score) at ≤6 months

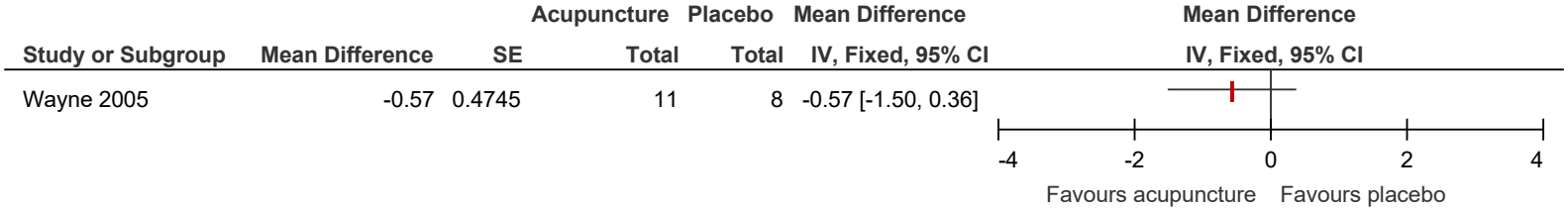


Figure 185: Spasticity outcome measures (Modified Ashworth scale elbow, 0-4, lower values are better, change score) at ≤6 months

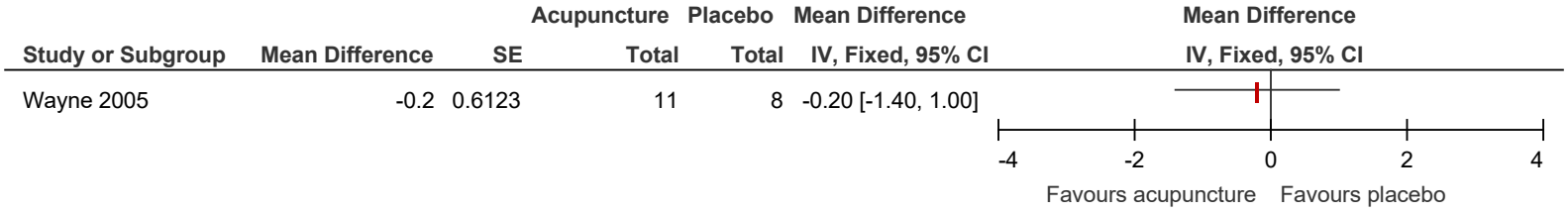


Figure 186: Physical function - general (FMA, 0-100, higher values are better, change score) at ≤6 months

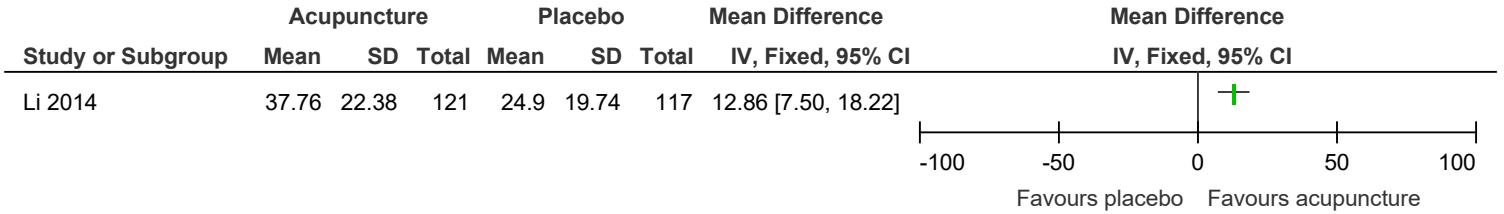


Figure 187: Physical function - upper limb (FMA-UE, 0-66, higher values are better, change score) at ≤6 months

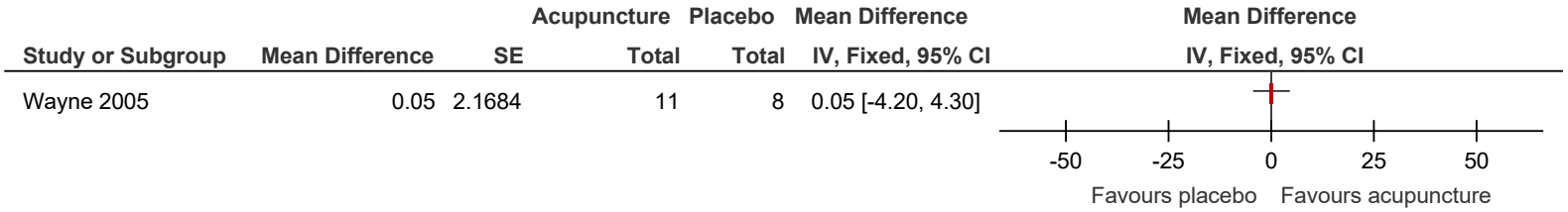


Figure 188: Pain (visual analogue scale, 0-10, lower values are better, change score) at ≤6 months

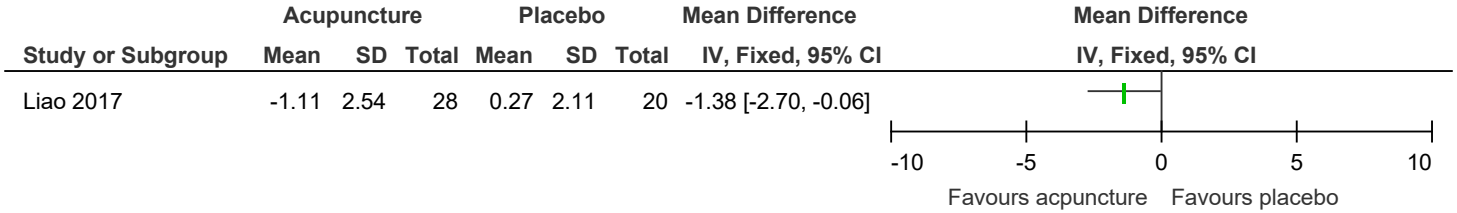


Figure 189: Activities of daily living (Barthel index, 0-100, higher values are better, change score) at ≤6 months

Study or Subgroup	Mean Difference	SE	Acupuncture Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Li 2014	13.25	2.5471	121	117	36.8%	13.25 [8.26, 18.24]
Liao 2017	1.14	6.5087	28	20	24.7%	1.14 [-11.62, 13.90]
Wayne 2005	0.11	1.7908	11	8	38.5%	0.11 [-3.40, 3.62]
Total (95% CI)			**160**	**145**	**100.0%**	**5.20 [-4.96, 15.36]**

Heterogeneity: Tau² = 66.55; Chi² = 18.06, df = 2 (P = 0.0001); I² = 89%

Test for overall effect: Z = 1.00 (P = 0.32)

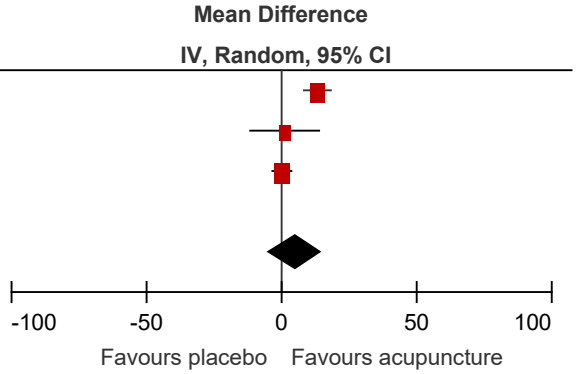


Figure 190: Stroke-specific Patient-Reported Outcome Measures (stroke specialisation QOL scale, 49-245, higher values are better, change score) at ≤6 months

Study or Subgroup	Acupuncture Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Li 2014	67.22	39.6	121	40.63	33.33	117	26.59 [17.30, 35.88]

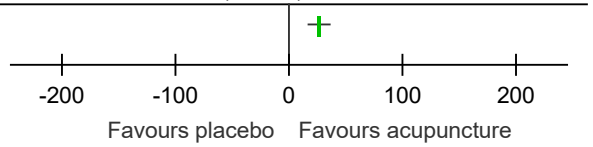
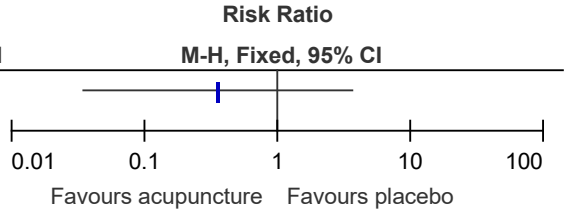


Figure 191: Withdrawal due to adverse events at ≤6 months

Study or Subgroup	Acupuncture Events	Acupuncture Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Liao 2017	1	28	2	20	0.36 [0.03, 3.67]



Acupuncture compared to usual care

Figure 192: Physical function - general (FMA total score, 0-226, higher values are better, change score) at ≤6 months

Study or Subgroup	Acupuncture Mean	Acupuncture SD	Acupuncture Total	Usual care Mean	Usual care SD	Usual care Total	Mean Difference IV, Fixed, 95% CI
Alexander 2004	5.5	13.8	14	7.7	12.3	15	-2.20 [-11.74, 7.34]

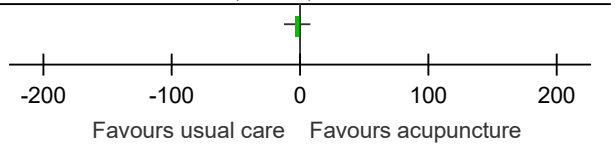


Figure 193: Physical function - general (FMA total motor score, 0-100, higher values are better, final values) at ≤6 months

	Acupuncture			Usual care				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Zhang 2021A	55.56	17.55	79	42.35	18.33	40	51.3%	13.21 [6.34, 20.08]	
Zhong 2002	69.4	27.1	48	31.7	24.1	48	48.7%	37.70 [27.44, 47.96]	
Total (95% CI)			**127**			**88**	**100.0%**	**25.15 [1.15, 49.14]**	

Heterogeneity: Tau² = 280.03; Chi² = 15.11, df = 1 (P = 0.0001); I² = 93%

Test for overall effect: Z = 2.05 (P = 0.04)

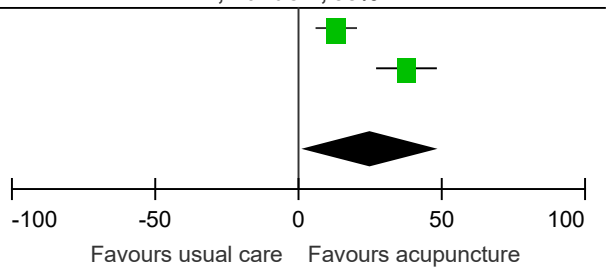


Figure 194: Activities of daily living (Barthel Index, 0-100, higher values are better, final values) at ≤6 months

	Acupuncture			Usual care				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Zhang 2021A	54.48	17.43	79	42.58	16.28	40	50.2%	11.90 [5.56, 18.24]	
Zhong 2002	82.5	16.9	48	50	16.9	48	49.8%	32.50 [25.74, 39.26]	
Total (95% CI)			**127**			**88**	**100.0%**	**22.17 [1.98, 42.35]**	

Heterogeneity: Tau² = 200.99; Chi² = 18.97, df = 1 (P < 0.0001); I² = 95%

Test for overall effect: Z = 2.15 (P = 0.03)

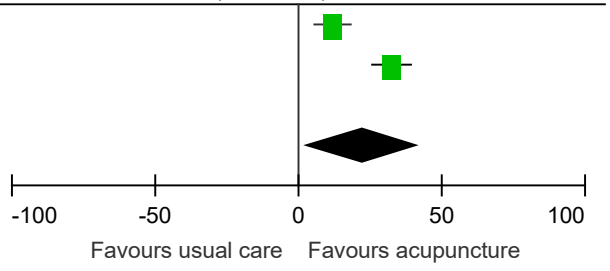


Figure 195: Activities of daily living (FIM, 18-126, higher values are better, change score) at ≤6 months

	Acupuncture			Usual care			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Alexander 2004	11.2	4.5	14	8.5	3.8	15	2.70 [-0.34, 5.74]	

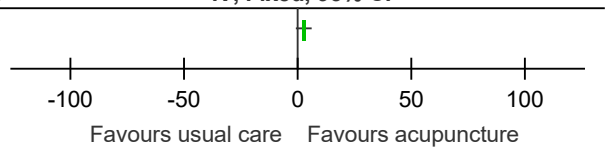
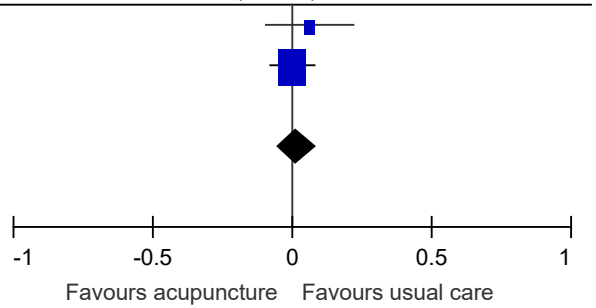


Figure 196: Withdrawal due to adverse events at ≤6 months

	Acupuncture		Usual care			Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Alexander 2004	1	16	0	16	22.3%	0.06 [-0.09, 0.22]	
Zhang 2021A	4	83	2	42	77.7%	0.00 [-0.08, 0.08]	
Total (95% CI)		**99**		**58**	**100.0%**	**0.01 [-0.06, 0.09]**	
Total events	5		2				

Heterogeneity: Chi² = 0.48, df = 1 (P = 0.49); I² = 0%

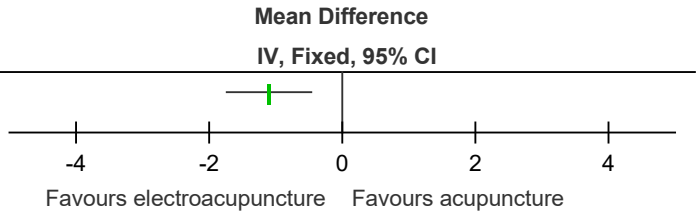
Test for overall effect: Z = 0.39 (P = 0.70)



Electroacupuncture compared to acupuncture

Figure 197: Spasticity outcome measures (Modified Ashworth scale, 0-5, lower values are better, final value) at ≤6 months

	Electroacupuncture			Acupuncture			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Moon 2003	2.1	0.8	15	3.2	0.79	10	-1.10 [-1.74, -0.46]



Electroacupuncture compared to usual care

Figure 198: Spasticity outcome measures (Composite spasticity scale, 0-16, lower values are better, final value) at ≤6 months

	Electroacupuncture			Usual care			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Gong 2009	7.62	1.45	124	7.31	1.32	116	0.31 [-0.04, 0.66]

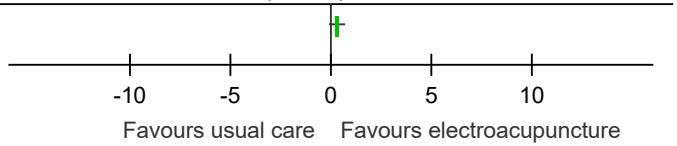


Figure 199: Physical function - lower limb (Fugl Meyer lower limb, 0-34, higher values are better, final value) at ≤6 months

	Electroacupuncture			Usual care			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Gong 2009	17.38	3.59	124	16.13	3.4	116	1.25 [0.37, 2.13]	

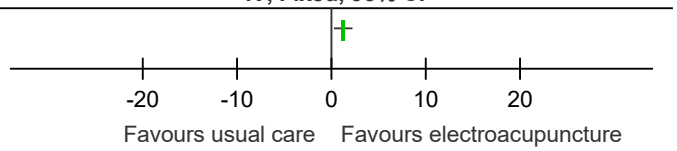
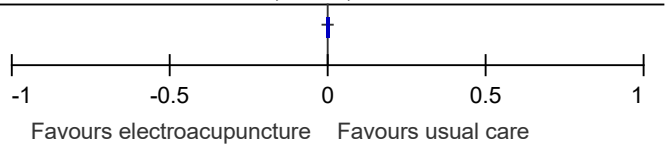


Figure 200: Withdrawal due to adverse events at ≤6 months

	Electroacupuncture		Usual care		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Gong 2009	0	124	0	116	0.00 [-0.02, 0.02]	



Appendix F – GRADE tables

Focal spasticity

Tizanidine compared to placebo

Table 65: Clinical evidence profile: tizanidine compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Tizanidine	Placebo	Relative (95% CI)	Absolute (95% CI)		
Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, change score) at ≤6 months (follow-up: 21 weeks; Scale from: 0 to 4)												
1	randomised trials	very serious[a]	not serious	serious[b]	very serious[c]	none	18	19	-	MD **0.16 higher** (0.46 lower to 0.78 higher)	⨁◯◯◯ Very low	CRITICAL
Withdrawal due to adverse events at ≤6 months (follow-up: 21 weeks)												
1	randomised trials	very serious[a]	not serious	serious[b]	very serious[c]	none	4/21 (19.0%)	0/19 (0.0%)	**OR 7.87** (1.02 to 60.71)	**190 more per 1,000** (from 10 more to 370 more)[d]	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias due to missing outcome data and bias in selection of the reported results)

b. Downgraded by 1 or 2 increments because of population indirectness (as 10-20% of the population had a traumatic brain injury rather than a stroke)

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

Onabotulinum toxin A (BOTOX) compared to tizanidine, placebo and usual care

Table 66: Clinical evidence profile: onabotulinum toxin A (BOTOX) compared to tizanidine

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Onabotulinum toxin A (BOTOX)	Tizanidine	Relative (95% CI)	Absolute (95% CI)		
Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, change scores) at ≤6 months (follow-up: 21 weeks; Scale from: 0 to 4)												
1	randomised trials	very serious[a]	not serious	serious[b]	serious[c]	none	19	18	-	MD **1.04 lower** (1.74 lower to 0.34 lower)	⨁◯◯◯ Very low	CRITICAL
Withdrawal due to adverse events at ≤6 months (follow-up: 21 weeks)												
1	randomised trials	very serious[a]	not serious	serious[b]	very serious[c]	none	3/20 (15.0%)	4/21 (19.0%)	**RR 0.79** (0.20 to 3.09)	**40 fewer per 1,000** (from 152 fewer to 398 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias due to missing outcome data and bias in selection of the reported results)

b. Downgraded by 1 or 2 increments because of population indirectness (as 10-20% of the population had a traumatic brain injury rather than a stroke)

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 67: Clinical evidence profile: onabotulinum toxin A (BOTOX) compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Onabotulinum toxin A (BOTOX)	Placebo	Relative (95% CI)	Absolute (95% CI)		
Person/participant generic health-related quality of life (EQ-5D, 0-1, higher values are better, final value) at ≤6 months (follow-up: 5 weeks; Scale from: 0 to 1)												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	14	14	-	MD **0.05 lower** (0.13 lower to 0.03 higher)	⨁⨁◯◯ Low	CRITICAL
Spasticity outcome (Modified Ashworth scale, Resistance to passive movement (REPAS) [different scale ranges], lower values are better, change scores) at ≤6 months (follow-up: mean 11 weeks)												
7	randomised trials	serious[b]	very serious[c]	not serious	serious[a]	none	517	490	-	SMD **0.68 SD lower** (1.2 lower to 0.15 lower)	⨁◯◯◯ Very low	CRITICAL
Spasticity outcome (Modified Ashworth scale, 0-4 , lower values are better, final values) at ≤6 months (follow-up: mean 6 months)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	18	18	-	MD **0.22 SD lower** (0.67 lower to 0.23 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Physical function - upper limb (ARAT, FMA-UE [different scale ranges, higher values are better, final values) at ≤6 months (follow-up: mean 11 weeks)												
3	randomised trials	not serious	not serious	not serious	serious[a]	none	72	75	-	SMD **0.26 SD higher** (0.06 lower to 0.59 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Physical function - upper limb (ARAT, 0-57, higher values are better, change score) at ≤6 months (follow-up: 20 weeks; Scale from: 0 to 57)												
1	randomised trials	very serious[d]	not serious	not serious	very serious[a]	none	16	7	-	MD **3.8 lower** (20.27 lower to 12.67 higher)	⨁◯◯◯ Very low	CRITICAL
Physical function - lower limb (FMA-LE, 0-34, higher values are better, final value) at ≤6 months (follow-up: 8 weeks; Scale from: 0 to 34)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Onabotulinum toxin A (BOTOX)	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	11	12	-	MD **1.2 higher** (2.47 lower to 4.87 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Pain (VAS, NRS, 0-10, lower vales are better, change score and final value) at ≤6 months (follow-up: 9 weeks; Scale from: 0 to 10)												
2	randomised trials	serious[e]	very serious[c]	not serious	serious[a]	none	251	253	-	MD **0.24 lower** (1.45 lower to 0.97 higher)	⨁◯◯◯ Very low	CRITICAL
Activities of daily living (Barthel index, 0-100, higher values are better, final value) at ≤6 months (follow-up: 8 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	11	12	-	MD **15.4 higher** (6.68 higher to 24.12 higher)	⨁⨁⨁⨁ High	CRITICAL
Activities of daily living (Disability assessment scale, 0-3, lower values are better, change scores) at ≤6 months (follow-up: 12 weeks; Scale from: 0 to 3)												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	136	99	-	MD **0.45 lower** (0.63 lower to 0.26 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Upper extremity, 0-100, higher values are better, final value) at ≤6 months (follow-up: 24 weeks; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	18	18	-	MD **2.95 higher** (0.49 higher to 5.41 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Energy, 0-100, higher values are better, final value) at ≤6 months (follow-up: 24 weeks; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	18	18	-	MD **0.56 higher** (1.17 lower to 2.29 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Family, 0-100, higher values are better, final value) at ≤6 months (follow-up: 24 weeks; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Onabotulinum toxin A (BOTOX)	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	18	18	-	MD **0.17 lower** (2.39 lower to 2.05 higher)	⨁⨁◯◯ Low	CRITICAL

Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Language, 0-100, higher values are better, final value) at ≤6 months (follow-up: 24 weeks; Scale from: 0 to 100)

1	randomised trials	not serious	not serious	not serious	serious[a]	none	18	18	-	MD **0.61 higher** (2.63 lower to 3.85 higher)	⨁⨁⨁◯ Moderate	CRITICAL

Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Mobility, 0-100, higher values are better, final value) at ≤6 months (follow-up: 24 weeks; Scale from: 0 to 100)

1	randomised trials	not serious	not serious	not serious	very serious[a]	none	18	18	-	MD **1.06 higher** (2.24 lower to 4.36 higher)	⨁⨁◯◯ Low	CRITICAL

Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Mood, 0-100, higher values are better, final value) at ≤6 months (follow-up: mean 24 weeks; Scale from: 0 to 100)

1	randomised trials	not serious	not serious	not serious	serious[a]	none	18	18	-	MD **1.05 higher** (2.26 lower to 4.36 higher)	⨁⨁⨁◯ Moderate	CRITICAL

Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Personality, 0-100, higher values are better, final value) at ≤6 months (follow-up: 24 weeks; Scale from: 0 to 100)

1	randomised trials	not serious	not serious	not serious	very serious[a]	none	18	18	-	MD **0.17 lower** (2.2 lower to 1.86 higher)	⨁⨁◯◯ Low	CRITICAL

Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Social roles, 0-100, higher values are better, final value) at ≤6 months (follow-up: 24 weeks; Scale from: 0 to 100)

1	randomised trials	not serious	not serious	not serious	very serious[a]	none	18	18	-	MD **0.16 lower** (1.2 lower to 0.88 higher)	⨁⨁◯◯ Low	CRITICAL

Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Vision, 0-100, higher values are better, final value) at ≤6 months (follow-up: 24 weeks; Scale from: 0 to 100)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Onabotulinum toxin A (BOTOX)	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	18	18	-	MD **0.11 lower** (0.85 lower to 0.63 higher)	⨁⨁◯◯ Low	CRITICAL
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Work, 0-100, higher values are better, final value) at ≤6 months (follow-up: 24 weeks; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	18	18	-	MD **0.5 higher** (1.42 lower to 2.42 higher)	⨁⨁◯◯ Low	CRITICAL
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Self-care, 0-100, higher values are better, final value) at ≤6 months (follow-up: 24 weeks; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	18	18	-	MD **1.04 higher** (1.54 lower to 3.62 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact Scale - Thinking, 0-100, higher values are better, final value) at ≤6 months (follow-up: 24 weeks; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	18	18	-	MD **0.22 lower** (1.5 lower to 1.06 higher)	⨁⨁◯◯ Low	CRITICAL
Withdrawal due to adverse events at ≤6 months (follow-up: mean 12 weeks)												
15	randomised trials	not serious	serious[f]	not serious	very serious[g]	none	49/1152 (4.3%)	32/1103 (2.9%)	**RD 0.01** (-0.01 to 0.03)	**10 more per 1,000** (from 10 fewer to 30 more)[h]	⨁◯◯◯ Very low	CRITICAL
Withdrawal due to adverse events at >6 months (follow-up: 52 weeks)												
1	randomised trials	serious[e]	not serious	not serious	serious[a]	none	0/139 (0.0%)	7/135 (5.2%)	**OR 0.13** (0.03 to 0.56)	**45 fewer per 1,000** (from 50 fewer to 22 fewer)	⨁⨁◯◯ Low	CRITICAL

1 **CI:** confidence interval; **MD:** mean difference; **OR:** odds ratio; **SMD:** standardised mean difference

Explanations

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

b. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias arising from the randomisation process, bias due to missing outcome data and bias in selection of reported result)

c. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

d. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias arising from the randomisation process and bias due to missing outcome data)

e. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias in selection of reported result)

f. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

g. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

h. Absolute effect calculated by risk difference due to zero events in at least one study arm

Table 68: Clinical evidence profile: onabotulinum toxin A (BOTOX) compared to usual care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Onaobotulinum toxin (BOTOX)	Usual care	Relative (95% CI)	Absolute (95% CI)		
Spasticity outcome measures (Clinical spasticity influx, Tardieu scale [different scale ranges] lower values are better, final value) at ≤6 months (follow-up: 12 weeks)												
2	randomised trials	serious[a]	very serious[b]	serious[c]	very serious[d]	none	45	49	-	SMD **1.43 SD lower** (4.46 lower to 1.61 higher)	⨁◯◯◯ Very low	CRITICAL
Physical function - lower limb (6 minute walk test, lower values are better, final value) at ≤6 months (follow-up: 12 weeks)												
1	randomised trials	not serious	not serious	serious	serious[d]	none	12	14	-	MD **0.08 lower** (0.42 lower to 0.26 higher)	⨁⨁◯◯ Low	CRITICAL
Physical function - lower limb (Fugl-meyer assessment, 0-34, higher values are better, final value) at ≤6 months (follow-up: 6 months; Scale from: 0 to 34) (follow-up: 12 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Onaobotulinum toxin (BOTOX)	Usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious[e]	not serious	serious[c]	not serious	none	33	35	-	MD **9.96 higher** (8.56 higher to 11.36 higher)	⨁◯◯◯ Very low	CRITICAL
Activities of daily living (FIM, 18-126, higher values are better, final values) at ≤6 months (follow-up: 12 weeks; Scale from: 18 to 126)												
1	randomised trials	very serious[f]	not serious	serious[c]	not serious	none	33	35	-	MD **12.1 higher** (7.03 higher to 17.7 higher)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **SMD:** standardised mean difference

Explanations

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias due to missing data and bias in the measurement of the outcome)

b. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

c. Downgraded by 1 increment because of population indirectness (where a mixed population of focal 70% and multifocal spasticity 30% were included)

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

e. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a bias arising from the randomisation process, bias due to deviation from intended intervention, bias due to missing outcome data and bias in measurement of the outcome)

f. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a bias arising from the randomisation process, bias due to missing outcome data and bias in measurement of the outcome)

Abobotulinum toxin A (Dysport) compared to tizanidine, placebo and usual care

Table 69: Clinical evidence profile: abobotulinum toxin A (Dysport) compared to tizanidine

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Abobotulinum toxin A (Dysport)	Tizanidine	Relative (95% CI)	Absolute (95% CI)		
Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, final value) at ≤6 months (follow-up: 24 weeks; Scale from: 0 to 4)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	34	34	-	MD **0.64 lower** (0.89 lower to 0.39 lower)	⨁⨁◯◯ Low	CRITICAL
Physical function - upper limb (ARAT, 0-57, higher values are better, final value) at ≤6 months (follow-up: 24 weeks; Scale from: 0 to 57)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	34	34	-	MD **0.56 lower** (3.06 lower to 1.94 higher)	⨁⨁◯◯ Low	CRITICAL
Withdrawal due to adverse events at ≤6 months (follow-up: 24 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	0/34 (0.0%)	20/34 (58.8%)	**OR 0.06** (0.02 to 0.17)	**590 fewer per 1,000** (from 760 fewer to 420 fewer)[b]	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

Explanations

a. Downgraded by 2 increments as the majority of the evidence was at very high risk of bias (due to bias arising from the randomisation process, bias due to deviations from the intended interventions and bias due to missing outcome data)

b. Absolute effect calculated by risk difference due to zero events in at least one study arm

Table 70: Clinical evidence profile: abobotulinum toxin A (Dysport) compared to neuromuscular electrical stimulation

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Abobotulinum toxin A (Dysport)	neuromuscular electrical stimulation	Relative (95% CI)	Absolute (95% CI)		
Spasticity outcome measures (Modified Ashworth scale, 0-5, lower values are better, final value) at												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	6	6	-	MD **0.11 higher** (1.2 lower to 1.42 higher)	⨁◯◯◯ Very low	CRITICAL
Withdrawal due to adverse events at ≤6 months												
1	randomised trials	serious[a]	not serious	not serious	very serious[c,d]	none	0/6 (0.0%)	0/6 (0.0%)	**RD 0.00** (-0.27 to -0.27)	**0 fewer per 1,000** (from 270 fewer to 270 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference

Explanations

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias arising from the randomisation process)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

d. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

Table 71: Clinical evidence profile: abobotulinum toxin A (Dysport) compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Abobotulinum toxin A (Dysport)	Placebo	Relative (95% CI)	Absolute (95% CI)		
Person/participant generic health-related quality of life (AQOL, 0-1, higher values are better, change score) at ≤6 months (follow-up: 20 weeks; Scale from: 0 to 1)												
1	randomised trials	serious[b]	not serious	not serious	serious[a]	none	54	42	-	MD **0.03 lower** (0.09 lower to 0.03 higher)	⨁⨁◯◯ Low	CRITICAL
Spasticity outcome (Modified Ashworth scale, ROC analysis [different scale ranges], lower values are better, change scores) at ≤6 months (follow-up: 8 weeks)												
4	randomised trials	serious[c]	serious[d]	not serious	serious[a]	none	313	177	-	SMD **0.8 SD lower** (1.17 lower to 0.43 lower)	⨁◯◯◯ Very low	CRITICAL
Spasticity outcome (Modified Ashworth scale [different scale ranges] lower values are better, final value) at ≤6 months (follow-up: mean 8 weeks)												
3	randomised trials	serious[e]	serious[d]	not serious	serious[a]	none	105	107	-	SMD **0.5 SD lower** (1.19 lower to 0.19 higher)	⨁◯◯◯ Very low	CRITICAL
Spasticity outcome (Modified Ashworth scale, 0-4, lower values are better, final value) at >6 months (follow-up: 9 months; Scale from: 0 to 4)												
1	randomised trials	serious[f]	not serious	not serious	serious[a]	none	20	20	-	MD **0.5 lower** (1.04 lower to 0.04 higher)	⨁⨁◯◯ Low	CRITICAL
Physical function - upper limb (Rivermead motor assessment arm, scale range unclear, lower values are better, change score) at ≤6 months (follow-up: mean 4 weeks)												
1	randomised trials	very serious[g]	not serious	not serious	very serious[a]	none	63	19	-	MD **0** (0.37 lower to 0.37 higher)	⨁◯◯◯ Very low	CRITICAL
Physical function - lower limb (2 min walk test, meters, higher values are better, final value) at ≤6 months (follow-up: 12 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Abobotulinum toxin A (Dysport)	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[f]	not serious	not serious	not serious	none	164	54	-	MD **0.84 lower** (9.56 lower to 7.88 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Pain (VAS, Global pain scale, 0-100, lower values are better, change score) at ≤6 months (follow-up: mean 12 weeks)												
2	randomised trials	serious[b]	not serious	not serious	serious[a]	none	134	125	-	MD **7.57 lower** (13.69 lower to 1.44 lower)	⨁⨁◯◯ Low	CRITICAL
Activities of daily living (Barthel index, disability assessment scale [different scale ranges], higher values are better, change scores) at ≤6 months (follow-up: mean 5 weeks)												
3	randomised trials	not serious	not serious	not serious	not serious	none	302	181	-	SMD **0.06 SD higher** (0.21 lower to 0.33 higher)	⨁⨁⨁⨁ High	CRITICAL
Stroke outcome - Modified Rankin scale (Modified Rankin scale, 0-6, higher values are better, change score) at ≤6 months (follow-up: 4 weeks; Scale from: 0 to 6)												
1	randomised trials	serious[b]	not serious	not serious	very serious[a]	none	80	83	-	MD **0.09 higher** (0.14 lower to 0.32 higher)	⨁◯◯◯ Very low	CRITICAL
Withdrawal due to adverse events at ≤6 months (follow-up: mean 14 weeks)												
7	randomised trials	not serious	serious[h]	not serious	serious[i]	none	31/543 (5.7%)	9/316 (2.8%)	**RD 0.02** (-0.01 to 0.04)	**20 more per 1,000** (from 10 fewer to 40 more)[j]	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **MD:** mean difference; **SMD:** standardised mean difference

Explanations

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

b. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias in selection of the reported result)

c. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias arising from the randomisation process and bias in selection of the reported result)

d. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

e. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias due to missing outcome data and bias in selection of the reported result)

f. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias due to missing outcome data)

g. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a bias arising from the randomisation process and bias in selection of the reported result)

h. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

i. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

j. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

Table 72: Clinical evidence profile: abobotulinum toxin A (Dysport) compared to usual care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Abobotulinum toxin A (Dysport)	usual care	Relative (95% CI)	Absolute (95% CI)		
Person/participant generic health-related quality of life (EQ5D, -0.11-1, higher values are better, final value) at ≤6 months (follow-up: 3 months; Scale from: -0.11 to 1)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	150	133	-	MD **0.03** (0.04 lower to 0.1 higher)	⨁◯◯◯ Very low	CRITICAL
Person/participant generic health-related quality of life (EQ5D, -0.11-1, higher values are better, final value) at >6 months (follow-up: 12 months; Scale from: -0.11 to 1)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	88	86	-	MD **0.05** (0.04 lower to 0.14 higher)	⨁◯◯◯ Very low	CRITICAL
Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, final value) at ≤6 months (follow-up: 3 months; Scale from: 0 to 4)												
1	randomised trials	serious[c]	not serious	not serious	not serious	none	163	151	-	MD **0.2 lower** (0.42 lower to 0.02 higher)	⨁⨁⨁◯ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Abobotulinum toxin A (Dysport)	usual care	Relative (95% CI)	Absolute (95% CI)		
Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, final value) at >6 months (follow-up: 12 months; Scale from: 0 to 4)												
1	randomised trials	serious[c]	not serious	not serious	not serious	none	92	97	-	MD **0.1 lower** (0.46 lower to 0.26 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Physical function - upper limb (ARAT, 0-57, higher values are better, final values) at ≤6 months (follow-up: 3 months; Scale from: 0 to 57)												
1	randomised trials	serious[c]	not serious	not serious	not serious	none	163	151	-	MD **1.1 higher** (2.06 lower to 4.26 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Physical function - upper limb (ARAT, 0-57, higher values are better, final value) at >6 months (follow-up: 12 months; Scale from: 0 to 57)												
1	randomised trials	serious[c]	not serious	not serious	not serious	none	92	97	-	MD **1.7 higher** (2.42 lower to 5.82 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Pain (VAS, 0-10, lower values are better, final value) at ≤6 months (follow-up: 3 months; Scale from: 0 to 10)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	163	151	-	MD **0.4 lower** (1.24 lower to 0.44 higher)	⨁⨁◯◯ Low	CRITICAL
Pain (VAS, 0-10, lower values are better, final value) at >6 months (follow-up: 12 months; Scale from: 0 to 10)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	92	97	-	MD **1.4 lower** (2.38 lower to 0.42 lower)	⨁◯◯◯ Very low	CRITICAL
Activities of daily living (Barthel index, 0-100, higher values are better, final value) at >6 months (follow-up: 3 months; Scale from: 0 to 100)												
1	randomised trials	serious[c]	not serious	not serious	not serious	none	92	97	-	MD **0.3 lower** (1.63 lower to 1.03 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Activities of daily living (Barthel index, 0-100, higher values are better, final value) at ≤6 months (follow-up: 12 months; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Abobotulinum toxin A (Dysport)	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[c]	not serious	not serious	not serious	none	163	151	-	MD **0** (1.6 lower to 1.6 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Strength, 0-100, higher values are better, final values) at ≤6 months (follow-up: 3 months; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	163	151	-	MD **0.9 higher** (4.31 lower to 6.11 higher)	⨁⨁◯◯ Low	CRITICAL
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Memory, 0-100, higher values are better, final values) at ≤6 months (follow-up: 3 months; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	163	151	-	MD **1.5 higher** (4.39 lower to 7.39 higher)	⨁⨁◯◯ Low	CRITICAL
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Emotion, 0-100, higher values are better, final values) at ≤6 months (follow-up: 3 months; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	163	151	-	MD **3.4 lower** (7.26 lower to 0.46 higher)	⨁⨁◯◯ Low	CRITICAL
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Communication, 0-100, higher values are better, final values) at ≤6 months (follow-up: 3 months; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	163	151	-	MD **3.1 higher** (2.95 lower to 9.15 higher)	⨁⨁◯◯ Low	CRITICAL
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - ADL, 0-100, higher values are better, final values) at ≤6 months (follow-up: 3 months; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	163	151	-	MD **0** (4.71 lower to 4.71 higher)	⨁⨁◯◯ Low	CRITICAL
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Mobility, 0-100, higher values are better, final values) at ≤6 months (follow-up: 3 months; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Abobotulinum toxin A (Dysport)	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	163	151	-	MD **1.3 lower** (7.41 lower to 4.81 higher)	⨁⨁◯◯ Low	CRITICAL

Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Hand function,0-100, higher values are better, final values) at ≤6 months (follow-up: 3 months; Scale from: 0 to 100)

1	randomised trials	very serious[a]	not serious	not serious	not serious	none	163	151	-	MD **1.2 higher** (3.65 lower to 6.05 higher)	⨁⨁◯◯ Low	CRITICAL

Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Participation/handicap, 0-100, higher values are better, final values) at ≤6 months (follow-up: 3 months; Scale from: 0 to 100)

1	randomised trials	very serious[a]	not serious	not serious	not serious	none	163	151	-	MD **0.4 higher** (6.2 lower to 7 higher)	⨁⨁◯◯ Low	CRITICAL

Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Physical domains, 0-100, higher values are better, final values) at ≤6 months (follow-up: 3 months; Scale from: 0 to 100)

1	randomised trials	very serious[a]	not serious	not serious	not serious	none	163	151	-	MD **0.1 higher** (4.18 lower to 4.38 higher)	⨁⨁◯◯ Low	CRITICAL

Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Stroke recovery, 0-100, higher values are better, final values) at ≤6 months (follow-up: 3 months; Scale from: 0 to 100)

1	randomised trials	very serious[a]	not serious	not serious	not serious	none	163	151	-	MD **0.3 lower** (5.08 lower to 4.48 higher)	⨁⨁◯◯ Low	CRITICAL

Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Strength, 0-100, higher values are better, final values) at >6 months (follow-up: 12 months; Scale from: 0 to 100)

1	randomised trials	very serious[a]	not serious	not serious	not serious	none	92	97	-	MD **1.8 higher** (5.8 lower to 9.4 higher)	⨁⨁◯◯ Low	CRITICAL

Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Memory, 0-100, higher values are better, final values) at >6 months (follow-up: 12 months; Scale from: 0 to 100)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Abobotulinum toxin A (Dysport)	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	92	97	-	MD **3.9 higher** (5.13 lower to 12.93 higher)	⨁⨁◯◯ Low	CRITICAL

Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Emotion, 0-100, higher values are better, final values) at >6 months (follow-up: 12 months; Scale from: 0 to 100)

1	randomised trials	very serious[a]	not serious	not serious	not serious	none	92	97	-	MD **1 lower** (7.5 lower to 5.5 higher)	⨁⨁◯◯ Low	CRITICAL

Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Communication,0-100, higher values are better, final values) at >6 months (follow-up: 12 months; Scale from: 0 to 100)

1	randomised trials	very serious[a]	not serious	not serious	not serious	none	92	97	-	MD **1.2 higher** (8.56 lower to 10.96 higher)	⨁⨁◯◯ Low	CRITICAL

Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - ADL, 0-100, higher values are better, final values) at >6 months (follow-up: 12 months; Scale from: 0 to 100)

1	randomised trials	very serious[a]	not serious	not serious	not serious	none	92	97	-	MD **2.5 higher** (5 lower to 10 higher)	⨁⨁◯◯ Low	CRITICAL

Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Mobility, 0-100, higher values are better, final values) at >6 months (follow-up: 12 months; Scale from: 0 to 100)

1	randomised trials	very serious[a]	not serious	not serious	not serious	none	92	97	-	MD **1 lower** (10.41 lower to 8.41 higher)	⨁⨁◯◯ Low	CRITICAL

Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Hand function, 0-100, higher values are better, final values) at >6 months (follow-up: 12 months; Scale from: 0 to 100)

1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	92	97	-	MD **6.8 higher** (0.68 lower to 14.28 higher)	⨁◯◯◯ Very low	CRITICAL

Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Participation/handicap,0-100, higher values are better, final values) at >6 months (follow-up: 12 months; Scale from: 0 to 100)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Abobotulinum toxin A (Dysport)	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	92	97	-	MD **0.4 higher** (10.66 lower to 11.46 higher)	⨁⨁◯◯ Low	CRITICAL
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Physical domains, 0-100, higher values are better, final values) at >6 months (follow-up: 12 months; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	92	97	-	MD **2.6 higher** (3.85 lower to 9.05 higher)	⨁⨁◯◯ Low	CRITICAL
Stroke-specific Patient-Reported Outcome Measures (Stroke Impact scale - Stroke recovery, 0-100, higher values are better, final values) at >6 months (follow-up: 12 months; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	92	97	-	MD **3.4 higher** (4.83 lower to 11.63 higher)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **MD:** mean difference

Explanations

a. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias due to deviations from the intended intervention and bias in measurement of the outcome)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias due to deviations from the intended intervention)

Incobotulinum toxin A (Xeomin) compared to oral baclofen, placebo and usual care

Table 73: Clinical evidence profile: incobotulinum toxin A (Xeomin) compared to oral baclofen

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Incobotulinum Toxin A (Xeomin)	Baclofen (oral)	Relative (95% CI)	Absolute (95% CI)		
Person/participant generic health-related quality of life (Romanian version of the general instrument 15D, 0-1, higher values are better, final value) at ≤6 months (follow-up: 6 months; Scale from: 0 to 1)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	17	17	-	MD **0.04 higher** (0.05 lower to 0.13 higher)	⨁◯◯◯ Very low	CRITICAL
Spasticity outcome measures (Tardieu scale, 0-4, lower values are better, final value) at ≤6 months (follow-up: 6 months; Scale from: 0 to 4)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	17	17	-	MD **0.03 lower** (0.52 lower to 0.46 higher)	⨁◯◯◯ Very low	CRITICAL
Physical function - upper limb (muscle strength, 0-5, higher values are better, final value) at ≤6 months (follow-up: 6 months; Scale from: 0 to 5)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	17	17	-	MD **0.26 higher** (0.1 lower to 0.62 higher)	⨁◯◯◯ Very low	CRITICAL
Activities of daily living (Barthel Index, 0-100, higher values are better, final value) at ≤6 months (follow-up: 6 months; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	17	17	-	MD **5.59 higher** (4.51 lower to 15.69 higher)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference

Explanations

a. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a mixture of bias arising from the randomisation process, bias due to deviations from the intended interventions, bias due to missing outcome data and bias in measurement of the outcome)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 74: Clinical evidence profile: incobotulinum toxin A (Xeomin) compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Incobotulinum toxin A (Xeomin)	Placebo	Relative (95% CI)	Absolute (95% CI)		
Spasticity outcome (Modified Ashworth scale, 0-4, lower values are better, change scores) at ≤6 months (follow-up: mean 6 weeks; Scale from: 0 to 4)												
2	randomised trials	not serious	not serious[a]	not serious	not serious	none	275	192	-	MD **0.3 lower** (0.5 lower to 0.1 lower)	⨁⨁⨁⨁ High	CRITICAL
Physical function - lower limb (10 meter walk test, seconds, lower values are better, change score) at ≤6 months (follow-up: 12 weeks)												
1	randomised trials	very serious[b]	not serious	not serious	serious[c]	none	56	60	-	MD **1.9 lower** (5.78 lower to 1.98 higher)	⨁◯◯◯ Very low	CRITICAL
Pain (Ankle pain score, scale range unclear, lower values are better, change score) at ≤6 months (follow-up: 12 weeks)												
1	randomised trials	serious[d]	not serious	not serious	not serious	none	104	104	-	MD **0.1 lower** (0.65 lower to 0.45 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Withdrawal due to adverse events at ≤6 months (follow-up: 12 weeks)												
3	randomised trials	not serious	not serious	not serious	very serious[c]	none	4/244 (1.6%)	7/212 (3.3%)	**RR 0.40** (0.12 to 1.29)	**20 fewer per 1,000** (from 29 fewer to 10 more)	⨁⨁◯◯ Low	CRITICAL
Withdrawal due to adverse events at >6 months (follow-up: 48 weeks)												
1	randomised trials	not serious	not serious	not serious	serious[e]	none	0/171 (0.0%)	0/88 (0.0%)	**RD 0.00** (-0.02 to 0.02)	**0 fewer per 1,000** (from 20 fewer to 20 more)[f]	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. While there is significant heterogeneity in the forest plot, all effect sizes are in the same direction and confidence intervals after the minimally important difference. Therefore, any inconsistency has been thought to not be important, and so this has not been downgraded for in this case

b. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias arising from the randomisation process, bias due to deviations from the intended interventions and bias due to missing outcome data)

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias arising from the randomisation process)

e. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

f. Absolute effect calculated by risk difference due to zero events in at least one study arm

Table 75: Clinical evidence profile: incobotulinum toxin A (Xeomin) compared to usual care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Incobotulinum toxin A (Xeomin)	Usual care	Relative (95% CI)	Absolute (95% CI)		
Spasticity outcome measures (Modified Ashworth scale, 0-5, lower values are better, change score and final value) at ≤6 months (follow-up: 14 weeks; Scale from: 0 to 5)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	9	8	-	MD **1 lower** (1.77 lower to 0.23 lower)	⨁◯◯◯ Very low	CRITICAL
Physical function - upper limb (Fugl-Meyer score, 0-66, higher values are better, final value) at ≤6 months (follow-up: 6 months; Scale from: 0 to 66)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	9	8	-	MD **0.3 higher** (4.84 lower to 5.44 higher)	⨁⨁◯◯ Low	CRITICAL
Activities of daily living (disability scale, 0-24, lower values are better, final value) at ≤6 months (follow-up: 6 months; Scale from: 0 to 24)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	9	8	-	MD **5.2 lower** (8.9 lower to 1.5 lower)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Incobotulinum toxin A (Xeomin)	Usual care	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse events at ≤6 months (follow-up: 6 months)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[c]	none	0/9 (0.0%)	0/9 (0.0%)	**RD 0.00** (-0.19 to 0.19)	**0 fewer per 1,000** (from 190 fewer to 190 more)[d]	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference

Explanations

a. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a mixture of bias due to deviations from the intended interventions, bias due to missing outcome data and bias in measurement of the outcome)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

d. Absolute effect calculated by risk difference due to zero events in at least one study arm

Functional electrical stimulation compared to placebo and usual care

Table 76: Clinical evidence profile: functional electrical stimulation compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Functional electrical stimulation	Placebo	Relative (95% CI)	Absolute (95% CI)		
Spasticity outcome measures (Composite spasticity scale, 0-100, lower values are better, final value) at ≤6 months (follow-up: 8 weeks; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Functional electrical stimulation	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	13	15	-	MD **14.2 lower** (82.85 lower to 54.45 higher)	⨁◯◯◯ Very low	CRITICAL
Physical function - lower limb (Timed up and go, seconds, lower values are better, final value) at ≤6 months (follow-up: 8 weeks)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	13	15	-	MD **3.3 lower** (21.46 lower to 14.86 higher)	⨁◯◯◯ Very low	CRITICAL
Physical function - lower limb (walking speed, m/s, higher values are better, change score) at ≤6 months (follow-up: 11 days)												
1	randomised trials	serious[c]	not serious	not serious	very serious[b]	none	13	13	-	MD **0.02 higher** (0.07 lower to 0.11 higher)	⨁◯◯◯ Very low	CRITICAL
Activities of daily living (FIM, 1-7, higher values are better, final value) at ≤6 months (follow-up: 11 days; Scale from: 1 to 7)												
1	randomised trials	serious[c]	not serious	not serious	very serious[b]	none	13	13	-	MD **0.1 higher** (0.72 lower to 0.92 higher)	⨁◯◯◯ Very low	CRITICAL
Withdrawal due to adverse events at ≤6 months (follow-up: 11 days)												
1	randomised trials	serious[c]	not serious	not serious	very serious[d]	none	0/16 (0.0%)	0/16 (0.0%)	**RD 0.00** (-0.11 to 0.11)	**0 fewer per 1,000** (from 110 fewer to 110 more)[e]	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference

Explanations

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias arising from the randomisation process)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias due to missing outcome data)

d. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

e. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

Table 77: Clinical evidence profile: functional electrical stimulation compared to usual care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Functional electrical stimulation	Usual care	Relative (95% CI)	Absolute (95% CI)		
Spasticity outcome measures (Modified Ashworth scale, Composite spasticity scale [different scale ranges], lower values are better, final values) at ≤6 months (follow-up: mean 8 weeks)												
2	randomised trials	very serious[a]	very serious[b]	not serious	serious[c]	none	46	42	-	SMD **0.99 SD lower** (2.1 lower to 0.11 higher)	⨁◯◯◯ Very low	CRITICAL
Spasticity outcome measures (Composite spasticity scale, %, 0-100, lower values are better, change score) at ≤6 months (follow-up: 8 weeks; Scale from: 0 to 100)												
1	randomised trials	serious[d]	not serious	not serious	serious[c]	none	13	13	-	MD **36.8 lower** (98.61 lower to 25.01 higher)	⨁⨁◯◯ Low	CRITICAL
Physical function - upper limb (Rivermead motor assessment hand, 0-13, higher values are better, final value) at ≤6 months (follow-up: 4 weeks; Scale from: 0 to 13)												
1	randomised trials	very serious[a]	not serious	not serious	serious[c]	none	15	15	-	MD **0.66 higher** (0.06 lower to 1.38 higher)	⨁◯◯◯ Very low	CRITICAL
Physical function - lower limb (Berg Balance Scale, FMA-LE [different scale ranges], higher values are better, final values) at ≤6 months (follow-up: mean 6 weeks)												
4	randomised trials	very serious[e]	very serious[b]	not serious	serious[c]	none	303	310	-	SMD **0.54 SD higher** (0.02 lower to 1.1 higher)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Functional electrical stimulation	Usual care	Relative (95% CI)	Absolute (95% CI)		
Physical function - lower limb (6 min walk, meters, higher values are better, final value) at ≤6 months (follow-up: 12 weeks)												
1	randomised trials	very serious[f]	not serious	not serious	serious[c]	none	20	24	-	MD **47.52 higher** (21.21 lower to 116.25 higher)	⨁◯◯◯ Very low	CRITICAL
Physical function - lower limb (timed up and go, seconds, lower values are better, final value) at ≤6 months (follow-up: 8 weeks)												
1	randomised trials	serious[d]	not serious	not serious	serious[c]	none	13	13	-	MD **11.3 lower** (31.25 lower to 8.65 higher)	⨁⨁◯◯ Low	CRITICAL
Activities of daily living (Barthel index, 0-100, higher values are better, final values) at ≤6 months (follow-up: mean 4 weeks; Scale from: 0 to 100)												
2	randomised trials	very serious[a]	not serious	not serious	not serious	none	34	33	-	MD **8.46 higher** (3.36 higher to 13.57 higher)	⨁⨁◯◯ Low	CRITICAL
Stroke-specific Patient-Reported Outcome Measures (Stroke-Specific Quality of Life, 49-245, higher values are better, final values) at ≤6 months (follow-up: 6 months; Scale from: 49 to 245)												
1	randomised trials	very serious[g]	not serious	not serious	not serious	none	242	253	-	MD **2.4 lower** (9.47 lower to 4.67 higher)	⨁⨁◯◯ Low	CRITICAL
Withdrawal due to adverse events at ≤6 months (follow-up: mean 13 weeks)												
4	randomised trials	very serious[h]	serious[i]	not serious	very serious[i]	none	9/304 (3.0%)	6/316 (1.9%)	**RD 0.01** (-0.02 to 0.04)	**10 more per 1,000** (from 20 fewer to 40 more)[k]	⨁◯◯◯ Very low	CRITICAL

1 **CI:** confidence interval; **MD:** mean difference; **SMD:** standardised mean difference

2 Explanations

a. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a mixture of bias arising from the randomisation process and bias due to missing outcome data)

b. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. Downgraded by 2 increments as the majority of the evidence was of high risk of bias (due to bias due to missing outcome data)

e. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a mixture of bias arising from the randomisation process, bias due to missing outcome data and bias in measurement of the outcome)

f. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a mixture of bias arising from the randomisation process and bias due to deviations from the intended intervention)

g. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias due to deviations from the intended intervention, bias due to missing outcome data and bias in measurement of the outcome)

h. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a mixture of bias arising from the randomisation process, bias due to deviations from the intended intervention and bias due to missing outcome data)

i. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

j. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

k. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

Neuromuscular electrical stimulation compared to transcutaneous electrical nerve stimulation, placebo and usual care

Table 78: Clinical evidence profile: neuromuscular electrical stimulation compared to transcutaneous electrical nerve stimulation

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Neuromuscular electrical stimulation	TENS	Relative (95% CI)	Absolute (95% CI)		
Spasticity outcome measure (modified Ashworth scale, 0-6, lower values are better, change score) at ≤6 months (follow-up: 8 weeks; Scale from: 0 to 6)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	36	36	-	MD **0.08 higher** (1.23 lower to 1.39 higher)	⨁◯◯◯ Very low	CRITICAL
Physical function - upper limb (Fugl-meyer- Upper limb, 0-66, higher values are better, change score) at ≤6 months (follow-up: 8 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Neuromuscular electrical stimulation	TENS	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	36	36	-	MD **0.6 lower** (21.57 lower to 20.37 higher)	⨁◯◯◯ Very low	CRITICAL
Pain (Numeric rating scale, 0-10, lower values are better, change score) at ≤6 months (follow-up: 8 weeks; Scale from: 0 to 10)												
1	randomised trials	very serious[c]	not serious	not serious	very serious[b]	none	36	36	-	MD **0.67 lower** (3.72 lower to 2.38 higher)	⨁◯◯◯ Very low	CRITICAL
Activities of daily living (Barthel index, 0-100, higher values are better, change score) at ≤6 months (follow-up: 8 weeks; Scale from: 0 to 100)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	36	36	-	MD **3.15 lower** (40.7 lower to 34.4 higher)	⨁◯◯◯ Very low	CRITICAL
Stroke-specific Patient-Reported Outcome Measures (SS-QOL, 49-245, higher values are better, change score) at ≤6 months (follow-up: 8 weeks; Scale from: 49 to 245)												
1	randomised trials	very serious[c]	not serious	not serious	very serious[b]	none	36	36	-	MD **5.13 higher** (44.55 lower to 54.81 higher)	⨁◯◯◯ Very low	CRITICAL
Withdrawal due to adverse events at ≤6 months (follow-up: 8 weeks)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	15/36 (41.7%)	8/36 (22.2%)	**RR 1.88** (0.91 to 3.86)	**196 more per 1,000** (from 20 fewer to 636 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias due to missing outcome data)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias due to missing outcome data and bias in measurement of the outcome)

Table 79: Clinical evidence profile: neuromuscular electrical stimulation compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal Spasticity - Neuromuscular electrical stimulation	placebo	Relative (95% CI)	Absolute (95% CI)		
Spasticity outcome measures (Modified Ashworth scale, Leeds adult/arm spasticity impact scale [different scale ranges], lower values are better, final values) at ≤6 months (follow-up: mean 9 weeks)												
3	randomised trials	serious[a]	not serious	not serious	not serious	none	57	51	-	SMD **0.02 SD lower** (0.41 lower to 0.36 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Physical function - upper limb (Fugl Meyer Assessment - Upper Extremity, 0-66, higher values are better, final values) at ≤6 months (follow-up: mean 9 weeks; Scale from: 0 to 66)												
3	randomised trials	serious[a]	not serious	not serious	serious[b]	none	57	51	-	MD **2.91 higher** (1.76 lower to 7.58 higher)	⨁⨁◯◯ Low	CRITICAL
Pain (Visual analogue scale, 0-10, lower values are better, final value) at ≤6 months (follow-up: 20 weeks; Scale from: 0 to 10)												
1	randomised trials	very serious[c]	not serious	not serious	very serious[b]	none	7	7	-	MD **1.3 higher** (1.4 lower to 4 higher)	⨁◯◯◯ Very low	CRITICAL
Activities of daily living (Functional Independence Measure Self-Care subscale, 0-100, higher values are better, final value) at ≤6 months (follow-up: 3 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious[d]	not serious	not serious	serious[b]	none	20	10	-	MD **5.81 higher** (0.89 lower to 12.51 higher)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal Spasticity - Neuromuscular electrical stimulation	placebo	Relative (95% CI)	Absolute (95% CI)		
Stroke-specific Patient-Reported Outcome Measures (Stroke impact scale, 0-100, higher values are better, final value) at ≤6 months (follow-up: 4 months; Scale from: 0 to 100)												
1	randomised trials	serious[e]	not serious	not serious	serious[b]	none	20	19	-	MD **3.26 higher** (3.41 lower to 9.93 higher)	⨁⨁◯◯ Low	CRITICAL
Additional health care contacts (prescription of spasticity medication) at ≤6 months (follow-up: 10 weeks)												
1	randomised trials	serious[e]	not serious	not serious	very serious[b]	none	5/24 (20.8%)	2/24 (8.3%)	**RR 2.50** (0.54 to 11.65)	**125 more per 1,000** (from 38 fewer to 888 more)	⨁◯◯◯ Very low	CRITICAL
Additional health care contacts (prescription of pain medication) at ≤6 months (follow-up: 10 weeks)												
1	randomised trials	serious[e]	not serious	not serious	serious[b]	none	16/24 (66.7%)	11/24 (45.8%)	**RR 1.45** (0.87 to 2.44)	**206 more per 1,000** (from 60 fewer to 660 more)	⨁⨁◯◯ Low	CRITICAL
Hospitalisation at ≤6 months (follow-up: 20 weeks)												
1	randomised trials	serious[e]	not serious	not serious	very serious[b]	none	0/24 (0.0%)	1/24 (4.2%)	**OR 0.14** (0.00 to 6.82)	**40 fewer per 1,000** (from 150 fewer to 70 more)[f]	⨁◯◯◯ Very low	CRITICAL
Withdrawal due to adverse events at ≤6 months (follow-up: mean 18 weeks)												
2	randomised trials	serious[e]	serious[g]	not serious	very serious[h]	none	5/44 (11.4%)	4/43 (9.3%)	**RD 0.02** (-0.11 to 0.15)	**20 more per 1,000** (from 110 fewer to 150 more)[f]	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio; **SMD:** standardised mean difference

Explanations

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias arising from the randomisation process and bias due to deviations from the intended interventions)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias due to deviations from the intended interventions and bias due to missing outcome data)

d. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias arising from the randomisation process and bias in selection of the reported result)

e. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias due to deviations from the intended interventions)

f. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

g. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

h. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

Table 80: Clinical evidence profile: neuromuscular electrical stimulation compared to usual care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal Spasticity - Neuromuscular electrical stimulation	usual care	Relative (95% CI)	Absolute (95% CI)		
Spasticity outcome measure (modified Ashworth scale [different scale ranges], lower values are better, change score) at ≤6 months (follow-up: 6 weeks)												
3	randomised trials	serious[a]	very serious[b]	not serious	serious[c]	none	76	58	-	SMD **0.96 lower** (2.12 lower to 0.2 higher)	⨁◯◯◯ Very low	CRITICAL
Spasticity outcome measure (modified Ashworth scale, composite spasticity scale [different scale ranges], lower values are better, final values) at ≤6 months (follow-up: 10 weeks)												
7	randomised trials	serious[d]	not serious	not serious	not serious	none	173	112	-	SMD **0.22 lower** (0.47 lower to 0.02 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Physical function - upper limb (Fugl-meyer UE, 0-66, higher values are better, change scores) at ≤6 months (follow-up: 8 weeks; Scale from: 0 to 66)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal Spasticity - Neuromuscular electrical stimulation	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[d]	not serious	not serious	very serious[c]	none	36	18	-	MD **0.45 lower** (22.96 lower to 22.06 higher)	⨁◯◯◯ Very low	CRITICAL
Physical function - upper limb (Fugl-meyer shoulder/elbow, UE, FIM, Box and block test [different scale ranges], higher values are better, final values) at ≤6 months (follow-up: 7.5 weeks)												
5	randomised trials	serious[e]	not serious	not serious	not serious	none	74	78	-	SMD **0.89 higher** (0.55 higher to 1.23 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Physical function - lower limb (Rivermead motor asessment scale, 0-23, higher values are better, change score) at ≤6 months (follow-up: 4 weeks; Scale from: 0 to 23)												
1	randomised trials	serious[d]	not serious	not serious	serious[c]	none	20	20	-	MD **0.9 higher** (0.6 lower to 2.4 higher)	⨁⨁◯◯ Low	CRITICAL
Physical function - lower limb (timed up and go, seconds, lower values are better, final value) at ≤6 months (follow-up: 6 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	50	16	-	MD **0.97 lower** (4.07 lower to 2.13 higher)	⨁⨁⨁⨁ High	CRITICAL
Physical function - lower limb (walking speed, m/s, higher values are better, final value) at ≤6 months (follow-up: 4 weeks)												
1	randomised trials	very serious[f]	not serious	not serious	not serious	none	10	10	-	MD **0.01 higher** (0.18 lower to 0.2 higher)	⨁⨁◯◯ Low	CRITICAL
Pain (numeric rating scale, 0-10, lower values are better, change score) at ≤6 months (follow-up: 8 weeks; Scale from: 0 to 10)												
1	randomised trials	very serious[g]	not serious	not serious	very serious[c]	none	36	18	-	MD **1.01 lower** (3.36 lower to 1.34 higher)	⨁◯◯◯ Very low	CRITICAL
Pain (verbal rating scale, 0-5, lower values are better, final values) at ≤6 months (follow-up: 36 weeks; Scale from: 0 to 5)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal Spasticity - Neuromuscular electrical stimulation	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[d]	not serious	not serious	serious[c]	none	33	36	-	MD **0.7 lower** (1.33 lower to 0.07 lower)	⨁⨁◯◯ Low	CRITICAL
Activities of daily living (Barthel index, 0-100, higher values are better, change score) at ≤6 months (follow-up: 8 weeks; Scale from: 0 to 100)												
1	randomised trials	serious[d]	not serious	not serious	very serious[c]	none	36	18	-	MD **1.41 lower** (25.65 lower to 22.83 higher)	⨁◯◯◯ Very low	CRITICAL
Activities of daily living (FIM, Barthel index [different scale ranges], higher values are better, final values) at ≤6 months (follow-up: 12 weeks)												
3	randomised trials	serious[h]	serious[c]	not serious	serious[c]	none	75	53	-	SMD **0.61 higher** (0.19 lower to 1.41 higher)	⨁◯◯◯ Very low	CRITICAL
Stroke-specific Patient-Reported Outcome Measures - Stroke-Specific Quality of Life (SS-QOL, 49-245, higher values are better, change score) at ≤6 months (follow-up: 8; Scale from: 49 to 245)												
1	randomised trials	very serious[g]	not serious	not serious	very serious[c]	none	36	18	-	MD **7.04 higher** (33.37 lower to 47.45 higher)	⨁◯◯◯ Very low	CRITICAL
Withdrawal due to adverse events at ≤6 months (follow-up: 10 weeks)												
11	randomised trials	serious[h]	serious[i]	not serious	very serious[j,k]	none	47/289 (16.3%)	29/211 (13.7%)	**RD 0.30** (0.04 to 0.09)	**30 fewer per 1,000** (from 40 fewer to 90 more)[j]	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **SMD:** standardised mean difference

Explanations

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias arising from the randomisation process, bias due to deviation from the intended interventions, bias due to missing outcome data and bias in selection of the reported result)

b. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias arising from the randomisation process)

e. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias arising from the randomisation process, bias due to deviation from the intended interventions, bias due to missing outcome data and bias in measurement of the outcome)

f. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias arising from the randomisation process, bias due to deviation from the intended interventions and bias due to missing outcome data)

g. Downgraded by 2 increments as the majority of the evidence was of high risk of bias (due to bias arising from the randomisation process and bias in the measurement of reported result)

h. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias arising from the randomisation process, bias due to deviation from the intended interventions and bias due to missing outcome data)

i. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

j. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

k. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

Transcutaneous electrical nerve stimulation compared to placebo and usual care

Table 81: Clinical evidence profile: transcutaneous electrical nerve stimulation compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - TENS	placebo	Relative (95% CI)	Absolute (95% CI)		
Spasticity outcome measures (Composite spasticity score. 0-16, lower values are better, final value and change score) at ≤6 months (follow-up: mean 7 weeks)												
2	randomised trials	serious[a]	very serious[b]	not serious	not serious	none	60	40	-	MD **0.88 lower** (2.34 lower to 0.59 higher)	⨁◯◯◯ Very low	CRITICAL
Spasticity outcome measures (Modified Ashworth Scale, 0-5, lower values are better, final values and change scores) at ≤6 months (follow-up: mean 6 weeks; Scale from: 0 to 5)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - TENS	placebo	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	serious[c]	not serious	not serious	serious[d]	none	67	65	-	MD **0.53 lower** (0.78 lower to 0.29 lower)	⨁⨁◯◯ Low	CRITICAL
Physical function - lower limb (Timed up and go, seconds, lower values are better, final values) at ≤6 months (follow-up: 7 weeks)												
3	randomised trials	serious[e]	serious[b]	not serious	serious[d]	none	85	56	-	MD **6.73 lower** (12.23 lower to 1.22 lower)	⨁◯◯◯ Very low	CRITICAL
Physical function - lower limb (10m walk, seconds, lower values are better, change score) at ≤6 months (follow-up: 6 weeks)												
1	randomised trials	serious[a]	not serious	not serious	serious[d]	none	20	20	-	MD **2.6 lower** (3.41 lower to 1.79 lower)	⨁⨁◯◯ Low	CRITICAL
Activities of daily living (Barthel index, 0-100, higher values are better, change score and final value) at ≤6 months (follow-up: mean 6 weeks; Scale from: 0 to 100)												
2	randomised trials	very serious[f]	very serious[b]	not serious	very serious[d]	none	52	51	-	MD **12.57 higher** (2.03 lower to 27.17 higher)	⨁◯◯◯ Very low	CRITICAL
Withdrawal due to adverse events at ≤6 months (follow-up: mean 8 weeks)												
8	randomised trials	serious[c]	serious[g]	not serious	very serious[h]	none	17/223 (7.6%)	13/170 (7.6%)	**RD -0.00** (-0.06 to 0.05)	**0 fewer per 1,000** (from 60 fewer to 50 more)[i]	⨁◯◯◯ Very low	CRITICAL

1 **CI:** confidence interval; **MD:** mean difference

2 ## Explanations

3 a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias arising from the randomisation process)

4 b. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

c. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias arising from the randomisation process, bias due to deviation from the intended intervention and bias due to missing outcome data)

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

e. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias due to missing outcome data)

f. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a mixture of bias arising from the randomisation process, bias due to deviation from the intended intervention and bias due to missing outcome data)

g. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

h. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

i. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

Table 82: Clinical evidence profile: transcutaneous electrical nerve stimulation compared to usual care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - TENS	usual care	Relative (95% CI)	Absolute (95% CI)		
Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, change score) at ≤6 months (follow-up: 8 weeks)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	36	18	-	MD **0.16 higher** (1.47 lower to 1.79 higher)	⨁◯◯◯ Very low	CRITICAL
Spasticity outcome measures (Modified Ashworth scale, composite spasticity score [different scale ranges], lower values are better, final values) at ≤6 months (follow-up: mean 8 weeks)												
3	randomised trials	very serious[c]	serious[d]	not serious	serious[b]	none	77	43	-	SMD **0.03 SD higher** (0.4 lower to 0.35 higher)	⨁◯◯◯ Very low	CRITICAL
Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, final value) at >6 months (follow-up: 3 years; Scale from: 0 to 4)												
1	randomised trials	serious[e]	not serious	not serious	serious[b]	none	18	10	-	MD **0.8 higher** (0.16 lower to 1.76 higher)	⨁⨁◯◯ Low	CRITICAL
Physical function - upper limb (Fugl-meyer, 0-66, higher values are better, change score and final value) at ≤6 months (follow-up: mean 10 weeks; Scale from: 0 to 66)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - TENS	usual care	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious[e]	not serious	not serious	very serious[b]	none	55	28	-	MD **1.6 lower** (13.54 lower to 10.34 higher)	⨁◯◯◯ Very low	CRITICAL
Physical function - upper limb (Fugl-meyer, 0-50, higher values are better, change score) at ≤6 months (follow-up: 8 weeks; Scale from: 0 to 50)												
1	randomised trials	serious[f]	not serious	not serious	serious[b]	none	26	18	-	MD **3.06 higher** (1.07 higher to 5.05 higher)	⨁⨁◯◯ Low	CRITICAL
Physical function - upper limb (Fugl-meyer, 0-66, higher values are better, final value) at >6 months (follow-up: 3 years; Scale from: 0 to 66)												
1	randomised trials	very serious[e]	not serious	not serious	very serious[b]	none	18	10	-	MD **4 lower** (16.55 lower to 8.55 higher)	⨁◯◯◯ Very low	CRITICAL
Physical function - lower limb (Timed up and go, seconds, lower values are better, final values) at ≤6 months (follow-up: mean 8 weeks)												
2	randomised trials	not serious	very serious[d]	not serious	very serious[b]	none	70	45	-	MD 1**0.70 lower** (29.56 lower to 8.15 higher)	⨁◯◯◯ Very low	CRITICAL
Physical function - lower limb (10m walking scale, seconds, lower values are better, final value) at ≤6 months (follow-up: 3 weeks)												
1	randomised trials	very serious[g]	not serious	not serious	serious[b]	none	19	13	-	MD **5.32 lower** (18.71 lower to 8.07 higher)	⨁◯◯◯ Very low	CRITICAL
Pain (Numeric rating scale, 0-10, lower values are better, change score) at ≤6 months (follow-up: 8 weeks; Scale from: 0 to 10)												
1	randomised trials	very serious[h]	not serious	not serious	serious[b]	none	36	18	-	MD **0.34 lower** (3.34 lower to 2.66 higher)	⨁◯◯◯ Very low	CRITICAL
Activities of daily living (Barthel index, 0-100, higher values are better, change score) at ≤6 months (follow-up: 8 weeks; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - TENS	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	36	18	-	MD **1.74 higher** (39.53 lower to 43.01 higher)	⨁◯◯◯ Very low	CRITICAL
Activities of daily living (functional independence measure, Barthel index [different scale ranges], higher values are better, final values) at ≤6 months (follow-up: mean 8 weeks)												
2	randomised trials	very serious[c]	not serious	not serious	not serious	none	37	23	-	SMD **0.03 SD higher** (0.49 lower to 0.55 higher)	⨁⨁◯◯ Low	CRITICAL
Activities of daily living (Barthel index, 0-100, higher values are better, final values) at >6 months (follow-up: 3 years; Scale from: 0 to 100)												
1	randomised trials	very serious[e]	not serious	not serious	very serious[b]	none	18	10	-	MD **11.6 higher** (4.26 lower to 27.46 higher)	⨁◯◯◯ Very low	CRITICAL
Stroke-specific Patient-Reported Outcome Measures (SS-QOL, 49-245, higher values are better, final values) at ≤6 months (follow-up: 8 weeks; Scale from: 49 to 245)												
1	randomised trials	very serious[h]	not serious	not serious	very serious[b]	none	36	18	-	MD **1.91 higher** (43.34 lower to 47.16 higher)	⨁◯◯◯ Very low	CRITICAL
Discontinuation at ≤6 months (follow-up: 9 weeks)												
4	randomised trials	serious[i]	serious[j]	not serious	very serious[b]	none	18/157 (11.5%)	9/87 (10.3%)	**RR 1.08** (0.53 to 2.20)	**8 more per 1,000** (from 49 fewer to 124 more)	⨁◯◯◯ Very low	CRITICAL
Discontinuation at >6 months (follow-up: 3 years)												
1	randomised trials	very serious[e]	not serious	not serious	serious[b]	none	6/26 (23.1%)	8/18 (44.4%)	**RR 0.52** (0.22 to 1.24)	**213 fewer per 1,000** (from 347 fewer to 107 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **SMD:** standardised mean difference

Explanations

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias due to missing outcome data)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a mixture of bias arising from the randomisation process, bias due to missing outcome data and bias in measurement of the outcome)

d. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

e. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a mixture of bias arising from the randomisation process and bias due to missing outcome data)

f. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias due to missing outcome data)

g. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias arising from the randomisation process and bias in measurement of the outcome)

h. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias due to missing outcome data and bias in measurement of the outcome)

i. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias arising from the randomisation process and bias due to missing outcome data)

j. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

Acupuncture compared to placebo and usual care

Table 83: Clinical evidence profile: acupuncture compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Acupuncture	placebo	Relative (95% CI)	Absolute (95% CI)		
Person/participant generic health-related quality of life (EQ-5D, -0.11-1, higher values are better, change score) at ≤6 months (follow-up: 2 weeks; Scale from: -0.11 to 1)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	11	12	-	MD **0.09 higher** (0.03 higher to 0.15 higher)	⨁⨁⨁◯ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Acupuncture	placebo	Relative (95% CI)	Absolute (95% CI)		
Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, final value) at ≤6 months (follow-up: mean 3 weeks; Scale from: 0 to 4)												
2	randomised trials	serious[b]	serious[c]	not serious	serious[d]	none	23	24	-	MD **0.58 lower** (1.35 lower to 0.2 higher)	⨁◯◯◯ Very low	CRITICAL
Physical function - upper limb (Fugl Meyer Assessment Upper Extremity, 0-66, higher values are better, change score) at ≤6 months (follow-up: 2 weeks; Scale from: 0 to 66)												
1	randomised trials	serious[a]	not serious	not serious	serious[d]	none	11	12	-	MD **4.18 higher** (0.34 lower to 8.7 higher)	⨁⨁◯◯ Low	CRITICAL
Physical function - upper limb (Box and block test, 0-150, higher values are better, final value) at ≤6 months (follow-up: 5 weeks; Scale from: 0 to 150)												
1	randomised trials	not serious	not serious	not serious	serious[d]	none	12	12	-	MD **3.59 higher** (2.03 lower to 9.21 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Physical function - lower limb (10m walk, seconds, lower values are better, final value) at ≤6 months (follow-up: 4 weeks)												
1	randomised trials	serious[e]	not serious	not serious	serious[d]	none	12	12	-	MD **6.15 lower** (17.19 lower to 4.89 higher)	⨁⨁◯◯ Low	CRITICAL
Activities of daily living (Barthel Index, 0-100, higher values are better, final values) at ≤6 months (follow-up: 4 weeks; Scale from: 0 to 100)												
1	randomised trials	serious[e]	not serious	not serious	very serious[d]	none	12	12	-	MD **5.41 higher** (3.29 lower to 14.11 higher)	⨁◯◯◯ Very low	CRITICAL
Withdrawal due to adverse events at ≤6 months (follow-up: mean 4 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Acupuncture	placebo	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	not serious	serious[f]	not serious	very serious[g]	none	0/93 (0.0%)	1/94 (1.1%)	**RD -0.01** (-0.05 to 0.03)	**10 fewer per 1,000** (from 50 fewer to 30 more)[h]	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference

Explanations

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias arising from the randomisation process)

b. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias arising from the randomisation process and bias due to deviations from the intended interventions)

c. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

e. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias due to deviations from the intended interventions)

f. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

g. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

h. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

Table 84: Clinical evidence profile: acupuncture compared to usual care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Acupuncture	usual care	Relative (95% CI)	Absolute (95% CI)		

Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, final value) at ≤6 months (follow-up: 28 days; Scale from: 0 to 4)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Acupuncture	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	30	29	-	MD **0.37 lower** (0.73 lower to 0.01 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Physical function - lower limb (Fugl-Meyer lower extremity, 0-34, higher values are better, final value) at ≤6 months (follow-up: 28 days; Scale from: 0 to 34)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	44	41	-	MD **5.76 higher** (1.88 higher to 9.64 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Activities of daily living (Barthel Index, 0-100, higher values are better, final value) at ≤6 months (follow-up: 28 days; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	30	29	-	MD **4.12 higher** (8.35 lower to 16.59 higher)	⨁⨁◯◯ Low	CRITICAL
Withdrawal due to adverse events at ≤6 months (follow-up: 28 days)												
2	randomised trials	not serious	not serious	not serious	serious[b]	none	0/100 (0.0%)	0/99 (0.0%)	**RD 0.00** (-0.03 to 0.03)	**0 fewer per 1,000** (from 30 fewer to 30 more)[c]	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **MD:** mean difference

Explanations

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

b. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

c. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

Combination therapy: Abobotulinum toxin A (Dysport) and transcutaneous electrical nerve stimulation compared to placebo and transcutaneous electrical nerve stimulation

Table 85: Clinical evidence profile: abobotulinum toxin A (Dysport) and transcutaneous electrical nerve stimulation compared to placebo and transcutaneous electrical nerve stimulation

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Abobotulinum toxin A (Dysport) + TENS	Placebo + TENS	Relative (95% CI)	Absolute (95% CI)		
Spasticity outcome measures (Modified Ashworth scale, 0-5, lower values are better, final value) at ≤6 months (follow-up: 6 months; Scale from: 0 to 5)												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	14	15	-	MD **0.3 lower** (1.08 lower to 0.48 higher)	⨁⨁◯◯ Low	CRITICAL
Pain (VAS, 0-100, lower values are better, final value) at ≤6 months (follow-up: 6 months; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	14	15	-	MD **18.2 lower** (35.37 lower to 1.03 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Withdrawal due to adverse events at ≤6 months (follow-up: 6 months)												
1	randomised trials	not serious	not serious	not serious	very serious[b]	none	0/14 (0.0%)	0/15 (0.0%)	**RD 0.00** (-0.12 to 0.12)	**0 fewer per 1,000** (from 120 fewer to 120 more)[c]	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **MD:** mean difference

Explanations

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

b. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

c. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

Combination therapy: Abobotulinum toxin A (Dysport) and neuromuscular electrical stimulation (NMES) compared to abobotulinum toxin A (Dysport) alone

Table 86: Clinical evidence profile: Abobotulinum toxin A (Dysport) and neuromuscular electrical stimulation compared to abobotulinum toxin A (Dysport) only

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Abobutulinum Toxin A (Dysport) + NMES	Abobutulinum Toxin A (Dysport) alone	Relative (95% CI)	Absolute (95% CI)		
Spasticity outcome measures (Modified Ashworth scale, 0-5, lower values are better, final value) at ≤6 months (follow-up: 12 weeks; Scale from: 0 to 5)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	6	6	-	MD **0.78 lower** (1.86 lower to 0.3 higher)	⨁⨁◯◯ Low	CRITICAL
Withdrawal due to adverse events at ≤6 months												
1	randomised trials	serious[a]	not serious	not serious	very serious[c,d]	none	0/6 (0.0%)	0/6 (0.0%)	**RD 0.00** (-0.27 to 0.27)	**0 fewer per 1,000** (from 270 fewer to 270 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference

Explanations

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias arising from the randomisation process)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

d. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

Combination therapy: Abobotulinum toxin A (Dysport) and neuromuscular electrical stimulation (NMES) compared to neuromuscular electrical stimulation (NMES) alone

Table 87: Clinical evidence profile: Abobotulinum toxin A (Dysport) and neuromuscular electrical stimulation compared to neuromuscular electrical stimulation only

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Abobutulinum Toxin A (Dysport) + NMES	NMES alone	Relative (95% CI)	Absolute (95% CI)		
Spasticity outcome measures (Modified Ashworth scale, 0-5, lower values are better, final value) at ≤6 months (follow-up: 12 weeks; Scale from: 0 to 5)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	6	6	-	MD **0.67 lower** (1.72 lower to 0.38 higher)	⨁⨁◯◯ Low	CRITICAL
Withdrawal due to adverse events at ≤6 months (follow-up: 12 weeks)												
1	randomised trials	serious[a]	not serious	not serious	very serious[c,d]	none	0/6 (0.0%)	0/6 (0.0%)	**RD 0.00** (-0.27 to 0.27)	**0 fewer per 1,000** (from 270 fewer to 270 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference

Explanations

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias arising from the randomisation process)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

d. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

Combination therapy: Onabotulinum toxin A (BOTOX) and functional electrical stimulation compared to onabotulinum toxin A (BOTOX) only

Table 88: Clinical evidence profile: onabotulinum toxin A (BOTOX) and functional electrical stimulation compared to onabotulinum toxin A (BOTOX) only

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focal spasticity - Onabotulinum toxin A (BOTOX) + Functional Electrical Stimulation	Onabotulinum toxin A (BOTOX) only	Relative (95% CI)	Absolute (95% CI)		
Spasticity outcome measures (Modified Ashworth scale, 0-4, lower values are better, final value) at ≤6 months (follow-up: 12 weeks; Scale from: 0 to 4)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	41	39	-	MD **0.62 lower** (0.88 lower to 0.36 lower)	⨁◯◯◯ Very low	CRITICAL
Physical function - lower limb (Fugl-meyer assessment, 0-34, higher values are better, final value) at ≤6 months (follow-up: 12 weeks; Scale from: 0 to 34)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	41	39	-	MD **8.28 higher** (7.96 higher to 8.6 higher)	⨁⨁◯◯ Low	CRITICAL
Activities of daily living (Barthel index, 0-100, higher values are better, final value) at ≤6 months (follow-up: 12 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	41	39	-	MD **20.3 higher** (16.21 higher to 24.39 higher)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **MD:** mean difference

Explanations

a. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias due to deviations from the intended interventions and bias due to missing outcome data)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Generalised spasticity

Tizanidine compared to oral baclofen

Table 89: Clinical evidence profile: tizanidine compared to oral baclofen

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Generalised spasticity - Tizanidine	Baclofen (oral)	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse events at >6 months (follow-up: 12 months)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	1/15 (6.7%)	4/15 (26.7%)	**RR 0.25** (0.03 to 1.98)	**200 fewer per 1,000** (from 259 fewer to 261 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias due to deviations from the intended interventions)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1 Intrathecal baclofen compared to usual care

2 Table 90: Clinical evidence profile: intrathecal baclofen compared to usual care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Generalised spasticity - Intrathecal baclofen	usual care	Relative (95% CI)	Absolute (95% CI)		
Person/participant generic health-related quality of life (EQ-5D-3L, -0.11-1, higher values are better, change score) at ≤6 months (follow-up: 6 months; Scale from: -0.11 to 1)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	25	26	-	MD **0.08 higher** (0.04 lower to 0.2 higher)	⨁◯◯◯ Very low	CRITICAL
Spasticity outcome measures (Modified Ashworth Scale, 0-4, lower values are better, change score) at ≤6 months (follow-up: 6 months; Scale from: 0 to 4)												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	25	26	-	MD **0.53 lower** (0.92 lower to 0.14 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Pain (NRS, 0-10, lower values are better, change score) at ≤6 months (follow-up: 6 months; Scale from: 0 to 10)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	25	26	-	MD **1.17 higher** (0.6 lower to 2.94 higher)	⨁⨁◯◯ Low	CRITICAL
Activities of daily living (Functional Independence Measure total score, 18-126, high values are better, change score) at ≤6 months (follow-up: 6 months; Scale from: 18 to 126)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	25	26	-	MD **5.26 higher** (0.59 lower to 11.11 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Stroke-specific Patient-Reported Outcome Measures (SS-QOL, 1-5, higher values are better, change score) at ≤6 months (follow-up: 6 months; Scale from: 1 to 5)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	25	26	-	MD **0.21 higher** (0.11 lower to 0.53 higher)	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Generalised spasticity - Intrathecal baclofen	usual care	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse events at ≤6 months (follow-up: 6 months)												
1	randomised trials	not serious	not serious	not serious	very serious[b]	none	1/31 (3.2%)	0/29 (0.0%)	**OR 6.93** (0.14 to 349.88)	**30 more per 1,000** (from 50 fewer to 120 more)[c]	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

Explanations

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias in measurement of the outcome)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

Acupuncture compared to placebo and usual care

Table 91: Clinical evidence profile: acupuncture compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Generalised spasticity - Acupuncture	placebo	Relative (95% CI)	Absolute (95% CI)		
Person/participant generic health-related quality of life (Nottingham health profile part 1, 0-100, higher values are better, change score) at ≤6 months (follow-up: 3 months; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	11	8	-	MD **1.27 lower** (7.5 lower to 4.96 higher)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Generalised spasticity - Acupuncture	placebo	Relative (95% CI)	Absolute (95% CI)		
Spasticity outcome measures (Modified Ashworth scale, unclear scale range, lower values are better, change score) at ≤6 months (follow-up: 12 weeks)												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	121	117	-	MD **5.4 lower** (7.81 lower to 2.99 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Spasticity outcome measures (Modified Ashworth scale wrist, 0-4, lower values are better, change score) at ≤6 months (follow-up: 3 months; Scale from: 0 to 4)												
1	randomised trials	serious[c]	not serious	not serious	serious[b]	none	11	8	-	MD **0.57 lower** (1.5 lower to 0.36 higher)	⨁⨁◯◯ Low	CRITICAL
Spasticity outcome measures (Modified Ashworth scale elbow, 0-4, lower values are better, change score) at ≤6 months (follow-up: 3 months; Scale from: 0 to 4)												
1	randomised trials	serious[c]	not serious	not serious	very serious[b]	none	11	8	-	MD **0.2 lower** (1.4 lower to 1 higher)	⨁◯◯◯ Very low	CRITICAL
Physical function - general (FMA, 0-100, higher values are better, change score) at ≤6 months (follow-up: 12 weeks; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	121	117	-	MD **12.86 higher** (7.5 higher to 18.22 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Physical function - upper limb (FMA-UE, 0-66, higher values are better, change score) at ≤6 months (follow-up: 3 months; Scale from: 0 to 66)												
1	randomised trials	serious[c]	not serious	not serious	not serious	none	11	8	-	MD **0.05 higher** (4.2 lower to 4.3 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Pain (visual analogue scale, 0-10, lower values are better, change score) at ≤6 months (follow-up: 8 weeks; assessed with: Visual analogue scale; Scale from: 0 to 10)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	28	20	-	MD **1.38 lower** (2.7 lower to 0.06 lower)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Generalised spasticity - Acupuncture	placebo	Relative (95% CI)	Absolute (95% CI)		
Activities of daily living (Barthel index, 0-100, higher values are better, change score) at ≤6 months (follow-up: mean 11 weeks; Scale from: 0 to 100)												
3	randomised trials	serious[d]	very serious[e]	not serious	very serious[b]	none	160	145	-	MD **5.2 higher** (4.96 lower to 15.36 higher)	⨁◯◯◯ Very low	CRITICAL
Stroke-specific Patient-Reported Outcome Measures (stroke specialisation QOL scale, 49-245, higher values are better, change score) at ≤6 months (follow-up: 12 weeks; Scale from: 49 to 245)												
1	randomised trials	not serious	not serious	not serious	not serious	none	121	117	-	MD **26.59 higher** (17.3 higher to 35.88 higher)	⨁⨁⨁⨁ High	CRITICAL
Withdrawal due to adverse events at ≤6 months (follow-up: mean 10 weeks)												
1	randomised trials	serious[d]	not serious	not serious	very serious[b]	none	1/28 (3.6%)	2/20 (10%)	**RR 0.36** (0.03 to 3.67)	**64 fewer per 1,000** (from 97 fewer to 267 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a mixture of bias due to missing outcome data and bias in selection of the reported result)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias due to missing outcome data)

d. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias due to deviations from the intended interventions and bias due to missing outcome data)

e. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

Table 92: Clinical evidence profile: acupuncture compared to usual care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Generalised spasticity - Acupuncture	usual care	Relative (95% CI)	Absolute (95% CI)		
Physical function - general (FMA total score, 0-226, higher values are better, change score) at ≤6 months (follow-up: 2 weeks; Scale from: 0 to 226)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	14	15	-	MD **2.2 lower** (11.74 lower to 7.34 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Physical function - general (FMA total motor score, 0-100, higher values are better, final values) at ≤6 months (follow-up: mean 4 weeks; Scale from: 0 to 100)												
2	randomised trials	serious[b]	very serious[c]	not serious	serious[d]	none	127	88	-	MD **25.15 higher** (1.15 higher to 49.14 higher)	⨁◯◯◯ Very low	CRITICAL
Activities of daily living (Barthel Index, 0-100, higher values are better, final values) at ≤6 months (follow-up: mean 4 weeks; Scale from: 0 to 100)												
2	randomised trials	serious[b]	very serious[c]	not serious	not serious	none	127	88	-	MD **22.17 higher** (1.98 higher to 42.35 higher)	⨁◯◯◯ Very low	CRITICAL
Activities of daily living (FIM, 18-126, higher values are better, change score) at ≤6 months (follow-up: 2 weeks; Scale from: 18 to 126)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	14	15	-	MD **2.7 higher** (0.34 lower to 5.74 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Withdrawal due to adverse events at ≤6 months (follow-up: mean 3 weeks)												
2	randomised trials	serious[a]	not serious	not serious	very serious[d]	none	5/99 (5.1%)	2/58 (3.4%)	**RR 1.33** (0.32 to 5.53)	**10 more per 1,000** (from 60 fewer to 90 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias arising from the randomisation process)

b. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to a mixture of bias arising from the randomisation process and bias due to deviations from the intended intervention)

c. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Electroacupuncture compared to acupuncture and usual care

Table 93: Clinical evidence profile: electroacupuncture compared to acupuncture

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Generalised spasticity - Electroacupuncture	Acupuncture	Relative (95% CI)	Absolute (95% CI)		
Spasticity outcome measures (Modified Ashworth scale, 0-5, lower values are better, final value) at ≤6 months (follow-up: 15 days; Scale from: 0 to 5)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	15	10	-	MD **1.1 lower** (1.74 lower to 0.46 lower)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **MD:** mean difference

Explanations

a. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias arising from the randomisation process, bias due to deviations from the intended interventions and bias in measurement of the outcome)

Table 94: Clinical evidence profile: electroacupuncture compared to usual care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Generalised spasticity - Electroacupuncture	usual care/no treatment	Relative (95% CI)	Absolute (95% CI)		
Spasticity Outcome Measures (Composite spasticity scale, 0-16, lower values are better, final value) at ≤6 months (follow-up: 6 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	124	116	-	MD **0.31 higher** (0.04 lower to 0.66 higher)	⨁⨁◯◯ Low	CRITICAL
Physical function - lower limb (Fugl-meyer lower limb, 0-34, higher values are better, final value) at ≤6 months (follow-up: 6 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	124	116	-	MD **1.25 higher** (0.37 higher to 2.13 higher)	⨁⨁◯◯ Low	CRITICAL
Withdrawal due to adverse events at ≤6 months (follow-up: 6 weeks)												
1	randomised trials	serious[b]	not serious	not serious	not serious	none	0/124 (0.0%)	0/116 (0.0%)	**RD 0.00** (-0.02 to 0.02)	**0 fewer per 1,000** (from 20 fewer to 20 more)[c]	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **MD:** mean difference

Explanations

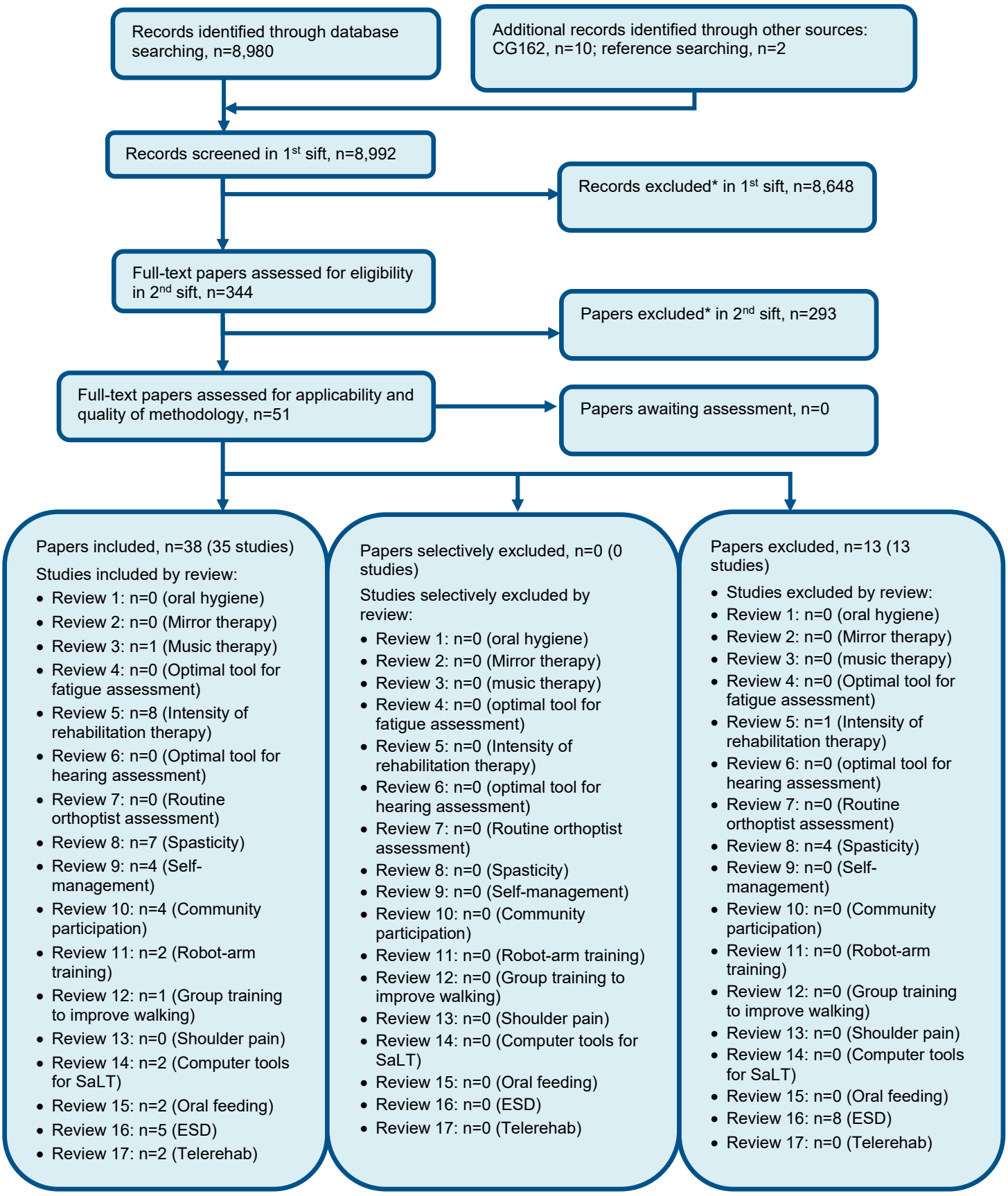
a. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias arising from the randomisation process and bias in measurement of the outcome)

b. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to bias arising from the randomisation process)

c. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

Appendix G – Economic evidence study selection

Figure 1: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

1 Appendix H – Economic evidence tables

2 H.1 Focal spasticity

3 H1.1 Botulinum toxin A

4 H1.1.1 Abobotulinum toxin A (Dysport®)

Study	Shackley 2012[111]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs). **Study design:** Within-trial analysis based on RCT included in the clinical review (Shaw 2010[113]). **Approach to analysis:** Analysis of individual-level resource use and EQ-5D. QALYs were estimated using an area under the curve approach using baseline and 3-month EQ-5D responses. National unit costs applied. Uncertainty was quantified using non-parametric bootstrapping.	**Population:** Adults with spasticity and reduced upper limb function due to stroke greater than one month. (protocol strata: focal spasticity) **Patient characteristics:** N = 283 (subgroup of whole trial population [85%] that had EQ-5D responses at baseline and 3 months) Mean age: NR; (for whole study median 67 years) Male: NR (for whole study 67.8%) **Intervention 1:** 4-week upper limb therapy programme (one hour of therapy twice	**Total costs (mean per patient):** Intervention 1: £1,796 Intervention 2: £2,170 Incremental (2−1): £374 (95% CI: -90 to £837; p=NR) **Cost breakdown – incremental (2-1) and 95% CI:** • Botulinum toxin: £151 (£145 to £157) • Upper limb therapy: £3 (-£7 to £13) • Antispasticity medication: £1 (-£21 to £22) • Other health care and social services: £219 (-£242 to £679) **Currency & cost year:**	**QALYs (mean per patient):** (From Shaw 2011[113]): Intervention 1: 0.081 Intervention 2: 0.085 Incremental (2−1): 0.004 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £93,500 per QALY gained (pa) (95% CI: NR; p=NR) Probability Intervention 2 cost effective (£20K/30K threshold): 36%/NR. **Analysis of uncertainty:** The following sensitivity analyses were explored and did not change conclusions about cost effectiveness: • Complete EQ-5D data at baseline and at 1 and 3 months rather than just baseline and 3 months (£68,857 per QALY gained). • A best-worst QALY analysis investigating the impact of alternative assumptions regarding the timing of health state changes would favour the use of botulinum toxin type A in both intervention groups (£62,333 per QALY gained).

Perspective: UK NHS and PSS **Time horizon:** 3 months **Treatment effect duration:**[(a)] 3 months **Discounting:** n/a	weekly provided by a study therapist). **Intervention 2:** Botulinum toxin type A (Abobotulinum toxin A [Dysport®]) given at baseline plus a 4-week upper limb therapy programme. Repeat botulinum toxin type A and/or therapy was available at three, six and nine months which is beyond the time horizon of this study. **Note:** both groups could use other antispasticity medication including gabapentin, oral baclofen, tizanidine, dantrolene, methocarbamol.	2007 UK pounds **Cost components incorporated:** Botulinum toxin type A, upper limb therapy sessions provided by chartered physiotherapists, other anti-spasticity medication, management of adverse events attributable to botulinum toxin type A (and/or upper limb therapy requiring a hospital contact) and other health care and social services resource use (e.g., GP, district nurse, physiotherapist, occupational therapist, clinical psychologist, home care services).		• Cost of botulinum toxin type A is zero (£55,750 per QALY gained). • Re-running the analysis following multiple imputation of missing data (£86,000 per QALY gained). In the above sensitivity analyses, the probability of botulinum toxin type A plus therapy being cost-effective at £20,000 threshold value did not exceed 39%.
Data sources				
Health outcomes: Within-RCT analysis of BoTULS trial (Shaw 2010)[113] included in clinical review. EQ-5D-3L collected at baseline and 3 months were used to calculate QALYs using an area under the curve approach. EQ-5D was also collected at 6 and 12 months but was not used in this analysis. **Quality-of-life weights:** EQ-5D-3L, UK population valuation tariff. **Cost sources:** Within-RCT analysis of resource use identified from case record forms, adverse event monitoring forms and participant questionnaires. Where data were missing, resource use was inferred. Assumptions were made regarding the length of time on specific anti-spasticity medications and the dosages taken. Assumptions also had to be made regarding the use of other health care and social services resources during the second month of the three-month analysis period. This was due to resource use questions in the participant assessment questionnaires asking about resource use over the previous month only. UK national unit costs applied.				
Comments				
Source of funding: UK National Institute for Health Research (NIHR). **Limitations:** 2005-2008 resource use and 2007 unit costs may not reflect current NHS context. 3-month time horizon will not fully capture differences in costs and outcomes: people were allowed repeat botulinum toxin A injections and/or upper limb therapy at 3, 6 and 9 months in the RCT which will not be captured; mean difference in EQ-5D was greater at 12 month follow-up than at 3 months and so differences appear to also continue beyond 3 months (although there was also much greater loss of participant responses in the RCT [85.2% at 3 months and 52.4% at 12 months] which was the rationale for not using this longer term data in the economic evaluation). Within-trial analysis				

	and so by definition only reflects one of a number of studies identified in the clinical review relating to abobotulinum toxin A. Assumptions had to be made regarding the use of other health care and social services resources during the second month of the three-month analysis period as questionnaires were completed at 1 and 3 months but only asked about the previous month. **Other:** CUA and underlying RCT were developed as part of the NIHR Health Technology Assessment (HTA) Programme.
	Overall applicability:[(b)] Partially applicable **Overall quality:**[(c)] Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; EQ-5D-3L= Euroqol 5 dimensions – 3 levels version (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); HTA= health technology assessment; ICER= incremental cost-effectiveness ratio; NR= not reported; PSS = personal social services; QALYs= quality-adjusted life years; SD= standard deviation.

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable/partially applicable/not applicable

(c) Minor limitations/potentially serious limitations/very serious limitations

H1.1.2 Incobotulinum toxin A (Xeomin®)

Study	**Makino 2019[72]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model based on RCT included in the clinical review (Kanovsky et al. 2009)[59] **Approach to analysis:** Markov model with states based on response (achieving 1 or more point gain from baseline in Ashworth Scale at 4 weeks post-injection) to botulinum toxin treatment. 12-week cycles. The number of	**Population:** Adults who have had a stroke more than 2 months prior, experiencing moderate to severe upper limb spasticity. (protocol strata: focal spasticity). **Cohort settings:** Start age: 57 years Male: 64% **Intervention 1:** Incobotulinum toxin A (Xeomin®]) for a maximum of four cycles (everyone receives 2 cycles; responders get	**Total costs (mean per patient):** Intervention 1: £2,687 Intervention 2: £4,840 Incremental (2-1): £2,153 (95% CI: £2,150 to £2,154; p=NR) **Currency & cost year:** 2016 Australian dollars converted to UK pounds (£)[(b)] **Cost components incorporated:** Drug acquisition (drug costs and dispensing fees) and administration	**QALYs (mean per patient):** Intervention 1: 1.876 Intervention 2: 1.800 **Incremental (2-1):** 0.0758/ (95% CI: 0.0747 to 0.0768; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £28,457 per QALY gained (pa). Probability Intervention 2 is cost effective (£20K/30K threshold): <10%/~55% (estimated from graph) **Analysis of uncertainty:** The following sensitivity analyses were explored and did not change conclusions about cost effectiveness: • Changing the model duration to 1-year (£20,226 per QALY gained), 2-years (£27,104 per QALY gained), and 10-years (£28,526 per QALY gained).

cycles you can receive botulinum toxin differs between comparators in the analysis. Response rate varies by cycle 1, 2 and 3+. Utility weights are assigned to response and no response states to estimate QALYs. **Perspective:** Australian healthcare system. **Time horizon:** 5 years **Treatment effect duration:**[(a)] until discontinuation due to lack of response (up to 5 years). **Discounting:** 5% applied to costs and outcomes.	additional cycles up to 4) **Intervention 2:** Unlimited incobotulinum toxin-A (Xeomin®) treatment cycles (everyone receives treatment for 2 cycles, responders continue to get additional cycles with no upper limit)	costs (a specialist consultation and other services associated with the administration procedure (e.g., injection, neuromuscular stimulation, ultrasound).		• Applying the upper and lower 95% CIs to response rate (£28,390 to £28,494 per QALY gained) and utility inputs (£21,343 to £42,686 per QALY gained). • Adjusting the treatment discontinuation and disease natural resolution to 5% (£28,468 per QALY gained) and 10% per cycle, respectively (£28,478 per QALY gained). • Adjusting the cost inputs by +/-£47 ($100) per cycle (£30,232 to £26,756 per QALY gained, respectively); and • Applying 0% (£28,502 per QALY gained) and 3.5% (£28,607 per QALY gained) discount rates to costs and outcomes, respectively.

Data sources

Health outcomes: Response rates were based on analysis of data for 1-5 injections from a an RCT included in the clinical review[(c)] (Kanovsky 2009[57]), and its open-label extension study (Kanovsky et al. 2011).[58] Utility weights for responders and non-responders were based on analysis of data from Kanovsky 2009[57] Patient demographics (age and sex) of the hypothetical model cohort were based on the extension study.[58] Mortality was incorporated into the model using Australian life tables. **Quality-of-life weights:** EQ-5D-3L, with Australian population tariff. **Cost sources:** Mean dose per injection incobotulinum toxin A based on extension study.[58] Average resource use per injection was taken from 2010–2014 Australian claims data analysis.[43] Australian national unit costs applied.

Comments

Source of funding: Merz Pharmaceuticals. **Limitations:** Australian 2010-2014 resource use and 2016 unit costs may not reflect current UK NHS context. EQ-5D-3L was calculated using Australian population valuation tariff was used but the NICE reference case specifies the UK tariff is preferred. Costs and health effects were discounted at a non-reference case rate (5% rather than 3.5%). Effectiveness based on data from Kanovsky 2009[59] RCT included in clinical review (and open label extension) and so only reflects this study and not the wider evidence base identified in the clinical review. Response rates are based on botulinum toxin group in trial only and so do not account for response rate in those not receiving treatment in base-case analysis, however this is added in a sensitivity analysis. EQ-5D is based on data from the same RCT but difference by randomised group is not reported and this is not discussed. EQ-5D questionnaires collection times were not reported and analysis methods for estimation for responders and non-responders were unclear. Only costs directly associated with the provision of injections were included; if disability reduced then potentially other costs could be impacted. Funded by Merz Pharmaceuticals (manufacturer of incobotulinum toxin A). **Other:** Patients in the extended treatment arm of the model received an

average of 6.49 injections compared with 3.43 injections in the comparator arm. In the extended treatment arm of the model, 14% of patients received 12 or more injections.	
Overall applicability:[(d)] Partially applicable	**Overall quality:**[(e)] Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); HTA= health technology assessment; ICER= incremental cost-effectiveness ratio; NR= not reported; PSS = personal social services; QALYs= quality-adjusted life years; SD= standard deviation.

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Converted using 2016 purchasing power parities[96]

(c) Clinical review did not extract outcomes from the Modified Ashworth scale (MAS) and Disability Assessment Scale (DAS) reported in Kanovsky 2009,[59] as it only reported the percentage of responders with an increase of at least 1 on the MAS and only the p-values for the DAS.

(d) Directly applicable/partially applicable/not applicable

(e) Minor limitations/potentially serious limitations/very serious limitations.

H1.1.3 Onabotulinum toxin A (BOTOX®)

Study	**Doan 2013[24]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs). **Study design:** Deterministic decision analytic model. **Approach to analysis:** Markov model with four disability level health states (none, mild, moderate, severe) based on the disability assessment scale (DAS). 12-week cycles. People start in moderate or severe state.	**Population:** Adults with upper-limb post-stroke spasticity (ULPSS) and moderate or severe disability (protocol strata: focal spasticity). **Cohort settings:** Start age: 72 years Male: 45% **Intervention 1:** Usual care, defined as routine physical therapy and occupational therapy (but not drug therapy).	**Total costs (mean per patient):** Scenario 1: Intervention 1: £3,601 Intervention 2: £4,700 Incremental (2−1): £1,099 (95% CI: NR; p=NR) Scenario 2: Intervention 1: £849 Intervention 2: £3,752 Incremental (2−1): £2,903 (95% CI: NR; p=NR) Scenario 3: Intervention 1: £38,517	**QALYs (mean per patient):** Scenarios 1, 2 and 3: Intervention 1: 1.538 Intervention 2: 1.645 Incremental (2−1): 0.107 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** Scenario 1: £10,271 per QALY gained (95% CI: NR) Probability Intervention 2 cost effective (£20K/30K threshold): NR/NR. Scenario 2: £27,134 per QALY gained (95% CI: NR) Probability Intervention 2 cost effective (£20K/30K threshold): NR/NR. Scenario 3: Dominates intervention 1 (lower costs and higher QALYs). (95% CI: NR)

Transitions between states are dependent on intervention received. Botulinum toxin A is discontinued if no disability reduction after 4 cycles. Utility weights are assigned to the different disability states to estimate QALYs. Costs are assigned based on intervention received. Costs are not assigned based on disability states except for informal care hours in scenario 3. **Perspective:** Scenarios 1 & 2: NHS Scotland 3: informal care costs also included. **Time horizon:** 5 years **Treatment effect duration:**[(a)] Until discontinuation (up to 5 years) **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Intervention 2:** Botulinum toxin A (onabotulinum toxin A [BOTOX®]; mean dose: 221.3 U/injection [SD: 18.8]) plus usual care.	Intervention 2: £36,618 Incremental (2−1): saves £1,899 (cost-saving) (95% CI: NR; p=NR) **Currency & cost year:** 2008-2010 UK pounds (£) **Cost components incorporated:** Scenario 1: Onabotulinum toxin A use, specialist office visits and day-hospital visits. Scenario 2: Onabotulinum toxin A use and specialist office visits only. Scenario 3: scenario one plus informal care costs.		Probability Intervention 2 cost effective (£20K/30K threshold): NR/NR. **Analysis of uncertainty:** The following sensitivity analyses were explored for Scenarios 1 and 2 and did not change conclusions about cost effectiveness: • Varying the model horizon 1-year time horizon (Scenario 1: £18,929 per QALY gained; Scenario 2: £41,027 per QALY gained) • Discontinue onabotulinum toxin A after no response (after 3 versus 4 cycles of non-response) (Scenario 1: £13,722 per QALY gained; Scenario 2: £35,491 per QALY gained) • Removing adjustment to crude utility weights (based on clinical trial data) that allowed for change in health utility during each cycle. (Scenario 1: £10,969 per QALY gained; Scenario 2: £28,979 per QALY gained) • Extended the time spent in 'Mild' or 'None' disability states. (Scenario 1: £10,045; Scenario 2: £26,836) Reducing the model time horizon to 1 year was the most sensitive variable to increase the ICER for both scenarios.

Data sources

Health outcomes: Transition probabilities from the moderate and severe states for UC plus onabotulinum toxin A were calculated using data from an RCT (n=126) included in the clinical review comparing UC+sham and UC+ObToxA single injection (Brashear et al. 2002)[7] and an open-label follow-up study that evaluated the efficacy and safety of 3 additional injections over 42-week period (Gordon et al. 2004).[36] Transition probabilities for UC were estimated using the placebo arm of Brashear et al. 2002[8] and assumed to be constant over time. Transition probabilities from the mild and moderate

states were estimated based on the time between injections in these trials and assumed to be the same for UC. Utility values for each disability-based health state were derived from post hoc analyses of data from multicentre open-label study (n = 279) by Doan et al. 2012.[23] Utility values for each model disability state were based on Doan 2012[23] analysis by DAS domain and DAS level combined with DAS domain distribution information from Brashear 2002 RCT[7]. Age and gender-specific mortality rates applied in both groups. Average age and proportion male/female for cohort were based on published data about people with stroke in Scotland. Gender-specific hazard ratios for mortality after stroke were taken from Carter (2007)[10] and applied to general population mortality rates from Scottish Decennial Life Tables 2000-2002.

Quality-of-life weights: EQ-5D-3L, US population valuation tariff. To allow model participants to change health utility during each cycle, the duration of time that patients spent in each disability state was adjusted (i.e., weighted) by the healthy utility associated with the disability state to derive QALYs.

Cost sources: Onabotulinum toxin A mean dose based on Brashear 2002 RCT;[7] mean from 1st dose in trial applied to all injections in model. Number of injections will depend on modelled effectiveness (mean in model not reported). Annual number of specialist office visits was based on clinical expert opinion (UC 2, UC+ObToxA 4). Resource use for day-hospital visits based on BoTULS RCT[115] Hours per week of caregiver time for each model disability state based on Doan 2012[23] analysis by DAS domain and level combined with DAS domain distribution information from Brashear 2002 RCT.[7] Healthcare unit costs from Scottish or UK national sources. Informal care costed using median hourly earnings in Scotland (£10.65).

Comments

Source of funding: Allergan Inc. **Limitations:** Resource use and unit costs may not reflect current NHS context (2008-2010 UK unit costs and older published resource use). EQ-5D-3L USA tariff was but the NICE reference case specifies the UK tariff is preferred. It is unclear if the 5-year time horizon is sufficiently long to capture all costs and health outcomes of treatment; it appears that in the model people continue to receive botulinum toxin if obtaining benefit and it is not reported whether there are still people receiving it at 5 years. Transition probabilities between disability-based health states with usual care and onabotulinum toxin A are based on 12-week data from Brashear 2002 RCT (USA 1999 to 2000) included in clinical review (and for onabotulinum toxin A only also a 42-week follow-up study) and so only reflects this study and not the wider evidence base identified in the clinical review. Scenario 2 justified inclusion of reduction in day hospitalisation rate with onabotulinum toxin A based on it being the only significant difference in the BOTULS RCT analysis but this study also reported statistically significant differences in the proportion of participants reporting contacts for practice nurse and social worker; and overall its cost analysis also found an increase in other costs with botulinum toxin A. Probabilistic analysis was not undertaken to quantify parameter uncertainty. Study funded by Allergan (manufacture onabotulinum toxin A). **Other:** This study was developed by the manufacturer following a second resubmission to the Scottish Medicines Consortium (SMC) for the approval of BOTOX® in NHS Scotland.[109]

Overall applicability:[(b)] Partially applicable **Overall quality:**[(c)] Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; EQ-5D-3L= Euroqol 5 dimensions – 3 levels version (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); HTA= health technology assessment; ICER= incremental cost-effectiveness ratio; NR= not reported; PSS = personal social services; QALYs= quality-adjusted life years; SD= standard deviation; UC= usual care.
(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.
(b) Directly applicable/partially applicable/not applicable
(c) Minor limitations/potentially serious limitations/very serious limitations

Study	**Lindsay, 2022[69]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**

Economic analysis: Cost-effectiveness analysis (health outcomes: Barthel Index (BI) and Action Research Arm Test (ARAT)) **Study design:** Secondary within-trial cost analysis based on RCT included in the clinical review (Lindsay 2021[70]) **Approach to analysis:** Cost analysis assessed outcomes associated with early treatment of spasticity with onaBoNT-A and the subsequent impact on resource utilisation compared to usual care at baseline and 6 months. ARAT and BI scores were used to generate a cost per unit of improvement in each of the measures. **Perspective:** NHS and PSS **Follow-up:** 6 months **Treatment effect duration:**[(a)] 6 months **Discounting:** n/a	**Population:** Adults who developed upper limb spasticity within six weeks of a first stroke and no useful arm function (i.e., ARAT grasp-score of <2). **Patient characteristics:** N=93 Start age: 68 years Male: 52% **Intervention 1:** Placebo/sham (n=48) 0.9% sodium chloride solution placebo. **Intervention 2:** Onabotulinum Toxin A (BOTOX®) (n=49) Intramuscular injections of Onabotulinum toxin-A were administered to all six muscles of the affected arm in predetermined doses.	**Total costs (mean (SD) per group):** Intervention 1: £24,676 (£11,539) Intervention 2: £23,595 (£11,682) Incremental cost (2 vs 1): saves £1,080.5 (95% CI (–£5,867, £3,706); p=0.655) **Contracture cost (Mean (SD) per group):** Intervention 1: £2,298 (£4,023) Intervention 2: £817 (£2,646) Incremental cost (2 vs 1): saves £1481.1 (95% CI: −£2893.5, −£68.7; p= 0.04) **Currency & cost year:** 2019 UK pounds (£) **Cost components incorporated:** Drug costs at discharge from hospital and at 3 and 6 months; length of stay (initial hospitalisation and readmission); intervention costs and treatments to manage contractures.	**BI improvement ≤6 months (2 vs 1):** Intervention 1: NR Intervention 2: NR Incremental (2 vs 1): 0.87 (95% CI: −1.55, 3.29; p=0.47) **ARAT score (mean CFB) at ≤6 months:[70]** Intervention 1: 12 Intervention 2: 14.3 Incremental MD (2 vs 1): 2.9, (95% CI: -5.8 to 11.6; p=0.51) From clinical review (2 vs 1):[70] Physical function - upper limb (ARAT) higher values are better, final values) at ≤6 months (SMD): 0.14 (95% CI: -0.30-0.57).	**ICER (Intervention 2 versus Intervention 1):** • Saves £1,240 per unit of improvement for the BI. • Saves £450 per unit of improvement for the ARAT The cost savings and mean differences of the BI and ARAT score at 6 months were not statistically significant between study groups. Cost savings of £1,481 for the treatment of contractures was statistically significant for the treatment group. **Analysis of uncertainty:** One-way sensitivity analyses applied the lower 5% and upper 95% CI bounds of the incremental total costs and outcomes for the BI and ARAT scores: Applying the upper 95% bounds improvement resulted in a cost per unit of improvement of £1,124 for the BI and £346 for the ARAT. This increased to £3,773 and £978 per point improvement when the lower 5% bounds were used for the BI and ARAT scores, respectively.

Data sources
Health outcomes: Within-trial analysis where the primary outcome was the Action Research arm test (ARAT), taken from RCT data reported in Lindsay 2021.[70] Barthel Index scores at 6 months were reported as part of the secondary analysis.[69] **Cost sources:** Details regarding participants' use of health services were documented within the study at two, four, six and 12 weeks following treatment and at six months post-stroke. These included GP visits, hospital visits and admissions as well as current medication use and any changes from discharge. Treatments to manage contractures were also recorded. Mean cost for the long-term management of contractures was £9,193, based on Radensky 2001[101] (US cost). Standard national unit costs applied.
Comments
Source of funding: National Institute for Health Research (NIHR) under its Research for Patient Benefit Programme (PB-PG-0808-16319). Allergan provided the drug used and an unrestricted educational grant to support this study. **Limitations:** QALYs not calculated as EQ-5D not reported. 2012-2013 resource use estimates may not reflect current UK context. Within-trial secondary analysis so costs and outcomes only reflect this trial with a small sample size and not the wider evidence base identified in the clinical review. 6-month follow-up may be insufficient to reflect differences in all costs and outcomes. Long-term costs for the management of contractures were taken from a 2001 US study (the method of currency conversion was also not reported). No probabilistic sensitivity analysis. **Other:** n/a
Overall applicability:[(c)] Partially applicable **Overall quality:**[(d)] Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; ARAT= action research arm test (scale 0-57, higher values are better); CFB= change from baseline; BI= modified Barthel Index (scale 0-100, higher values are better); EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; QALYs= quality-adjusted life years; PSA= Probabilistic sensitivity analysis; SMD = standardised mean difference.

a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

b) Directly applicable / Partially applicable / Not applicable

c) Minor limitations / Potentially serious Limitations / Very serious limitations

H1.1.3 Onabotulinum toxin A (BOTOX®) versus Abobotulinum toxin A (Dysport®)

Study	Danchenko, 2022[18]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis (health outcome: QALYs) **Study design:** Probabilistic (dynamic) decision analytic model.	**Population:** Separate populations were applied to two analyses: **AUL:** Adults (≥18 years old) upper-limb spasticity presenting for treatment with BoNT-A in routine clinical practice (91.3% had spasticity caused by a brain injury (stroke/trauma/other).	**Total costs (mean per patient):** **AUL:** Intervention 1: £34,138 Intervention 2: £33,834 Incremental (2−1): Saves £304 (95% CI: NR; p=NR)	**QALYs (mean per patient):** **AUL:** Intervention 1: 0.573/0.579[(b)] Intervention 2: 0.595/ 0.604 Incremental (2−1):	**ICER (Intervention 2 versus Intervention 1):** AboBoNT-A was dominant (less expensive and more effective) in 100% of iterations for AUL and 99% of iterations for ALL. Probability Intervention 2 cost effective (£20K/30K threshold): 100% for both AUL and ALL indications/NR

Approach to analysis: Decision tree model comprised of two mutually exclusive health states defined by response vs. non-response to therapy. Separate analyses were conducted for adults with upper limb (AUL) and lower limb (ALL) spasticity, with response defined by MAS and GAS for lower and upper limb, respectively. Utility weights are assigned to response and no response states to estimate QALYs. **Perspective:** NHS and PSS. **Time horizon:** 1 year **Treatment effect duration:**[a] 1 year **Discounting:** NA	**ALL:** Post-stroke adults (≥19 years old) with lower-limb spasticity. **Cohort settings (AUL/ALL):** n=953/NR Mean age: 54/NR Male: 56%/NR **AUL:** **Intervention 1:** OnabotulinumtoxinA (Botox®; n=198) given every 29 weeks. Mean (SD) dose: 256 units (136 U) **Intervention 2:** AbobotulinumtoxinA (Dysport®; n=555) given every 32 weeks. Mean (SD) dose: 843 units (353 U) **ALL:** **Intervention 1:** OnabotulinumtoxinA (Botox®) assumed to be given every 12 weeks. Mean (SD) dose: 400 units (NR) **Intervention 2:** AbobotulinumtoxinA (Dysport®) assumed to be given every 12 weeks. Mean (SD) dose: 1,500 units (NR)	**ALL:** Intervention 1: £36,089 Intervention 2: £35,695 Incremental (2−1): Saves £394 (95% CI: NR; p=NR) **Currency & cost year:** 2018-2020 UK pounds (£) **Cost components incorporated:** Treatment acquisition and administration, healthcare appointments, and concomitant oral medications.	0.022/0.025[b] (95% CI: NR; p=NR) **ALL:** Intervention 1: 0.491/ 0.500[b] Intervention 2: 0.501/ 0.509[b] Incremental (2−1): 0.01/0.009[b] (95% CI: NR; p=NR)	**Analysis of uncertainty:** Scenario analyses showed the results for both indications to be robust for the following changes: adverse event disutilities (included vs. excluded); treatment wastage (included vs. excluded); the data source for healthcare costs and the number of injections received by non-responders (one only vs. multiple injections) The only scenario where aboNT-A did not dominate onaBoNT-A was when ALL non-responders received one injection, which resulted in higher costs (incr. £215) and higher QALYs (incr. 0.01) for aboNT-A group (ICER of £21,234).
Data sources				
Health outcomes: Treatment response rates in the AUL indication (characterized by GAS) were taken from an international prospective observational study conducted to assess the impact of BoNT-A on upper limb spasticity in adults (ULIS III).[128] Treatment efficacy in the ALL indication (characterized by				

MAS) was obtained from a systematic review and network meta-analysis in post-stroke.[108] Utility values for the AUL indication were based on Doan 2012,[23] which reported utility values by DAS domain and DAS level combined with DAS domain distribution information from Brashear 2002 RCT[7] The "responder" utility was calculated as the average of utility values associated with "no disability" and "mild disability" states from Doan 2012[23]. Non-responder utility was the average utility associated with "moderate disability" and "severe disability". For the ALL indication, utility values were informed by an aboBoNT-A post-hoc analysis of an RCT and an open-label extension phase[83] that collected walking speed data and EQ-5D-5L responses. Utility values for patients who were "household walkers" (0.5400), "limited community ambulators" (0.4918), and "community ambulators" (0.4049) were reported, where it was assumed that a "response" was "household walkers" and non-response "limited community ambulators". **Quality-of-life weights:** EQ-5D-3L, US population valuation tariff (AUL indication) and EQ-5D-5L (tariff not reported) for the ALL indication. **Cost sources:** For the AUL indication, doses were taken from ULIS-III study. [128] For the ALL indication, doses used in pivotal trials were assumed in lieu of real-world data.[26, 27] Resource use estimates for BoNT-A responders and non-responders were based on the median and range of reported averages of a survey administered to a geographically representative sample of UK clinicians with experience treating AUL spasticity only (n=11)[50]. National unit costs applied.

Comments

Source of funding: Ispen (Manufacturer of AboNT-A (Dysport®)). **Limitations:** Control group was not incorporated into the analysis. Unclear whether AUL population is comprised of ≥80% stroke survivors. Utility values for ALL indication were calculated using EQ-5D-5L when NICE reference case prefers EQ-5D-3L. Utility values used, although taken from people with post-stroke spasticity, were not based on the same measure of response used in this analysis: MAS and GAS, but rather based on EQ-5D data for different walking speeds and DAS, respectively. Outcomes used for response rates have shortcomings as the MAS does not necessarily correlate directly with health-related quality of life (HRQoL) as a theoretical construct, while the subjective nature and variability in the assessment of GAS scores do not easily facilitate comparisons between patients or groups. Treatment response rates in the AUL indication was based on observational data. Resource use estimates were based on a survey of 12 UK physicians and not a systematic review of the literature. Resource use estimates and dosing assumptions for AUL were applied to the ALL indication as real-world data for ALL was not available. Assumption applied to frequency of treatment doses for ALL indication as no comparative data available. One year time horizon may not sufficiently capture all costs and outcomes associated with the interventions. Utility inputs for ALL were not based on a stroke-specific population. Study was funded by manufacturer (Ipsen) of AboNT-A (Dysport). **Other:** Utility values for the AUL indication were also used in the CUA by Doan 2013[24] included in this review.

Overall applicability:[(c)] Partially applicable **Overall quality:**[(d)] Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; ALL= Adults with lower limb [spasticity]; AUL= Adults with upper limb [spasticity]; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health]; GAS= Goal attainment scale; ICER= incremental cost-effectiveness ratio; MAS = modified Ashworth scale; NR= not reported; QALYs= quality-adjusted life years; PSA= Probabilistic sensitivity analysis.

a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

b) QALYs based on response status result from differential utilities by responders vs. non-responders and difference in response rates by treatment.

c) Directly applicable / Partially applicable / Not applicable

d) Minor limitations / Potentially serious Limitations / Very serious limitations

1 **H1.1.4 Dry needling versus placebo/sham**

2

Study	Fernandez-Sanchis 2022[32]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis (health outcome: QALYs) **Study design:** Within-trial analysis of an observational study (Zaldivar 2021[16] ((n=80) with no modelled extrapolation. **Approach to analysis:** Analysis of treatment costs and EQ-5D. QALYs were estimated using an area under the curve approach using baseline and 4-and-8-week EQ-5D responses. Bootstrapping was undertaken to estimate uncertainty in the ICER. Cost-effectiveness results were also presented to indicate the cost per responder to treatment based on MMAS scores. **Perspective:** Spanish public healthcare system **Follow-up:** 4 and 8 weeks **Treatment effect duration:**[(a)] NA	**Population:** Adults (≥18 years old) diagnosed with stroke in the subacute phase (1–3 months) resulting in upper limb spasticity. **Cohort settings:** Mean age (SD): 73.2 (13.3) years Male: 50% **Intervention 1:** Control group (n=40) who received standard physiotherapy, 45-minute sessions were given five days per week for 8 weeks. **Intervention 2:** Intervention group (n=40) received standard physiotherapy plus dry needling with the DNHS® technique. DNHS® treatment was included in six of the standard treatment sessions (weeks 1, 2, 3, 4, 6 and 8).	**4-week total costs (mean per patient (SD)):** Intervention 1: £17,077 (£1,852) Intervention 2: £20,786 (£1,921) **Incremental (2−1):** £3,709 (95% CI: NR; p=NR) **8-week total costs (mean per patient):** Intervention 1: £34,376 (£3,604) Intervention 2: £41,604 (£3,892) **Incremental (2−1):** £7,229 (95% CI: NR; p=NR) **Currency & cost year:** 2016 euros converted to UK pounds (£)[(b)] **Cost components incorporated:** Dry needling materials, cost per physiotherapy session and average cost per day of neurological patients.	**4-week QALY gain (mean per patient):** Intervention 1: 0.006 (95% CI: NR; p=1.000) Intervention 2: 0.029 (95% CI: NR; p<0.001) **Incremental (2−1):** 0.023 (95% CI: NR; p=NR) **8-week QALY gain (mean per patient):** Intervention 1: 0.011 (95% CI: NR; p=1.000) Intervention 2: 0.044 (95% CI: NR; p<0.001) **Incremental (2−1):** 0.033 (95% CI: NR; p=NR)	**4-week ICER (Intervention 2 versus Intervention 1):** • 4 weeks: £161,283 (95% CI: NR; p=NR) • 8 weeks: £216,527 (95% CI: NR; p=NR) Probability Intervention 2 cost effective (£26,645 (€25,000) threshold): • 4 weeks: 7.5% • 8 weeks: 8% **Analysis of uncertainty:** The results of the cost-effectiveness analysis using responder rates were positive in all cases for DNHS®. The results also indicated that 4 weeks of treatment could be more profitable than treatments lasting 8 weeks, considering the cost per responder: the mean difference between cost per responder at 4 weeks was £39,593 cheaper than at 8 weeks.

Discounting: NA				

Data sources

Health outcomes: Within-trial analysis of a single-centre, observational, prospective, single cohort study[16] where the primary outcome was response to treatment, which was measured using MMAS values collected at baseline and at 4 and 8 weeks. A patient was considered to have responded to treatment if an improvement by 1 point or more on the scale was detected between the first measurement and the last. The data were transformed to obtain the percentage of patients responding to treatment in both branches of the trial at 4 and 8 weeks. With the same timeline, EQ-5D-5L responses were converted into utility scores. QALYs were then estimated for each subject using area under the curve analysis. **Quality-of-life weights:** Within-trial analysis using EQ-5D-5L with Spanish preference weights applied. **Cost sources:** References for cost sources were not reported, however unit costs such as the average cost of a dry needling treatment session provided in the Spanish public health system for a stroke patient was reported to cost approximately £17 (£1.70 + £15.30 for the dry needling material plus the physiotherapy session). The cost of physiotherapy session was determined based on the official bulletins of five representative autonomous communities, ranging from £8.30-£21.40 per session. There were no differences between groups for the cost of physiotherapy sessions as dry needling was performed without altering the number or duration of sessions. The average costs per patient stay were assessed according to levels of care based on data from the year 2016 provided by Guadarrama Hospital.

Comments

Source of funding: The University of San Jorge and the University of Zaragoza. **Limitations:** Spanish healthcare system may not reflect current UK NHS practice. QALYs were estimated using EQ-5D-5L (Spanish tariff) when the NICE reference case currently prefers EQ5D-3L (UK tariff). Baseline outcomes and intervention effects were based on single non-randomised observational study excluded from clinical review. Estimates of resource use were based on data from the trial population and not a systematic review. 8-week follow-up may not sufficiently assess the full costs and benefits Only intervention related healthcare costs and resource use incorporated into the analysis; no downstream resource use included. References for unit costs (including cost year - with the exception of costs per patient stay) were not reported. One conflict of interest was declared as the DNHS® technique was registered by a study author. **Other:** Zaldivar 2021[16] was excluded from the clinical review as it is non-randomised study when sufficient randomised evidence was identified.

Overall applicability:[(c)] Partially applicable **Overall quality:**[(d)] Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; DNHS= dry needling for hypertonia and spasticity; EQ-5D-5L= EuroQol 5 dimensions 5 levels (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; MMAS= modified modified Ashworth scale (scale 0-4, lower values are better); NA= not applicable; NR= not reported; QALYs= quality-adjusted life years.

a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

b) Converted using 2016 purchasing power parities[96]. References for unit costs were not reported but 2016 was assumed as this was the same year used to assess the average cost per patient stay.

c) Directly applicable / Partially applicable / Not applicable

d) Minor limitations / Potentially serious limitations / Very serious limitations

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Appendix I – Health economic model

Original economic analysis was reported in a separate document (Evidence Review P – Spasticity model write up).

Appendix J – Excluded studies

Clinical studies

Table 95: Studies excluded from the clinical review

Study	Code [Reason]
Abo, M., Shigematsu, T., Hara, H. et al. (2020) Efficacy and Safety of OnabotulinumtoxinA 400 Units in Patients with Post-Stroke Upper Limb Spasticity: Final Report of a Randomized, Double-Blind, Placebo-Controlled Trial with an Open-Label Extension Phase. Toxins 12(2): 18	- Comparator in study does not match that specified in this review protocol
Abramovich, S. G., Drobyshev, V. A., Pyatova, A. E. et al. (2020) Comprehensive Use of Dynamic Electrical Neurostimulation and Botulinum Toxin Therapy in Patients with Post-Stroke Spasticity. Journal of Stroke & Cerebrovascular Diseases 29(11): 105189	- Data not reported in an extractable format or a format that can be analysed
Ambrosini, E., Parati, M., Ferriero, G. et al. (2020) Does cycling induced by functional electrical stimulation enhance motor recovery in the subacute phase after stroke? A systematic review and meta-analysis. Clinical Rehabilitation 34(11): 1341-1354	- Systematic review used as source of primary studies
Ambrosini, E, Ferrante, S, Pedrocchi, A et al. (2011) Cycling induced by electrical stimulation improves motor recovery in postacute hemiparetic patients: A randomized controlled trial. Stroke 42(4): 1068-73.	- Population not relevant to this review protocol *Excludes people with low spasticity levels (modified Ashworth scale <2) and does not report spasticity related outcomes*
Amini, M., Shamili, A., Frough, B. et al. (2016) Combined effect of botulinum toxin and splinting on motor components and function of people suffering a stroke. Medical Journal of the Islamic Republic of Iran 30: 373	- Study design not relevant to this review protocol *Non-randomised study where there is sufficient randomised evidence for the intervention*
Andringa, A., van de Port, I., van Wegen, E. et al. (2019) Effectiveness of Botulinum Toxin Treatment for Upper Limb Spasticity Poststroke Over Different ICF Domains: A Systematic Review and Meta-Analysis. Archives of Physical Medicine & Rehabilitation 100(9): 1703-1725	- Systematic review used as source of primary studies
Anonymous (2004) Acupuncture does not help spasticity following stroke (n=25). Acupuncture in Medicine 22(4): 224-225	- Commentary only

Study	Code [Reason]
Anonymous (2020) Erratum to: IncobotulinumtoxinA Treatment in Upper-Limb Poststroke Spasticity in the Open-Label Extension Period of PURE: Efficacy in Passive Function, Caregiver Burden, and Quality of Life (PM&R, (2020), 12, 5, (491-499), 10.1002/pmrj.12265). PM and R 12(7): 736	- Secondary publication of an included study that does not provide any additional relevant information
Anonymous (2016) Erratum: Randomized, placebo-controlled trial of incobotulinumtoxinA for upper-limb post-strokespasticity (Muscle Nerve, (2015), 53, 3, (415-421), 10.1002/mus.24776). Muscle and Nerve 54(1): 170	- Secondary publication of an included study that does not provide any additional relevant information
Arbizu, Tx, Martinez, J. A., Rubio, F. et al. (1988) Clinical evaluation and tolerance of tizanidine (DS 103-282) and baclofen in patients with chronic spasticity due to cerebrovascular accidents. Revista espanola de neurologia 3(4): 291-296	- Full text paper not available
Ashford, S. and Turner-Stokes, L. (2013) Systematic review of upper-limb function measurement methods in botulinum toxin intervention for focal spasticity. Physiotherapy Research International 18(3): 178-89	- Systematic review used as source of primary studies
Bae, Yh, Ko, Yj, Chang, Wh et al. (2014) Effects of robot-assisted gait training combined with functional electrical stimulation on recovery of locomotor mobility in chronic stroke patients: A randomized controlled trial. Journal of Physical Therapy Science 26(12): 1949-53.	- Population not relevant to this review protocol *Does not explicitly mention spasticity with no spasticity related outcomes*
Baguley, I. J., Nott, M. T., Turner-Stokes, L. et al. (2011) Investigating muscle selection for botulinum toxin-A injections in adults with post-stroke upper limb spasticity. Journal of Rehabilitation Medicine 43(11): 1032-7	- Secondary publication of an included study that does not provide any additional relevant information
Bakheit, A. M. O., Pittock, S., Moore, A. P. et al. (2001) A randomized double blind placebo controlled study of the efficacy and safety of botulinum toxin type A in upper limb spasticity in patients with stroke. European journal of neurology 8: 559-565	- Duplicate reference
Bakheit, A. M., Pittock, S., Moore, A. P. et al. (2001) A randomized, double-blind, placebo-controlled study of the efficacy and safety of botulinum toxin type A in upper limb spasticity in patients with stroke. European Journal of Neurology 8(6): 559-65	- Duplicate reference

Study	Code [Reason]
Bao, X., Luo, J. N., Shao, Y. C. et al. (2020) Effect of functional electrical stimulation plus body weight-supported treadmill training for gait rehabilitation in patients with poststroke: a retrospective case-matched study. European journal of physical & rehabilitation medicine. 56(1): 34-40	- Study design not relevant to this review protocol
Baricich, A., Picelli, A., Carda, S. et al. (2019) Electrical stimulation of antagonist muscles after botulinum toxin type A for post-stroke spastic equinus foot. A randomized single-blind pilot study. Annals of Physical & Rehabilitation Medicine 62(4): 214-219	- Comparator in study does not match that specified in this review protocol
Bauer, P., Krewer, C., Golaszewski, S. et al. (2015) Functional electrical stimulation-assisted active cycling--therapeutic effects in patients with hemiparesis from 7 days to 6 months after stroke: a randomized controlled pilot study. Archives of Physical Medicine & Rehabilitation 96(2): 188-96	- Population not relevant to this review protocol *Only a third of the population had an MAS score >0 before intervention*
Bayle, N., Maisonobe, P., Raymond, R. et al. (2020) Composite active range of motion (CXA) and relationship with active function in upper and lower limb spastic paresis. Clinical Rehabilitation 34(6): 803-811	- Secondary publication of an included study that does not provide any additional relevant information
Bensoussan, L., Lotito, G., Viton, J. M. et al. (2012) Effect on postural control of spastic equinovirus foot treatment with botulinum toxin in stroke patients: randomized, controlled, multicenter trial. Annals of physical and rehabilitation medicine 55(s1): e102	- Conference abstract
Bhakta, B. B.; Cozens, J. A.; Chamberlain, M. A. (1999) The impact of botulinum toxin type-A (dysport) treatment on the disabling effects of severe upper limb spasticity following stroke: a randomized, double-blind, placebo-controlled trial. Toxins'99	- Conference abstract
Bhakta, B. B., Cozens, J. A., Chamberlain, M. A. et al. (1999) A randomised double blind placebo controlled trial of botulinum toxin treatment on the disabling effects of severe arm spasticity in stroke. Cerebrovascular diseases (basel, switzerland) 9 (Suppl 1): 124	- Conference abstract
Bhakta, B. B., Cozens, J. A., Chamberlain, M. A. et al. (2000) Impact of botulinum toxin type A on disability and carer burden due to arm spasticity	- Data not reported in an extractable format or a format that can be analysed

Study	Code [Reason]
after stroke: a randomised double blind placebo controlled trial. Journal of Neurology, Neurosurgery & Psychiatry 69(2): 217-21	
Bhakta, B. B., Cozens, J. A., Chamberlain, M. A. et al. (2000) Randomized double-blind placebo-controlled trial of botulinum toxin treatment on the disabling effects of severe arm spasticity in stroke. Clinical rehabilitation 14: 213	- Conference abstract
Bhakta, B. B.; O'Connor, R. J.; Cozens, J. A. (2008) Associated reactions after stroke: a randomized controlled trial of the effect of botulinum toxin type A. Journal of Rehabilitation Medicine 40(1): 36-41	- No relevant outcomes reported
Bhakta, B. and Cozens, J. A. (1996) Botulinum toxin treatment in stroke patients with severe upper limb spasticity. Clinical rehabilitation 10(1): 85-86	- Commentary only
Bhatt, H.; Sharma, C.; Mochizuki, S. (2013) The effect of combined upper limb rehabilitation and botulinum toxin injections on electrophysiological, clinical, and behavioural outcomes in post-stroke spasticity. Stroke; a journal of cerebral circulation 44(12): e227	- Conference abstract
Bollens, B., Gustin, T., Stoquart, G. et al. (2013) A randomized controlled trial of selective neurotomy versus botulinum toxin for spastic equinovarus foot after stroke. Neurorehabilitation & Neural Repair 27(8): 695-703	- Comparator in study does not match that specified in this review protocol
Brashear, A. (2003) Use of botulinum toxin type A in poststroke spasticity. Expert Review of Neurotherapeutics 3(3): 271-7	- Review article but not a systematic review
Brashear, A., Gordon, M. F., Elovic, E. et al. (2001) A multicenter, double-blind, randomized, placebo-controlled, parallel study of the safety and efficacy of BOTOX (Botulinum toxin Type A) purified neurotoxin in the treatment of focal upper limb spasticity post-stroke. American academy of neurology 53rd annual meeting	- Conference abstract
Burbaud, P., Wiart, L., Dubos, J. L. et al. (1996) A randomised, double blind, placebo controlled trial of botulinum toxin in the treatment of spastic foot in hemiparetic patients. Journal of Neurology, Neurosurgery & Psychiatry 61(3): 265-9	- Cross-over trial

Study	Code [Reason]
Burridge, J. H., Taylor, P. N., Hagan, S. A. et al. (1997) The effects of common peroneal stimulation on the effort and speed of walking: a randomized controlled trial with chronic hemiplegic patients. Clinical Rehabilitation 11(3): 201-10	- Population not relevant to this review protocol
Cai, Y., Zhang, C. S., Liu, S. et al. (2017) Electroacupuncture for Poststroke Spasticity: A Systematic Review and Meta-Analysis. Archives of Physical Medicine & Rehabilitation 98(12): 2578-2589.e4	- Systematic review used as source of primary studies
Cai, Y.; Zhang, C. S.; Zhang, A. L.; Da Costa, C.; Xue, C. C.; Wen, Z.; Electroacupuncture for Poststroke Spasticity: Results of a Pilot Pragmatic Randomized Controlled Trial; Journal of Pain & Symptom Management; 2021; vol. 61 (no. 2); 305-314	- Study removed at the request of the committee as a subsequent published study (Dai, et al. 2022) reported results that were similar and unlikely to be so due to chance. The committee note that this study was published beforehand and was registered in a clinical trial database. However, due to the uncertainty in the second study, the committee agreed to exclude both studies.
Chae, J., Yu, D. T., Walker, M. E. et al. (2005) Intramuscular electrical stimulation for hemiplegic shoulder pain: a 12-month follow-up of a multiple-center, randomized clinical trial. American Journal of Physical Medicine & Rehabilitation 84(11): 832-42	- Population not relevant to this review protocol
Chang, M. A. (2015) Possible Adverse Effects of Repeated Botulinum Toxin A Injections to Decrease Post-Stroke Spasticity in Adults Undergoing Rehabilitation: A Review of the Literature. Journal of Allied Health 44(3): 140-4	- Systematic review used as source of primary studies
Chen, F. J., Chen, Z. Y., Liang, X. Z. et al. (2003) Botulinum toxin type A for limb functional recover in high spasticity patients with stroke. Chinese journal of clinical rehabilitation 7(25): 3478-3479	- Study not reported in English
Chen, P., Liu, T.-W., Kwong, P.W.H. et al. (2022) Bilateral Transcutaneous Electrical Nerve Stimulation Improves Upper Limb Motor Recovery in Stroke: A Randomized Controlled Trial. Stroke 53(4): 1134-1140	- Population not relevant to this review protocol *No information about spasticity in the inclusion criteria or outcomes*
Chen, S. C., Chen, Y. L., Chen, C. J. et al. (2005) Effects of surface electrical stimulation on the muscle-tendon junction of spastic gastrocnemius in stroke patients. Disability & Rehabilitation 27(3): 105-10	- Data not reported in an extractable format or a format that can be analysed

Study	Code [Reason]
Chen, Y., Zhou, H., Jin, T. et al. (2018) Clinical observation of the phased acupuncture for ischemic stroke hemiplegia. Zhongguo zhen jiu [Chinese acupuncture & moxibustion] 38(10): 1027-1034	- Study not reported in English
Chen, Y, Du, ZH, Chen, HY et al. (2022) Effect of staged acupuncture on serum irisin level and neurological rehabilitation in patients with ischemic stroke. Zhongguo zhen jiu [Chinese acupuncture & moxibustion] 42(8): 857-862	- Study not reported in English
Childers, M. K., Brashear, A., Jozefczyk, P. B. et al. (1999) A multicenter, double-blind, placebo-controlled dose response trial of botulinum toxin type A (Botox) in upper limb spasticity post-stroke. Neurology 52 (Suppl 2): a295	- Conference abstract
Childers, M. K., Stacy, M., Cooke, D. L. et al. (1996) Comparison of two injection techniques using botulinum toxin in spastic hemiplegia. American Journal of Physical Medicine & Rehabilitation 75(6): 462-9	- Data not reported in an extractable format or a format that can be analysed
Cho, H. Y., In, T. S., Cho, K. H. et al. (2013) A single trial of transcutaneous electrical nerve stimulation (TENS) improves spasticity and balance in patients with chronic stroke. Tohoku Journal of Experimental Medicine 229(3): 187-93	- Study design not relevant to this review protocol *Less than 1 week of follow up (1 day)*
Clark, P. C., Aycock, D. M., Reiss, A. et al. (2015) Potential benefits for caregivers of stroke survivors receiving BTX-A and exercise for upper extremity spasticity. Rehabilitation Nursing Journal 40(3): 188-96	- Study design not relevant to this review protocol *FU period is only 1 day*
Cozean, C. D.; Pease, W. S.; Hubbell, S. L. (1988) Biofeedback and functional electric stimulation in stroke rehabilitation. Archives of Physical Medicine & Rehabilitation 69(6): 401-5	- No relevant outcomes reported
Creamer, M. J., Cloud, G., Kossmehl, P. P. K. et al. (2019) Intrathecal baclofen effect on pain and quality of life in post-stroke spasticity: sisters randomized trial. Neuromodulation conference22ndannualmeetingofthenorthamericanneuromodulationsocietynans2019unitedstates22 (3): e94	- Conference abstract
Cuenca Zaldivar, J. N., Calvo, S., Bravo-Esteban, E. et al. (2021) Effectiveness of dry needling for	- Study design not relevant to this review protocol

Study	Code [Reason]
upper extremity spasticity, quality of life and function in subacute phase stroke patients. Acupuncture in Medicine 39(4): 299-308	
Cuenca Zaldívar JN, Calvo S, Bravo-Esteban E et al. (2021) Effectiveness of dry needling for upper extremity spasticity, quality of life and function in subacute phase stroke patients. Acupuncture in medicine : journal of the British Medical Acupuncture Society 39(4): 299-308	- Study design not relevant to this review protocol *Non-randomised study and outcomes are not adjusted for by the confounders stated in the protocol*
Cui, L. H.; Zhang, T.; Yang, L. Y. (2009) Efficacy of three antispasmodics on limb spasticity in patients after stroke: a comparative analysis. Chinese journal of cerebrovascular diseases 6(9): 466-470	- Study not reported in English
Cui, L. and Zhang, T. (2006) Domestic botulinum toxin type A injection in the treatment of post-stroke patients with upper extremity spasticity. Chinese journal of neurology 39(7): 463-466	- Study not reported in English
Dai, H.; Chen, Z.; Xie, Z.; Peng, Y.; Evaluation of the efficacy of electroacupuncture in poststroke spasticity: results of a randomized controlled trial; Revista de Psiquiatria Clinica; 2022; vol. 49 (no. 1); 11-18	- Study removed at the request of the committee as a previously published study (Cai, et al. 2021) reported results that were similar and unlikely to be so due to chance. The committee note that this study was published second and was not registered in a clinical trial database. The committee agreed to exclude this study due to concerns about the originality of the work.
Dashtipour, K., Chen, J. J., Walker, H. W. et al. (2015) Systematic literature review of abobotulinumtoxinA in clinical trials for adult upper limb spasticity. American Journal of Physical Medicine & Rehabilitation 94(3): 229-38	- Systematic review used as source of primary studies
Datta Gupta, A., Visvanathan, R., Cameron, I. et al. (2019) Efficacy of botulinum toxin in modifying spasticity to improve walking and quality of life in post-stroke lower limb spasticity - a randomized double-blind placebo controlled study. BMC Neurology 19(1): 96	- Protocol only
de Beyl, D. Z., Csiba, L., Yakovleff, A. et al. (2000) A multicenter, double-blind, placebo-controlled trial to evaluate dosing, safety, and efficacy of intramuscular botulinum toxin type a for the management of upper limb spasticity poststroke. European journal of neurology 7 (Suppl 3): 23	- Conference abstract

Study	Code [Reason]
de Boer, K. S., Arwert, H. J., de Groot, J. H. et al. (2008) Shoulder pain and external rotation in spastic hemiplegia do not improve by injection of botulinum toxin A into the subscapular muscle. Journal of Neurology, Neurosurgery & Psychiatry 79(5): 581-3	- Data not reported in an extractable format or a format that can be analysed
de Sousa, D. G., Harvey, L. A., Dorsch, S. et al. (2016) Functional electrical stimulation cycling does not improve mobility in people with acquired brain injury and its effects on strength are unclear: a randomised trial. Journal of Physiotherapy 62(4): 203-8	- Comparator in study does not match that specified in this review protocol
Demetrios, M., Gorelik, A., Louie, J. et al. (2014) Outcomes of ambulatory rehabilitation programmes following botulinum toxin for spasticity in adults with stroke. Journal of Rehabilitation Medicine 46(8): 730-7	- Comparator in study does not match that specified in this review protocol
Demetrios, M., Khan, F., Turner-Stokes, L. et al. (2013) Multidisciplinary rehabilitation following botulinum toxin and other focal intramuscular treatment for post-stroke spasticity. Cochrane Database of Systematic Reviews: cd009689	- Study does not contain an intervention relevant to this review protocol
Demetrios, M.; Ng, L.; Khan, F. (2012) The effectiveness of outpatient rehabilitation following botulinum toxin type A (BONT-A) treatment for upper and lower limb spasticity in persons with stroke. Neurorehabilitation and neural repair 26(6): 716	- Conference abstract
Deng, Y. J. (2015) Acupuncture Jiaji Point combined with exercise therapy for the treatment of hemiplegia spasticity after stroke. Journal of clinical acupuncture and moxibustion [zhen jiu lin chuang za zhi] 31(12): 13-16	- Study not reported in English
Desalbres, U. (2018) Efficiency of botulinum toxin injection for spastic equinovarus foot in post stroke hemiparetic patients.	- Conference abstract
Dimitrova, R., James, L., Liu, C. et al. (2020) Safety of OnabotulinumtoxinA with Concomitant Antithrombotic Therapy in Patients with Muscle Spasticity: A Retrospective Pooled Analysis of Randomized Double-Blind Studies. CNS Drugs 34(4): 433-445	- Secondary publication of an included study that does not provide any additional relevant information

Study	Code [Reason]
Doan, Q. V., Gillard, P., Brashear, A. et al. (2013) Cost-effectiveness of onabotulinumtoxinA for the treatment of wrist and hand disability due to upper-limb post-stroke spasticity in Scotland. European Journal of Neurology 20(5): 773-80	- Economic evidence only
Doan, T. N.; Kuo, M. Y.; Chou, L. W. (2021) Efficacy and Optimal Dose of Botulinum Toxin A in Post-Stroke Lower Extremity Spasticity: A Systematic Review and Meta-Analysis. Toxins 13(6): 18	- Systematic review used as source of primary studies
Dong, Y., Wu, T., Hu, X. et al. (2017) Efficacy and safety of botulinum toxin type A for upper limb spasticity after stroke or traumatic brain injury: a systematic review with meta-analysis and trial sequential analysis. European journal of physical & rehabilitation medicine. 53(2): 256-267	- Population not relevant to this review protocol
Dressler, D., Rychlik, R., Kreimendahl, F. et al. (2015) Long-term efficacy and safety of incobotulinumtoxinA and conventional treatment of poststroke arm spasticity: a prospective, non-interventional, open-label, parallel-group study. BMJ Open 5(12): e009358	- Study design not relevant to this review protocol
Dunne, J. W. (2005) Effect of botulinum toxin type-A (BOTOX) on lower limb spasticity during stroke rehabilitation. Journal of clinical neuroscience 12(3): 333	- Conference abstract
Dunne, J. W., Gracies, J. M., Hayes, M. et al. (2012) A prospective, multicentre, randomized, double-blind, placebo-controlled trial of onabotulinumtoxinA to treat plantarflexor/invertor overactivity after stroke. Clinical Rehabilitation 26(9): 787-97	- Data not reported in an extractable format or a format that can be analysed
Elovic, E., Brashaer, A., Munin, M. et al. (2016) Sustained efficacy with incobotulinumtoxina in upper-limb post-stroke spasticity over 48 weeks (a phase 3, placebo-controlled study with an open-label extension). 68th annual meeting of the american academy of neurology	- Conference abstract
Embrey, D. G., Holtz, S. L., Alon, G. et al. (2010) Functional electrical stimulation to dorsiflexors and plantar flexors during gait to improve walking in adults with chronic hemiplegia. Archives of Physical Medicine & Rehabilitation 91(5): 687-96	- Cross-over trial

Study	Code [Reason]
Eraifej, J., Clark, W., France, B. et al. (2017) Effectiveness of upper limb functional electrical stimulation after stroke for the improvement of activities of daily living and motor function: a systematic review and meta-analysis. Systematic Reviews 6(1): 40	- Systematic review used as source of primary studies
Fan, L. B., Liu, S. Z., Wang, Z. T. et al. (2015) Application of electroacupuncture plus movement therapy in recovering neurologic function of patients with spastic hemiplegia. Shanghai journal of acupuncture and moxibustion [shang hai zhen jiu za zhi] 34(12): 1178-1180	- Study not reported in English
Fan, W., Kuang, X., Hu, J. et al. (2020) Acupuncture therapy for poststroke spastic hemiplegia: A systematic review and meta-analysis of randomized controlled trials. Complementary Therapies in Clinical Practice 40: 101176	- Systematic review used as source of primary studies
Feller, C. N., Awad, A. J., Nelson, M. E. S. et al. (2021) Low Rate of Intrathecal Baclofen Pump Catheter-Related Complications: Long-Term Study in Over 100 Adult Patients Associated With Reinforced Catheter. Neuromodulation 11: 11	- Population not relevant to this review protocol
Feng, X. (2017) Electroacupuncture in the Du meridian for upper limb spasticity after stroke, a randomized controlled trial.	- Conference abstract
Fernandez-de-Las-Penas, C., Perez-Bellmunt, A., Llurda-Almuzara, L. et al. (2021) Is Dry Needling Effective for the Management of Spasticity, Pain, and Motor Function in Post-Stroke Patients? A Systematic Review and Meta-Analysis. Pain Medicine 22(1): 131-141	- Systematic review used as source of primary studies
Fietzek, U. M., Kossmehl, P., Schelosky, L. et al. (2014) Early botulinum toxin treatment for spastic pes equinovarus--a randomized double-blind placebo-controlled study. European Journal of Neurology 21(8): 1089-1095	- Population not relevant to this review protocol
Fink, M., Rollnik, J. D., Bijak, M. et al. (2004) Needle acupuncture in chronic poststroke leg spasticity. Archives of Physical Medicine & Rehabilitation 85(4): 667-72	- Data not reported in an extractable format or a format that can be analysed
Fletcher-Smith, J. C., Walker, D. M., Allatt, K. et al. (2019) The ESCAPS study: a feasibility	- No relevant outcomes reported

Study	Code [Reason]
randomized controlled trial of early electrical stimulation to the wrist extensors and flexors to prevent post-stroke complications of pain and contractures in the paretic arm. Clinical Rehabilitation 33(12): 1919-1930	
Foley, N., Pereira, S., Salter, K. et al. (2013) Treatment with botulinum toxin improves upper-extremity function post stroke: a systematic review and meta-analysis. Archives of Physical Medicine & Rehabilitation 94(5): 977-89	- Systematic review used as source of primary studies
Fu, Q. Y., Chen, G. L., Meng, F. Q. et al. (2005) Effect of type A botulinus toxin on immunological function in the treatment of post-stroke limb spasticity: a randomized, double-blind, placebo-controlled trial. Chinese journal of clinical rehabilitation 9(13): 16-17	- Study not reported in English
Gelber, D. A., Good, D. C., Dromerick, A. et al. (2001) Open-label dose-titration safety and efficacy study of tizanidine hydrochloride in the treatment of spasticity associated with chronic stroke. Stroke 32(8): 1841-6	- Study design not relevant to this review protocol
Ghroubi, S., Alila, S., Elleuch, W. et al. (2020) Efficacy of botulinum toxin A for the treatment of hemiparesis in adults with chronic upper limb spasticity. The Pan African medical journal 35: 55	- Study design not relevant to this review protocol
Glanz, M, Klawansky, S, Stason, W et al. (1996) Functional electrostimulation in poststroke rehabilitation: a meta-analysis of the randomized controlled trials. Archives of Physical Medicine and Rehabilitation 77(6): 549-53.	- Systematic review used as source of primary studies
Glass, A. and Hannah, A. (1974) A comparison of dantrolene sodium and diazepam in the treatment of spasticity. Paraplegia 12(3): 170-174	- Population not relevant to this review protocol
Gordon, M. F., Brashear, A., Elovic, E. et al. (2002) A multicenter, open-label study of the safety and efficacy of repeated botulinum toxin type A doses in poststroke, focal, upper limb spasticity. Neurology 58(suppl3): a221	- Conference abstract
Gracies, J. M., Esquenazi, A., Brashear, A. et al. (2017) Efficacy and safety of abobotulinumtoxinA in spastic lower limb: Randomized trial and extension. Neurology 89(22): 2245-2253	- Secondary publication of an included study that does not provide any additional relevant information

Study	Code [Reason]
Guo, F., Yue, W., Ren, L. et al. (2006) Botulinum toxin type A plus rehabilitative training for improving the motor function of the upper limbs and activities of daily life in patients with stroke and brain injury. Neural Regeneration Research 1(9): 859-861	- Population not relevant to this review protocol
Guo, Xiaoli, Zhang, Xiaoying, Sun, Meng et al. (2022) Modulation of Brain Rhythm Oscillations by Xingnao Kaiqiao Acupuncture Correlates with Stroke Recovery: A Randomized Control Trial. Journal of integrative and complementary medicine 28(5): 436-444	- Population not relevant to this review protocol *No mention of spasticity in the inclusion criteria or the outcomes*
Gupta, A. D. (2018) Efficacy of botulinum toxin A on walking and quality of life in post-stroke lower limb spasticity - a randomized double-blind placebo controlled study.	- Conference abstract
Gupta, A. D., Chu, W. H., Howell, S. et al. (2018) A systematic review: efficacy of botulinum toxin in walking and quality of life in post-stroke lower limb spasticity. Systematic Reviews 7(1): 1	- Systematic review used as source of primary studies
Hara, Y., Ogawa, S., Tsujiuchi, K. et al. (2008) A home-based rehabilitation program for the hemiplegic upper extremity by power-assisted functional electrical stimulation. Disability & Rehabilitation 30(4): 296-304	- Data not reported in an extractable format or a format that can be analysed
Harmon, R. L.; Woolley, S. M.; Horn, L. J. (1996) Use of clonidine for spasticity arising from stroke and brain injury: a pilot placebo-controlled trial. Archives of physical medicine and rehabilitation 77: 934	- Conference abstract
Hedera, P., Esquenazi, A., Christian, A. B. et al. (2018) Frequency and dosing of repeated abobotulinumtoxinA injections in non-gastrocnemius soleus complex muscles in adults with lower limb spasticity following a stroke or traumatic brain injury. Pm&R 10(9): 32	- Conference abstract
Hesse, S., Mach, H., Froehlich, S. et al. (2011) The early Botulinum Toxin A injection may prevent a disabling finger flexor stiffness six months later in subacute stroke patients. Neurologie und rehabilitation 17(56): 233-238	- Study not reported in English
Ho, E., Hoover, P., Chari, V. et al. (2017) A double blinded dual centers investigation of the	- Conference abstract

Study	Code [Reason]
use of acupuncture for the treatment of spasticity in chronic stroke patients - pilot study. International journal of stroke 12(4suppl1): 85	
Hokazono, A., Etoh, S., Jonoshita, Y. et al. (2021) Combination therapy with repetitive facilitative exercise program and botulinum toxin type A to improve motor function for the upper-limb spastic paresis in chronic stroke: A randomized controlled trial. Journal of Hand Therapy 26: 26	- Data not reported in an extractable format or a format that can be analysed
Hong, Z., Sui, M., Zhuang, Z. et al. (2018) Effectiveness of Neuromuscular Electrical Stimulation on Lower Limbs of Patients With Hemiplegia After Chronic Stroke: A Systematic Review. Archives of Physical Medicine & Rehabilitation 99(5): 1011-1022.e1	- Systematic review used as source of primary studies
Horng, M. S. (2005) Acupuncture shows no benifit over sham treatment for stroke rehabilitation. Journal of Clinical Outcomes Management 12(12): 607-608	- Commentary only
Hu, X. L., Tong, K. Y., Li, R. et al. (2012) The effects of electromechanical wrist robot assistive system with neuromuscular electrical stimulation for stroke rehabilitation. Journal of Electromyography & Kinesiology 22(3): 431-9	- Study design not relevant to this review protocol
Huang, H, Chen, J, Qiu, F et al. (2022) Effect of electroacupuncture on motor function and gait in patients with post-stroke spasticity in lower limbs. Zhongguo zhen jiu [Chinese acupuncture & moxibustion] 42(1): 23-27	- Study not reported in English
Huang, X. Y., Xia, Q. F., Zhu, H. W. et al. (2020) Therapeutic effect on post-stroke spastic paralysis of upper extremity treated with combination of kinematic-acupuncture therapy and rehabilitation training. Zhongguo zhen jiu [Chinese acupuncture & moxibustion] 40(5): 473-478	- Study not reported in English
Hughes, A., Baguley, I., De Graaff, S. et al. (2008) Botulinum toxin (Dysport) in upper limb spasticity following stroke - a placebo controlled study. Journal of clinical neuroscience 15: 355-356	- Conference abstract
Im, S., Park, G. Y., Kwon, S. G. et al. (2012) Preliminary results of botulinum toxin A injected proximally into the gastrocnemus in post-stroke	- Conference abstract

Study	Code [Reason]
lower limb spasticity. Cerebrovascular diseases (basel, switzerland) 33(suppl2): 527-528	
Iskra, DA, Kovalenko, AP, Koshkarev, MA et al. (2019) Combination of central and peripheral muscle relaxants in the treatment of post-stroke spasticity. Zhurnal nevrologii i psikhiatrii imeni s skorsakova119(12vyp2): 51-57	- Study not reported in English
Ivanhoe, C. B., Francisco, G. E., McGuire, J. R. et al. (2006) Intrathecal baclofen management of poststroke spastic hypertonia: implications for function and quality of life. Archives of Physical Medicine & Rehabilitation 87(11): 1509-15	- Study design not relevant to this review protocol
Jahangir, A. W., Tan, H. J., Norlinah, M. I. et al. (2007) Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after stroke. Medical Journal of Malaysia 62(4): 319-22	- Data not reported in an extractable format or a format that can be analysed
Janssen, T. W., Beltman, J. M., Elich, P. et al. (2008) Effects of electric stimulation-assisted cycling training in people with chronic stroke. Archives of Physical Medicine & Rehabilitation 89(3): 463-9	- Population not relevant to this review protocol *Does not mention the population having spasticity and does not measure spasticity-related outcomes*
Jia, C., Zhang, H., Ni, G. et al. (2017) Spasmodic hemiplegia after stroke treated with scalp acupuncture, music therapy and rehabilitation: a randomized controlled trial. Zhongguo zhen jiu [Chinese acupuncture & moxibustion] 37(12): 1271-1275	- Study not reported in English
Jia, S., Liu, Y., Shen, L. et al. (2020) Botulinum Toxin Type A for Upper Limb Spasticity in Poststroke Patients: A Meta-analysis of Randomized Controlled Trials. Journal of Stroke & Cerebrovascular Diseases 29(6): 104682	- Systematic review used as source of primary studies
Johansson, B. B., Haker, E., von Arbin, M. et al. (2001) Acupuncture and transcutaneous nerve stimulation in stroke rehabilitation: a randomized, controlled trial. Stroke 32(3): 707-13	- Population not relevant to this review protocol *Does not mention whether the population had spasticity and does not report any spasticity-related outcome measures*
Johansson, K., Lindgren, I., Widner, H. et al. (1993) Can sensory stimulation improve the functional outcome in stroke patients?. Neurology 43(11): 2189-92	- Population not relevant to this review protocol *Does not mention the population having spasticity and does not report spasticity-specific outcome measures*

Study	Code [Reason]
Johnson, C. A., Burridge, J. H., Strike, P. W. et al. (2004) The effect of combined use of botulinum toxin type A and functional electric stimulation in the treatment of spastic drop foot after stroke: a preliminary investigation. Archives of Physical Medicine & Rehabilitation 85(6): 902-9	- Data not reported in an extractable format or a format that can be analysed
Johnson, C. A., Wood, D. E., Swain, I. D. et al. (2002) A pilot study to investigate the combined use of botulinum neurotoxin type a and functional electrical stimulation, with physiotherapy, in the treatment of spastic dropped foot in subacute stroke. Artificial Organs 26(3): 263-6	- Data not reported in an extractable format or a format that can be analysed
Johnstone, A., Grigoras, I., Petitet, P. et al. (2021) A single, clinically relevant dose of the GABAB agonist baclofen impairs visuomotor learning. Journal of Physiology 599(1): 307-322	- Population not relevant to this review protocol
Kanovsky, P., Elovic, E. P., Hanschmann, A. et al. (2020) Duration of Treatment Effect Using IncobotulinumtoxinA for Upper-limb Spasticity: A Post-hoc Analysis. Frontiers in neurology [electronic resource]. 11: 615706	- Secondary publication of an included study that does not provide any additional relevant information
Kanovsky, P., Grafe, S., Comes, G. et al. (2008) Efficacy and safety of NT 201 (Xeomin) in upper limb spasticity after stroke: a double-blind placebo-controlled randomized multi-center trial. Neurorehabilitation and neural repair 22(5): 568-569	- Conference abstract
Kanovsky, P., Sassin, I., Comes, G. et al. (2008) Efficacy and safety of NT 201 (Xeomin) in the upper limb post-stroke spasticity in a double-blind placebo-controlled randomized multi-center trial. Movement disorders 23(suppl1): 377	- Study not reported in English
Kanovsky, P., Slawek, J., Denes, Z. et al. (2011) Efficacy and safety of treatment with incobotulinum toxin A (botulinum neurotoxin type A free from complexing proteins; NT 201) in post-stroke upper limb spasticity. Journal of Rehabilitation Medicine 43(6): 486-92	- Secondary publication of an included study that does not provide any additional relevant information
Karaahmet, O. Z., Gurcay, E., Unal, Z. K. et al. (2019) Effects of functional electrical stimulation-cycling on shoulder pain and subluxation in patients with acute-subacute stroke: a pilot study. International Journal of Rehabilitation Research 42(1): 36-40	- Population not relevant to this review protocol

Study	Code [Reason]
Karakus, D., Erso, Z. M., Koyuncu, G. et al. (2013) Effects of functional electrical stimulation on wrist function and spasticity in stroke: A randomized controlled study. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi 59(2): 97-102	- No relevant outcomes reported
Katrak, P. H., Cole, A. M., Poulos, C. J. et al. (1992) Objective assessment of spasticity, strength, and function with early exhibition of dantrolene sodium after cerebrovascular accident: a randomized double-blind study. Archives of Physical Medicine & Rehabilitation 73(1): 4-9	- Cross-over trial
Ketel, W. B. and Kolb, M. E. (1984) Long-term treatment with dantrolene sodium of stroke patients with spasticity limiting the return of function. Current Medical Research & Opinion 9(3): 161-9	- Data not reported in an extractable format or a format that can be analysed *Reported adverse events for the initial phase where all people received dantrolene only. Does not report any other outcomes in a usable manner.*
Kimura, A., Abo, M., Kawate, N. et al. (2010) Efficacy and safety of Botulinum Toxin Type A in treating lower limb spasticity in post stroke patients : m a multicentre, double-blind, placebo controlled trial followed by an open-label trial. Japanese journal of rehabilitation medicine 47(9): 626-636	- Study not reported in English
Kong, K. (2005) A 24-weeks prospective, multicentre, randomized, double-blind, placebo-controlled study of Dysport (Botulinum toxin A) injection for early post-stroke upper limb spasticity (ABCDE-S: asian Botulinum Toxin Clinical Trial Designed for Early Stroke Spastici. Journal of the neurological sciences 238 (Suppl 1): S72-S73	- Conference abstract
Kong, K. H.; Neo, J. J.; Chua, K. S. (2007) A randomized controlled study of botulinum toxin A in the treatment of hemiplegic shoulder pain associated with spasticity. Clinical Rehabilitation 21(1): 28-35	- No relevant outcomes reported
Kosem, Murat; Ata, Emre; Yilmaz, Figen (2022) Does Dry Needling Increase the Efficacy of Botulinum Toxin Injection in the Management of Post-Stroke Spasticity: A Randomized Controlled Study. Noro psikiyatri arsivi 59(2): 110-115	- Data not reported in an extractable format or a format that can be analysed *Medians and interquartile ranges*
Laddha, D., Ganesh, G. S., Pattnaik, M. et al. (2016) Effect of Transcutaneous Electrical Nerve Stimulation on Plantar Flexor Muscle Spasticity	- Data not reported in an extractable format or a format that can be analysed

Study	Code [Reason]
and Walking Speed in Stroke Patients. Physiotherapy Research International 21(4): 247-256	
Landau, W. M., Dobkin, B. H., Buitrago, M. M. et al. (2003) Botulinum toxin for spasticity after stroke. New england journal of medicine 348(3): 258-259	- Commentary only
Lannin, N. A., Ada, L., English, C. et al. (2020) Effect of Additional Rehabilitation After Botulinum Toxin-A on Upper Limb Activity in Chronic Stroke: The InTENSE Trial. Stroke 51(2): 556-562	- Comparator in study does not match that specified in this review protocol
Lannin, N., Ratcliffe, J., Crotty, M. et al. (2012) Feasibility study of a randomised controlled trial protocol to examine clinical and cost effectiveness of therpay after botulinum toxin-A in people with spasticity after stroke. International journal of stroke 7(suppl1): 29	- Conference abstract
Lazzaro, C., Baricich, A., Picelli, A. et al. (2020) AbobotulinumtoxinA and rehabilitation vs rehabilitation alone in post-stroke spasticity: A cost-utility analysis. Journal of Rehabilitation Medicine 52(2): 07	- Economic evidence only
Lee, S. W., Yun, J. M., Son, J. W. et al. (2007) The Effect of Electroacupuncture on Upper-Extremity Spasticity of Stroke Patients. The journal of korean oriental medicine = taehan han'eui hakhoe chi 28(3): 492-501	- Study not reported in English
Lin, S., Sun, Q., Wang, H. et al. (2018) Influence of transcutaneous electrical nerve stimulation on spasticity, balance, and walking speed in stroke patients: A systematic review and meta-analysis. Journal of Rehabilitation Medicine 50(1): 3-7	- Systematic review used as source of primary studies
Lindsay, C. (2013) Early Use of Botulinum Toxin in post Stroke Spasticity (EUBoSS).	- Conference abstract
Lindsay, C. (2015) Muscle strength at twelve weeks following the early use of botulinum toxin to treat post stroke spasticity. Clinical rehabilitation 29(10): 1018	- Conference abstract
Lindsay, C, Kouzouna, A, Simcox, C et al. (2016) Pharmacological interventions other than botulinum toxin for spasticity after stroke. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies *Cochrane review. Includes interventions not relevant to the protocol and pools the effects of*

Study	Code [Reason]
	all different interventions together in the analysis, which is not appropriate in the definitions from the protocol for this review.
Liu, X.; Bao, C.; Dong, G. (2014) Using acupoint-to-acupoint penetrative needling to treat post-stroke spastic paralysis: a clinical progress review. Journal of Traditional Chinese Medicine 34(5): 609-15	- Review article but not a systematic review
Lu, J. Y., Tu, W. Z., Zheng, D. Y. et al. (2010) Effects of acupuncture on different acupoints in combination with rehabilitation on hemiplegic muscle spasticity in hemiplegia patients. Zhongguo zhen jiu [Chinese acupuncture & moxibustion] 30(7): 542-546	- Study not reported in English
Mahmood, A., Veluswamy, S. K., Hombali, A. et al. (2019) Effect of Transcutaneous Electrical Nerve Stimulation on Spasticity in Adults With Stroke: A Systematic Review and Meta-analysis. Archives of Physical Medicine & Rehabilitation 100(4): 751-768	- Systematic review used as source of primary studies
Makino, K., Tilden, D., Guarnieri, C. et al. (2019) Cost Effectiveness of Long-Term Incobotulinumtoxin-A Treatment in the Management of Post-stroke Spasticity of the Upper Limb from the Australian Payer Perspective. PharmacoEconomics Open 3(1): 93-102	- Economic evidence only
Mancini, F., Sandrini, G., Moglia, A. et al. (2005) A randomised, double-blind, dose-ranging study to evaluate efficacy and safety of three doses of botulinum toxin type A (Botox) for the treatment of spastic foot. Neurological Sciences 26(1): 26-31	- Comparator in study does not match that specified in this review protocol
Marciniak, C., McAllister, P., Walker, H. et al. (2017) Efficacy and Safety of AbobotulinumtoxinA (Dysport) for the Treatment of Hemiparesis in Adults With Upper Limb Spasticity Previously Treated With Botulinum Toxin: Subanalysis From a Phase 3 Randomized Controlled Trial. Pm & R 9(12): 1181-1190	- Secondary publication of an included study that does not provide any additional relevant information
Marciniak, C., Munin, M. C., Brashear, A. et al. (2020) IncobotulinumtoxinA Treatment in Upper-Limb Poststroke Spasticity in the Open-Label Extension Period of PURE: Efficacy in Passive Function, Caregiver Burden, and Quality of Life. Pm & R 12(5): 491-499	- Secondary publication of an included study that does not provide any additional relevant information

Study	Code [Reason]
Marciniak, C., Munin, M. C., Brashear, A. et al. (2019) IncobotulinumtoxinA Efficacy and Safety in Adults with Upper-Limb Spasticity Following Stroke: Results from the Open-Label Extension Period of a Phase 3 Study. Advances in Therapy 36(1): 187-199	- Secondary publication of an included study that does not provide any additional relevant information
Marciniak, C., Patel, A. T., Munin, M. C. et al. (2016) Efficacy and safety of repeated incobotulinumtoxina injections for upper-limb post-stroke spasticity. Archives of physical medicine and rehabilitation 97(10): e10	- Conference abstract
Marvulli, R., Mastromauro, L., Romanelli, E. et al. (2016) How botulinum toxin type A- occupational therapy (OT)-functional electrical stimulation (FES) modify spasticity and functional recovery in patients with upper limb spasticity post stroke. Clinical Immunology, Endocrine and Metabolic Drugs 3(1): 62-67	- Data not reported in an extractable format or a format that can be analysed
Maupas, E., Marque, P., Roques, C. F. et al. (2004) Modulation of the transmission in group II heteronymous pathways by tizanidine in spastic hemiplegic patients. Journal of Neurology, Neurosurgery & Psychiatry 75(1): 130-5	- Study design not relevant to this review protocol
McCormick, Z. L., Chu, S. K., Binler, D. et al. (2016) Intrathecal Versus Oral Baclofen: A Matched Cohort Study of Spasticity, Pain, Sleep, Fatigue, and Quality of Life. Pm & R 8(6): 553-62	- Population not relevant to this review protocol
McIntyre, A., Lee, T., Janzen, S. et al. (2012) Systematic review of the effectiveness of pharmacological interventions in the treatment of spasticity of the hemiparetic lower extremity more than six months post stroke. Topics in Stroke Rehabilitation 19(6): 479-90	- Systematic review used as source of primary studies
Mehmet, T. I. L. K. I. C. I., Ebru, A. L. E. M. D. A. R. O. G. L. U., Sibel, M. A. N. D. I. R. O. G. L. U. et al. (2017) The Effect of Upper Extremity Electrical Stimulation in Addition to Conventional Rehabilitation in Individuals with Chronic Stroke: randomized Controlled Study. Journal of physical medicine & rehabilitation sciences / fiziksel tup ve rehabilitasyon bilimleri dergisi 20(3): 126-133	- Data not reported in an extractable format or a format that can be analysed
Merz Pharmaceuticals Gmb, H. (2016) Efficacy and safety study of botulinum toxin type a against placebo to treat spasticity in the arm after a stroke (PURE).	- Conference abstract

Study	Code [Reason]
Mills, P. B. and Dossa, F. (2016) Transcutaneous Electrical Nerve Stimulation for Management of Limb Spasticity: A Systematic Review. American Journal of Physical Medicine & Rehabilitation 95(4): 309-18	- Systematic review used as source of primary studies
Mochizuki, G. (2015) Assessment and management of post-stroke spasticity with botulinum toxin-A. Clinical acupuncture journal	- Conference abstract
Montane, E.; Vallano, A.; Laporte, J. R. (2004) Oral antispastic drugs in nonprogressive neurologic diseases: a systematic review. Neurology 63(8): 1357-63	- Systematic review used as source of primary studies
Namsawang, Juntip and Muanjai, Pornpimol (2022) Combined Use of Transcutaneous Electrical Nerve Stimulation and Short Foot Exercise Improves Navicular Height, Muscle Size, Function Mobility, and Risk of Falls in Healthy Older Adults. International journal of environmental research and public health 19(12)	- Population not relevant to this review protocol *Healthy older adults*
Nollet, F. and ten Kate, J. (1998) A randomised, placebo-controlled trial of botulinum toxin for the treatment of spastic equinus of the foot in stroke patients. Revalidata 20(june): 29-30	- No supplier found
Nunez-Cortes, R., Cruz-Montecinos, C., Latorre-Garcia, R. et al. (2020) Effectiveness of Dry Needling in the Management of Spasticity in Patients Post Stroke. Journal of Stroke & Cerebrovascular Diseases 29(11): 105236	- Systematic review used as source of primary studies
O'Dell, M. W., Brashear, A., Jech, R. et al. (2018) Dose-Dependent Effects of AbobotulinumtoxinA (Dysport) on Spasticity and Active Movements in Adults With Upper Limb Spasticity: Secondary Analysis of a Phase 3 Study. Pm & R 10(1): 1-10	- Secondary publication of an included study that does not provide any additional relevant information
Oh, H. M., Park, G. Y., Choi, Y. M. et al. (2018) The Effects of Botulinum Toxin Injections on Plantar Flexor Spasticity in Different Phases After Stroke: A Secondary Analysis From a Double-Blind, Randomized Trial. Pm & R 10(8): 789-797	- Secondary analysis of an unavailable excluded study
Olvey, E. L.; Armstrong, E. P.; Grizzle, A. J. (2010) Contemporary pharmacologic treatments for spasticity of the upper limb after stroke: a systematic review. Clinical Therapeutics 32(14): 2282-303	- Systematic review used as source of primary studies

Study	Code [Reason]
Park, S. W., Yi, S. H., Lee, J. A. et al. (2014) Acupuncture for the treatment of spasticity after stroke: a meta-analysis of randomized controlled trials. Journal of Alternative & Complementary Medicine 20(9): 672-82	- Systematic review used as source of primary studies
Patel, A., Geis, C., Alter, K. et al. (2017) Safety and efficacy of high-dose onabotulinumtoxina for post-stroke upper limb spasticity: results of a double-blind, placebo-controlled trial. Neurology 88(16suppl1)	- Conference abstract
Patel, A., Ward, A., Geis, C. et al. (2016) Impact of early intervention with onabotulinumtoxina treatment in adult patients with post-stroke lower limb spasticity. Neurology 86(16suppl1)	- Conference abstract
Pennati, G. V., Da Re, C., Messineo, I. et al. (2015) How could robotic training and botolinum toxin be combined in chronic post stroke upper limb spasticity? A pilot study. European journal of physical & rehabilitation medicine. 51(4): 381-7	- Comparator in study does not match that specified in this review protocol
Perini, G., Bertoni, R., Thorsen, R. et al. (2021) Sequentially applied myoelectrically controlled FES in a task-oriented approach and robotic therapy for the recovery of upper limb in post-stroke patients: A randomized controlled pilot study. Technology & Health Care 29(3): 419-429	- Comparator in study does not match that specified in this review protocol
Petr, Kanovsky, Jaroslaw, Slawek, Zoltan, Denes et al. (2011) Efficacy and safety of Incobotulinum toxin A (botulinum toxin type A free from complexing proteins;NT 201) in post stroke upper limb spasticity. Journal of rehabilitation medicine 43: 486-492	- Data not reported in an extractable format or a format that can be analysed
Peurala, S. H., Tarkka, I. M., Pitkanen, K. et al. (2005) The effectiveness of body weight-supported gait training and floor walking in patients with chronic stroke. Archives of Physical Medicine & Rehabilitation 86(8): 1557-64	- Population not relevant to this review protocol
Phadke, C. P., Balasubramanian, C. K., Holz, A. et al. (2015) Adverse Clinical Effects of Botulinum Toxin Intramuscular Injections for Spasticity. Canadian Journal of Neurological Sciences 43(2): 298-310	- Study design not relevant to this review protocol
Picelli, A., Dambruoso, F., Bronzato, M. et al. (2014) Efficacy of therapeutic ultrasound and	- Data not reported in an extractable format or a format that can be analysed

Study	Code [Reason]
transcutaneous electrical nerve stimulation compared with botulinum toxin type A in the treatment of spastic equinus in adults with chronic stroke: a pilot randomized controlled trial. Topics in Stroke Rehabilitation 21suppl1: S8-16	
Picelli, A., Tamburin, S., Bonetti, P. et al. (2012) Botulinum toxin type A injection into the gastrocnemius muscle for spastic equinus in adults with stroke: a randomized controlled trial comparing manual needle placement, electrical stimulation and ultrasonography-guided injection techniques. American Journal of Physical Medicine & Rehabilitation 91(11): 957-64	- Comparator in study does not match that specified in this review protocol
Pisters, M. F., Blois, Dd, Bernards, A. T. M. et al. (2004) Effect of botulinum toxin injection on gait and comfort during walking in a hemiparetic patient with lower extremity spasticity following stroke. Nederlands tijdschrift fysiotherapie 114(2): 41-44	- Study not reported in English
Pong, Y. P. (2015) Botulinim Toxin Type A Injections by Different Guidance in Stroke Patients With Spasticity on Upper Extremities.	- Conference abstract
Qi, L., Han, Z., Zhou, Y. et al. (2018) Dynamic scalp acupuncture combined with PNF therapy for upper limb motor impairment in ischemic stroke spastic hemiplegia. Zhongguo zhen jiu [Chinese acupuncture & moxibustion] 38(3): 234-238	- Study not reported in English
Qu, Y., Sheng, M., Jiang, Y. et al. (2003) Rehabilitation therapy centralized on facilitation and acupuncture on upper extremities spasm after stroke. Chinese Journal of Clinical Rehabilitation 7(1): 136	- Comparator in study does not match that specified in this review protocol
Rodgers, H. (2008) BOTULS Study What is the clinical effect and cost effectiveness of treatment of upper limb spasticity due to stroke with botulinum toxin?.	- Conference abstract
Rodgers, H., Shaw, L., Price, C. et al. (2008) Study design and methods of the BoTULS trial: a randomised controlled trial to evaluate the clinical effect and cost effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A. Trials [Electronic Resource] 9: 59	- Protocol only
Rosales, R., Goh, K. J., Kumthornthip, W. et al. (2017) Effect of early use of AbobotulinumtoxinA	- Conference abstract

Study	Code [Reason]
(Dysport®) after stroke on spasticity progression: first results of a pilot study. Neurology 66(16suppl)	
Rychlik, R., Kreimendahl, F., Schnur, N. et al. (2016) Quality of life and costs of spasticity treatment in German stroke patients. Health Economics Review 6(1): 27	- Study design not relevant to this review protocol
Sabut, S. K., Sikdar, C., Kumar, R. et al. (2011) Functional electrical stimulation of dorsiflexor muscle: effects on dorsiflexor strength, plantarflexor spasticity, and motor recovery in stroke patients. Neurorehabilitation 29(4): 393-400	- Duplicate reference
Sabut, Sk, Sikdar, C, Kumar, R et al. (2011) Functional electrical stimulation of dorsiflexor muscle: Effects on dorsiflexor and motor strength, plantarflexor spasticity, recovery in stroke patients. Neurorehabilitation 29(4): 393-400.	- Duplicate reference
Salom-Moreno, J., Sanchez-Mila, Z., Ortega-Santiago, R. et al. (2014) Changes in spasticity, widespread pressure pain sensitivity, and baropodometry after the application of dry needling in patients who have had a stroke: a randomized controlled trial. Journal of Manipulative & Physiological Therapeutics 37(8): 569-79	- No relevant outcomes reported
Sanchez Mila, Zacarias, Velazquez Saornil, Jorge, Campon Chekroun, Angelica et al. (2022) Effect of Dry Needling Treatment on Tibial Musculature in Combination with Neurorehabilitation Treatment in Stroke Patients: Randomized Clinical Study. International journal of environmental research and public health 19(19)	- Follow up period <1 week *Intervention was given for 1 session and follow up was immediately after that session, therefore any effects are unlikely to be relevant for the committee to make a decision on*
Sanchez-Mila, Z.; Salom-Moreno, J.; Fernandez-de-Las-Penas, C. (2018) Effects of dry needling on post-stroke spasticity, motor function and stability limits: a randomised clinical trial. Acupuncture in Medicine 36(6): 358-366	- Study design not relevant to this review protocol
Santamato, A., Panza, F., Intiso, D. et al. (2017) Long-term safety of repeated high doses of incobotulinumtoxinA injections for the treatment of upper and lower limb spasticity after stroke. Journal of the Neurological Sciences 378: 182-186	- Study design not relevant to this review protocol *FU period is only 10 min post intervention*

Study	Code [Reason]
Santamato, A., Panza, F., Ranieri, M. et al. (2013) Efficacy and safety of higher doses of botulinum toxin type A NT 201 free from complexing proteins in the upper and lower limb spasticity after stroke. Journal of Neural Transmission 120(3): 469-76	- Study design not relevant to this review protocol
Schaechter, J. D., Connell, B. D., Stason, W. B. et al. (2007) Correlated change in upper limb function and motor cortex activation after verum and sham acupuncture in patients with chronic stroke. Journal of Alternative & Complementary Medicine 13(5): 527-32	- No relevant outcomes reported
Schauer, R., Kofler, M., Singer, M. et al. (2001) Is spasticity really as bad as its reputation? Intrathecal baclofen in poststroke spasticity. Neurorehabilitation and neural repair 15(4): 318	- Conference abstract
Schockert, T., Schnitker, R., Boroojerdi, B. et al. (2009) Cortical Activation by Yamamoto New Scalp Acupuncture (YNSA) in the treatment of stroke patients a sham-controlled study aided by Functional Magnetic Resonance Imaging (fMRI). Deutsche zeitschrift fur akupunktur 52(1): 21-29	- Study not reported in English
Sentandreu Mañó, T., Salom Terrádez, J. R., Tomás, J. M. et al. (2011) Electrical stimulation in the treatment of the spastic hemiplegic hand after stroke: a randomized study. Medicina clinica 137(7): 297-301	- Study not reported in English
Shackley, P., Shaw, L., Price, C. et al. (2012) Cost-effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A: results from the botulinum toxin for the upper limb after stroke (BoTULS) trial. Toxins 4(12): 1415-26	- Secondary publication of an included study that does not provide any additional relevant information
Shahimoridi, D., Vakilian, A. R., Moghadam Ahmadi, A. et al. (2020) Comparing the Effect of Functional Electrical Stimulation and Functional Exercise Therapy on the Treatment of Ischemic Stroke: a Randomized Clinical Trial. Journal of rafsanjan university of medical sciences 19(1): 23-38	- Study not reported in English
Shariat, A., Nakhostin Ansari, N., Honarpishe, R. et al. (2021) Effect of cycling and functional electrical stimulation with linear and interval patterns of timing on gait parameters in patients	- Comparator in study does not match that specified in this review protocol

Study	Code [Reason]
after stroke: a randomized clinical trial. Disability & Rehabilitation 43(13): 1890-1896	
Sharif, F., Ghulam, S., Malik, A. N. et al. (2017) Effectiveness of Functional Electrical Stimulation (FES) versus Conventional Electrical Stimulation in Gait Rehabilitation of Patients with Stroke. Jcpsp, Journal of the College of Physicians & Surgeons - Pakistan 27(11): 703-706	- Comparator in study does not match that specified in this review protocol
Sharififar, S.; Shuster, J. J.; Bishop, M. D. (2018) Adding electrical stimulation during standard rehabilitation after stroke to improve motor function. A systematic review and meta-analysis. Annals of Physical & Rehabilitation Medicine 61(5): 339-344	- Systematic review used as source of primary studies
Sharma, S., Wein, T., Satkunam, L. et al. (2012) Impact of onabotulinumtoxina therapy in patients with post-stroke spasticity (PSS): findings from the BOTOX economic spasticity trial (BEST). Stroke; a journal of cerebral circulation 43(11): e116	- Conference abstract
Shaw, L. C., Price, C. I., van Wijck, F. M. et al. (2011) Botulinum Toxin for the Upper Limb after Stroke (BoTULS) Trial: effect on impairment, activity limitation, and pain. Stroke 42(5): 1371-9	- Secondary publication of an included study that does not provide any additional relevant information
Shaw, L. C., Price, C., van Wijck, F. et al. (2009) BOTULS: a multi-centre randomised controlled trial to evaluate the clinical effect of treating upper limb spasticity due to stroke with botulinum toxin type A. Cerebrovascular diseases (basel, switzerland) 27(suppl6): 42	- Duplicate reference
Shaw, L., Barnes, M., Ford, G. et al. (2009) Final results from the BoTULS trial: a randomised controlled trial to evaluate the clinical effect of treating post stroke upper limb spasticity with botulinum toxin. International journal of stroke 4(suppl2): 10	- Conference abstract
Shaw, L., Price, C., van Wijck, F. et al. (2010) Final results from the BoTULS trial: a multicentre randomized controlled trial to evaluate the clinical effect of treating post-stroke upper limb spasticity with botulinum toxin type A. Clinical rehabilitation 24: 955-956	- Conference abstract
Shaw, L., Price, C., van Wijck, F. et al. (2009) A randomized controlled trial to evaluate the clinical	- Duplicate reference

Study	Code [Reason]
effect and cost effectiveness of treating upper limb spasticity due to stroke with botulinum toxin: one month results. Clinical rehabilitation 23(8): 757-758	
Shaw, L., Price, C., Van Wijck, F. et al. (2008) RCT to evaluate the clinical effect and cost-effectiveness of treating upper limb spasticity due to stroke with botulinum toxin. International journal of stroke 3(suppl1): 139	- Conference abstract
Smith, S. J., Ellis, E., White, S. et al. (2000) A double-blind placebo-controlled study of botulinum toxin in upper limb spasticity after stroke or head injury. Clinical Rehabilitation 14(1): 5-13	- Data not reported in an extractable format or a format that can be analysed
Stein, C., Fritsch, C. G., Robinson, C. et al. (2015) Effects of Electrical Stimulation in Spastic Muscles After Stroke: Systematic Review and Meta-Analysis of Randomized Controlled Trials. Stroke 46(8): 2197-205	- Systematic review used as source of primary studies
Sun, L. C., Chen, R., Fu, C. et al. (2019) Efficacy and Safety of Botulinum Toxin Type A for Limb Spasticity after Stroke: A Meta-Analysis of Randomized Controlled Trials. BioMed Research International 2019: 8329306	- Systematic review used as source of primary studies
Sun, R., Tian, L., Fang, X. et al. (2017) Clinical study of post-stroke upper limb spasmodic hemiplegia treated with jingou diaoyu needling technique and Bobath therapy. Zhongguo zhen jiu [Chinese acupuncture & moxibustion] 37(4): 372-376	- Study not reported in English
Tang, X., Tang, C. L., Xu, F. M. et al. (2012) Effect of scalp acupuncture combined with body acupuncture on limb function in subacute stroke patients. Zhen CI yan jiu = acupuncture research 37(6): 488-492	- Study not reported in English
Thakre, P. I.; Qureshi, M. I.; Naqvi, W. M. (2020) Neuro developmental techniques with functional electrical stimulation reduces shoulder dysfunction in young stroke population: A Quasi-experimental novel rehabilitative approach. International Journal of Research in Pharmaceutical Sciences 11(Special Issue 4): 1650-1656	- Study design not relevant to this review protocol

Study	Code [Reason]
Tong, S., Su, L., Lü, H. B. et al. (2013) Observation on the efficacy of acupuncture at key acupoints combined with rehabilitation therapy for spasmodic hemiplegia after cerebral infarction. Zhongguo zhen jiu [Chinese acupuncture & moxibustion] 33(5): 399-402	- Study not reported in English
Turcu-Stiolica, A.; Subtirelu, M. S.; Bumbea, A. M. (2020) Cost-utility analysis of incobotulinumtoxin-A compared with conventional therapy in the management of post-stroke spasticity in Romania. Frontiers in Pharmacology 10 (no pagination)	- Economic evidence only
Turkel, C. C., Bowen, B., Liu, J. et al. (2006) Pooled analysis of the safety of botulinum toxin type A in the treatment of poststroke spasticity. Archives of Physical Medicine & Rehabilitation 87(6): 786-92	- Study design not relevant to this review protocol
Turkel, C.; Dru, R.; Liu, J. (2002) Double-blind, randomized, dose-ranging study of Botox (botulinum toxin type A) purified neurotoxin complex for treating focal spasticity post-stroke. Archives of pharmacology 365(suppl2): r47	- Conference abstract
Turner-Stokes, L., Baguley, I. J., De Graaff, S. et al. (2010) Goal attainment scaling in the evaluation of treatment of upper limb spasticity with botulinum toxin: a secondary analysis from a double-blind placebo-controlled randomized clinical trial. Journal of Rehabilitation Medicine 42(1): 81-9	- Secondary publication of an included study that does not provide any additional relevant information
Vados, L., Ferreira, A., Zhao, S. et al. (2015) Effectiveness of acupuncture combined with rehabilitation for treatment of acute or subacute stroke: a systematic review. Acupuncture in Medicine 33(3): 180-7	- Systematic review used as source of primary studies
Valencia-Chulian, R., Heredia-Rizo, A. M., Moral-Munoz, J. A. et al. (2020) Dry needling for the management of spasticity, pain, and range of movement in adults after stroke: A systematic review. Complementary Therapies in Medicine 52: 102515	- Systematic review used as source of primary studies
van Bloemendaal, Maijke, Bus, Sicco A, Nollet, Frans et al. (2021) Feasibility and Preliminary Efficacy of Gait Training Assisted by Multichannel Functional Electrical Stimulation in Early Stroke Rehabilitation: A Pilot Randomized Controlled	- Population not relevant to this review protocol *Excluded people with severe spasticity, did not measure spasticity as an outcome, therefore likely did not study spasticity specifically and is unlikely to be a relevant population*

Study	Code [Reason]
Trial. Neurorehabilitation and neural repair 35(2): 131-144	
Wang, B. H., Lin, C. L., Li, T. M. et al. (2014) Selection of acupoints for managing upper-extremity spasticity in chronic stroke patients. Clinical Interventions In Aging 9: 147-56	- No relevant outcomes reported
Wang, J. F., Yang, F. M., Wang, W. F. et al. (2016) Clinical observation on Xingnao Tongdu acupuncture therapy in the treatment of post-stroke spastic. Guangming journal of chinese medicine [guang ming zhong yi] 31(13): 1916-1918	- Study not reported in English
Wang, J., Pei, J., Cui, X. et al. (2017) Individualized scalp acupuncture for motor dysfunction in stroke: a randomized controlled trial. Zhongguo zhen jiu [Chinese acupuncture & moxibustion] 37(9): 918-924	- Study not reported in English
Wang, X. C., Liu, T., Wang, J. H. et al. (2020) Post-stroke hand spasm treated with penetrating acupuncture combined with kinesiotherapy: a randomized controlled trial. Zhongguo zhen jiu [Chinese acupuncture & moxibustion] 40(1): 21-25	- Study not reported in English
Wang, Y. Z., Xie, H., Li, G. M. et al. (2015) Clinical observation of nerve-trunk stimulation plus electroacupuncture at antagonistic points for post-stroke upper-limb spasm. Shanghai journal of acupuncture and moxibustion [shang hai zhen jiu za zhi] 34(6): 518-520	- Study not reported in English
Ward, A., Roberts, G., Warner, J. et al. (2005) Cost-effectiveness of botulinum toxin type a in the treatment of post-stroke spasticity. Journal of Rehabilitation Medicine 37(4): 252-7	- Economic evidence only
Wein, T. H., Geis, C., Ayyoub, Z. et al. (2016) Sustained benefit with repeated treatments of onabotulinumtoxina in post-stroke lower limb spasticity: 1-year open-label final results from a double-blind, placebo-controlled, phase 3 trial. 68th annual meeting of the american academy of neurology	- Conference abstract
Wein, T., Esquenazi, A., Jost, W. H. et al. (2016) OnabotulinumtoxinA Treatment in Post-stroke Lower Limb Spasticity: long-term Results From a	- Conference abstract

Study	Code [Reason]
Phase 3 Study. Stroke; a journal of cerebral circulation 47(suppl1)	
Wen, Z. (2018) Electro-acupuncture for post-stroke spasticity: a randomized controlled trial.	- Conference abstract
Werring, D. (2009) A phase IV randomised, placebo controlled, double-blind, single centre, out-patient trial to investigate the functional benefit of botulinum toxin injections combined with physiotherapy treatment for spasticity of the upper limb after stroke.	- Conference abstract
Wissel, J., Fheodoroff, K., Hoonhorst, M. et al. (2020) Effectiveness of AbobotulinumtoxinA in Post-stroke Upper Limb Spasticity in Relation to Timing of Treatment. Frontiers in neurology [electronic resource]. 11: 104	- Comparator in study does not match that specified in this review protocol
Wissel, J., Ganapathy, V., Ward, A. B. et al. (2016) OnabotulinumtoxinA Improves Pain in Patients With Post-Stroke Spasticity: Findings From a Randomized, Double-Blind, Placebo-Controlled Trial. Journal of Pain & Symptom Management 52(1): 17-26	- No relevant outcomes reported
Wolf, S. (2011) Evaluation of BOTOX® with rehabilitation therapy for the treatment of wrist and hand spasticity in post-stroke patients (botox/rehab). Annals of physical and rehabilitation medicine conference(var.pagings): e137	- Conference abstract
Wu, C-yi; Hung, J-W; Chen, Y-W (2020) Effects of Robotic-assisted Training Frequency on Functional Performance in Patients With Spastic Hemiplegic Stroke After Botulinum Toxin Injection. Archives of Physical Medicine and Rehabilitation 101(11): e49	- Conference abstract
Wu, T. (2015) The Effectiveness of Early Botulinum Toxin A Injection for Lower Limbs Spasticity in Subacute Stroke Adults.	- Conference abstract
Wu, T., Li, J. H., Song, H. X. et al. (2016) Effectiveness of Botulinum Toxin for Lower Limbs Spasticity after Stroke: A Systematic Review and Meta-Analysis. Topics in Stroke Rehabilitation 23(3): 217-23	- Systematic review used as source of primary studies

Study	Code [Reason]
Wu, Z. J., Hu, K. M., Guo, Y. G. et al. (2014) Acupuncture combined with speech rehabilitation training for post-stroke spasmodic dysphonia: A multicenter randomized controlled trial. World Journal of Acupuncture - Moxibustion 24(4): 12-16	- Data not reported in an extractable format or a format that can be analysed
Xu, L., Wang, M., Li, F. et al. (2017) Acupuncture combined with rehabilitation training for the limb spasm after stroke. Zhongguo zhen jiu [Chinese acupuncture & moxibustion] 37(7): 696-700	- Study not reported in English
Yablon, S. A., Brin, M. F., VanDenburgh, A. M. et al. (2011) Dose response with onabotulinumtoxinA for post-stroke spasticity: a pooled data analysis. Movement Disorders 26(2): 209-15	- Study design not relevant to this review protocol
Yadchi, M. (2012) Comparison of the efficacy of intra-muscular Botulinum toxin type A with oral Tizanidine in the treatment of upper limb spasticity and functional improvement due to cerebral stroke.	- Conference abstract
Yamaguchi, T., Tanabe, S., Muraoka, Y. et al. (2012) Immediate effects of electrical stimulation combined with passive locomotion-like movement on gait velocity and spasticity in persons with hemiparetic stroke: a randomized controlled study. Clinical Rehabilitation 26(7): 619-28	- Data not reported in an extractable format or a format that can be analysed
Yan, T. B.; Hui-Chan, C. W.; Li, L. S. (2006) Effects of functional electrical stimulation on the improvement of motor function of patients with acute stroke: a randomized controlled trial. Zhonghua yi xue za zhi 86(37): 2627-2631	- Study not reported in English
Yang, H. T.; Zhuang, L. X.; Liu, Y. (2013) Efficacy observation on post-stroke spastic hemiplegia treated with temporal three-needle and spastic three-needle therapy. Zhongguo zhen jiu [Chinese acupuncture & moxibustion] 33(10): 889-892	- Study not reported in English
Yang, J. S., Gao, X., Sun, R. et al. (2015) Effect of Electroacupuncture Intervention on Rehabilitation of Upper Limb Motor Function in Patients with Ischemic Stroke. Zhen CI yan jiu = acupuncture research 40(6): 489-492	- Study not reported in English

Study	Code [Reason]
Yang, K., Zhang, H., Hu, G. et al. (2021) Electroacupuncture for patients with spasticity after stroke: A protocol for systematic review and meta-analysis. Medicine 100(7): e24859	- Protocol only
Yang, Y., Liang, Q., Wan, X. et al. (2018) Safety and efficacy of botulinum toxin type A made in China for treatment of post-stroke upper limb spasticity: a randomized double-blind controlled trial. Chinese journal of neurology 51(5): 355-363	- Study not reported in English
Yao, J. R., Wang, D. S., Ni, X. B. et al. (2004) Efficacy of baclofen combined with rehabilitation training in stroke patients with spastic hemiplegia. Chinese journal of clinical rehabilitation 8(10): 1814-1815	- Study not reported in English
Yavuzer, G., Oken, O., Atay, M. B. et al. (2007) Effect of sensory-amplitude electric stimulation on motor recovery and gait kinematics after stroke: a randomized controlled study. Archives of Physical Medicine & Rehabilitation 88(6): 710-4	- Study does not contain an intervention relevant to this review protocol
Yelnik, A. P., Colle, F. M., Bonan, I. V. et al. (2007) Treatment of shoulder pain in spastic hemiplegia by reducing spasticity of the subscapular muscle: a randomised, double blind, placebo controlled study of botulinum toxin A. Journal of Neurology, Neurosurgery & Psychiatry 78(8): 845-8	- No relevant outcomes reported
Yue, Z. H. (2005) Evaluation of therapeutic effect of muscle region needling for post-stroke spasticity a randomized controlled trial. Chinese Journal of Clinical Rehabilitation 9(9): 240-241	- Comparator in study does not match that specified in this review protocol
Yue, Z. H., Li, L., Chang, X. R. et al. (2012) Comparative study on effects between electroacupuncture and acupuncture for spastic paralysis after stroke. Zhongguo zhen jiu [Chinese acupuncture & moxibustion] 32(7): 582-586	- Study not reported in English
Zhang, C., Zhang, R., Xu, M. et al. (2014) Baclofen for stroke patients with persistent hiccups: A randomized, double-blind, placebo-controlled trial. Trials 15(1)	- Population not relevant to this review protocol
Zhang, H. M. and Tang, Q. (2011) Rehabilitation evaluation on post-stroke abnormal movement pattern prevented and treated with acupuncture	- Study not reported in English

Study	Code [Reason]
and rehabilitation. Zhongguo zhen jiu [Chinese acupuncture & moxibustion] 31(6): 487-492	
Zhang, J.; Zhu, L.; Tang, Q. (2021) Electroacupuncture with rehabilitation training for limb spasticity reduction in post-stroke patients: A systematic review and meta-analysis. Topics in Stroke Rehabilitation 28(5): 340-361	- Systematic review used as source of primary studies
Zhang, Q., Wang, Y., Ji, G. et al. (2020) Standardization of rehabilitation program for post-apoplectic limb spasm treated by Tongjing Tiaoxing tuina and scalp acupuncture with physical therapy. Medicine 99(21): e20368	- Comparator in study does not match that specified in this review protocol
Zhang, Y. M., Liu, L. A., Shi, N. et al. (2015) Clinical study on electroacupuncture at motor points of antagonistic muscles plus rehabilitation for post-stroke strephenopodia. Shanghai journal of acupuncture and moxibustion [shang hai zhen jiu za zhi] 34(3): 197-200	- Study not reported in English
Zhang, Z. M., Feng, C. L., Pi, Z. K. et al. (2008) Observation on clinical therapeutic effect of acupuncture on upper limb spasticity in the patient of poststroke. Zhongguo zhen jiu [Chinese acupuncture & moxibustion] 28(4): 257-260	- Study not reported in English
Zhu, J. M., Zhuang, R., He, J. et al. (2020) Yin-yang balance penetrating acupuncture combined with rehabilitation training on upper limb spasticity in stroke hemiplegia. Zhongguo zhen jiu [Chinese acupuncture & moxibustion] 40(7): 697-701	- Study not reported in English
Zhu, Y., Zhang, L., Ouyang, G. et al. (2013) Acupuncture in subacute stroke: no benefits detected. Physical Therapy 93(11): 1447-55	- Population not relevant to this review protocol

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2006 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 96: Studies excluded from the health economic review

Reference	Reason for exclusion
Lazzaro 2020[63]	Excluded due to very serious limitations as the model inputs for effectiveness and resource use estimates are based on expert

Reference	Reason for exclusion
	opinion. The study was also partially applicable as an Italian setting may not reflect current NHS context.
Rychlik 2016[104]	Excluded due to a combination of applicability and methodological limitations. Study was not a cost-utility analysis and it is a within-study evaluation of a non-randomised comparison not included in the clinical review and does not adjust for any potential confounding factors. Specifically, the botulinum toxin A group appear to have higher care needs at baseline and higher care costs in the analysis which do not appear to be adjusted in any way. The study was also partially applicable reasons include: German societal perspective may not reflect current NHS context, cost data sources were not referenced and QALYS were not calculated.
Fheodoroff 2022[33]	Fheodoroff 2022 was excluded due to very serious limitations. The analysis assumed improvements to spasticity improves survival and resource use estimates were taken from Lazzaro 2020.[63] Lazzaro was excluded as rated very serious limitations as the model inputs for effectiveness and resource use estimates are based on expert opinion.
Fernandez-Sanchis 2022{, #5094}	Fernandez-Sanchis 2022 was excluded due to a combination of applicability and methodological limitations. The comparison of dry needling was to sham which is not considered an appropriate comparator for estimating cost effectiveness of non-pharmacological interventions. Other applicability concerns and limitations included: Spanish healthcare context with 2011-2019; within-trial analysis of a single RCT with a small sample; short follow up (2-weeks); no downstream costs included; cost included for sham comparator; no probabilistic sensitivity analysis and a conflict of interest (DNHS® technique registered by a study author).

References of excluded HE studies

Fernandez-Sanchis D, Brandin-de la Cruz N, Jimenez-Sanchez C, Gil-Calvo M, Herrero P, Calvo S. Cost-Effectiveness of Upper Extremity Dry Needling in Chronic Stroke. Healthcare (Basel). 2022; 10(1)

Fheodoroff K, Danchenko N, Whalen J, Balcaitiene J, Magalhaes B, Szulc E et al. Modelling Long-Term Outcomes and Risk of Death for Patients with Post-Stroke Spasticity Receiving Abobotulinumtoxina Treatment and Rehabilitation Therapy. Journal of Rehabilitation Medicine. 2022; 54:jrm00303

Lazzaro C, Baricich A, Picelli A, Caglioni PM, Ratti M, Santamato A. AbobotulinumtoxinA and rehabilitation vs rehabilitation alone in post-stroke spasticity: A cost-utility analysis. Journal of Rehabilitation Medicine. 2020; 52(2):07

Rychlik R, Kreimendahl F, Schnur N, Lambert-Baumann J, Dressler D. Quality of life and costs of spasticity treatment in German stroke patients. Health Economics Review. 2016; 6(1):27

Appendix K – Research recommendations – full details

Research recommendation

What is the clinical and cost-effectiveness of acupuncture and electroacupuncture to treat spasticity in people who have had a stroke?

Why this is important

Spasticity is a common post-stroke condition that can very painful and debilitating. Current practice to manage spasticity and access to specialist treatment varies between NHS trusts. This review examined a number of different interventions to manage spasticity and found evidence to support recommendations for several of these treatment options. Evidence to support less conventional intervention such as acupuncture and electroacupuncture is growing however there was not enough evidence available in this review to support a consider recommendation. The committee therefore agreed to recommend that high quality randomised controlled trials should be conducted to assess acupuncture and electropuncture compared to sham acupuncture and usual care with cost effectiveness data included.

Rationale for research recommendation

Importance to 'patients' or the population	Spasticity is a disabling and painful post stroke condition that affects many stroke survivors and negatively impacts health-related quality of life. Effective management of this condition is therefore of great importance to patients. Interventions that are currently not part of current practice, but which may help reduce post-stroke spasticity should be further explored to ensure a range of effective treatments options are available to stroke survivors in an NHS setting.
Relevance to NICE guidance	There is a growing body of evidence to support more alternative therapies such as acupuncture and electroacupuncture for the management of post-stroke spasticity. This review was unable to make a positive recommendation for these interventions due to the lack of available evidence and cost effectiveness data. High quality research would help to answer the original review question and inform future NICE guidance.
Relevance to the NHS	Evidence to support more alternative therapies such as acupuncture and electroacupuncture for the management of post-stroke spasticity is growing. These interventions are not current practice in an NHS setting so recommending these interventions would lead to a large resource impact. High quality evidence that includes health economic data is needed to help assess whether these interventions should be implemented in the NHS.
National priorities	None identified.
Current evidence base	This review included a number of studies comparing acupuncture and electroacupuncture to usual care or placebo and reported a number of positive outcomes. However, in the majority of

	these cases this evidence came from very small studies which were of very low methodological quality and did not include health economic data.
Equality considerations	No specific equality considerations were identified. The committee noted that in general throughout the guideline, people with communication and cognitive difficulties, older people and people who have had a previous stroke or transient ischaemic attack were excluded from trials but are people that the guideline is for. Therefore, research should aim to include these people where possible.

1

2 **Modified PICO table**

3

Population	Inclusion: • Adults (age ≥16 years) who have had a first or recurrent stroke and have focal or multifocal spasticity of the upper or lower limb (including people after subarachnoid haemorrhage). Exclusion: • Children (age <16 years) • People who have had a transient ischaemic attack
Intervention	• Electroacupuncture • Acupuncture
Comparator	• Sham acupuncture (Acupuncture without electrical stimulation can be used as the sham comparison to electroacupuncture, this arm should be a sham comparison arm to compare against acupuncture) • Usual care
Outcome	• Person/participant generic health-related quality of life • Carer generic health-related quality of life • Spasticity outcome measures • Physical function • Pain • Activities of daily living • Stroke-specific Patient-Reported Outcome Measures • Additional health care contacts • Hospitalisation • Stroke outcome – modified Rankin scale • Cost effectiveness data/resource use • Withdrawal due to adverse events
Study design	• Randomised controlled trial

Timeframe	6 months
Additional information	Subgroup analyses for quantitative data: • Severity of spasticity (as measured by modified Ashworth scale: mild, moderate, severe, very severe) • Severity of stroke (NIHSS: mild, moderate, severe, very severe) • Time after stroke at the start of the trial (hyperacute, acute, subacute, chronic)

Research recommendation

What is the clinical and cost-effectiveness of BOTOX, Dysport and Xeomin compared to each other and usual care for people with focal spasticity after stroke?

Why this is important

Spasticity is a common post stroke condition that can very painful and debilitating. Current practice to manage spasticity and access to specialist treatment varies between NHS trusts. This review examined a number of different interventions to manage spasticity and found evidence to support recommendations for botulinum toxin injections but only in the form of abobotulinum toxin (Dysport) and only in specific circumstances. Further research comparing botulinum toxin with different medicinal forms and usual care is required.

Rationale for research recommendation

Importance to 'patients' or the population	Spasticity is a disabling and painful post stroke condition that affects a large number of stroke survivors and negatively impacts health related quality of life. Effective management of this condition is therefore of great importance to patients and currently this varies between NHS trusts. Further research is needed to ensure that effective interventions are recommended in NICE guidance and are more accessible for patients.
Relevance to NICE guidance	This review was able to make a positive recommendation for botulinum toxin type A but only with specific caveats. Further research to assess the effectiveness and cost effectiveness of different forms of botulinum toxin compared to each other and usual care is required to help to answer the original review question and inform future NICE guidance.
Relevance to the NHS	Management of spasticity and access to specialist services varies between different NHS trusts. Botulinum toxin injections are expensive. Therefore, health economic data is required to recommend these interventions. Further research will help to make care more standardised across the NHS.
National priorities	None identified.
Current evidence base	This review showed that abobotulinum toxin (Dysport) was effective but only when 500 units was administered every 3 months and monitored

	for effectiveness, being discontinued if ineffective. Evidence was available for other forms of botulinum toxin but despite several outcomes reporting clinical effectiveness these were not cost effective. However, there were limitations in the availability of evidence for health economic modelling so if more evidence is available then this may help inform future work.
Equality considerations	No specific equality considerations were identified. The committee noted that in general throughout the guideline, people with communication and cognitive difficulties, older people and people who have had a previous stroke or transient ischaemic attack were excluded from trials but are people that the guideline is for. Therefore, research should aim to include these people where possible.

Modified PICO table

Population	Inclusion: • Adults (age ≥16 years) who have had a first or recurrent stroke and have focal or multifocal spasticity (including people after subarachnoid haemorrhage). Exclusion: • Children (age <16 years) • People who have had a transient ischaemic attack

Intervention	• Botulinum toxin type A
	  ○ Onabotulinum toxin A (BOTOX®) (maximum recommended dose is 200-240 units in the arm, 300 units in the leg for a single injection)
	  ○ Abobotulinum toxin A (Dysport®) (maximum recommended dose is 1500 units in the arm or leg in a single adult injection session)
	  ○ Incobotulinum toxin A (Xeomin®) (maximum recommended dose is 500 units in the arm and no more than 250 units in the shoulder muscles in a single adult injection session)

Comparator	• Each other • Usual care
Outcome	• Person/participant generic health-related quality of life • Carer generic health-related quality of life • Spasticity outcome measures • Physical function

	• Pain • Activities of daily living • Stroke-specific Patient-Reported Outcome Measures • Additional health care contacts • Hospitalisation • Stroke outcome – modified Rankin scale • Cost effectiveness data/resource use • Withdrawal due to adverse events
Study design	• Randomised controlled trial
Timeframe	6 months
Additional information	Subgroup analyses for quantitative data: • Severity of spasticity (as measured by modified Ashworth scale: mild, moderate, severe, very severe) • Severity of stroke (NIHSS: mild, moderate, severe, very severe) • Time after stroke at the start of the trial (hyperacute, acute, subacute, chronic)

Research recommendation

What is the clinical and cost-effectiveness of neuromuscular electrical stimulation, transcutaneous electrical stimulation and functional electrical stimulation compared to usual care for people who have had a stroke?

Why this is important

Spasticity is a common post-stroke condition that can very painful and debilitating. Current practice to manage spasticity and access to specialist treatment varies between NHS trusts. This review examined a number of different interventions to manage spasticity and found evidence to support recommendations for several of these treatment options. Evidence to support less conventional interventions such as electrotherapy is growing. There was evidence to support recommending these. However, the evidence was limited and further research is required to show if any form of electrotherapy is superior to any other. The committee therefore agreed to recommend that a high quality randomised controlled trial should be conducted to assess electrotherapy compared to each other and usual care with cost effectiveness data included.

Rationale for research recommendation

Importance to ‘patients’ or the population	Spasticity is a disabling and painful post stroke condition that affects many stroke survivors and negatively impacts health-related quality of life. Effective management of this condition is therefore of great importance to patients. Interventions that are currently not part of current practice, but which may help reduce post-stroke spasticity should be further explored to ensure a range of effective treatments options are available to stroke survivors in an NHS setting.

Relevance to NICE guidance	There is a growing body of evidence to support the use of electrotherapy for post-stroke spasticity. This review made a recommendation on the use of electrotherapy. However, the evidence was limited and there was no evidence comparing the different types of electrotherapy to each other. High quality research would help to answer the original review question and inform future NICE guidance.
Relevance to the NHS	Evidence to support more alternative therapies such as electrotherapy for the management of post-stroke spasticity is growing. These interventions are used inconsistently in current practice. More health economic evidence is necessary to help assess whether these interventions should be implemented in the NHS. Understanding if all of the electrotherapy techniques are as effective as each other is important to ensure that the most effective treatment is being given.
National priorities	None identified.
Current evidence base	This review included a number of studies comparing electrotherapy to usual care or placebo and reported a number of positive outcomes. However, in the majority of these cases this evidence came from very small studies which were of very low methodological quality and did not include health economic data. There was no evidence comparing different types of electrotherapy to each other.
Equality considerations	No specific equality considerations were identified. The committee noted that in general throughout the guideline, people with communication and cognitive difficulties, older people and people who have had a previous stroke or transient ischaemic attack were excluded from trials but are people that the guideline is for. Therefore, research should aim to include these people where possible.

1 Modified PICO table

Population	Inclusion: Adults (age ≥16 years) who have had a first or recurrent stroke and have focal or multifocal spasticity of the upper or lower limb (including people after subarachnoid haemorrhage). Exclusion: Children (age <16 years) People who have had a transient ischaemic attack
Intervention	• Transcutaneous electrical nerve stimulation (TENS) • Neuromuscular electrical stimulation (NMES) • Functional Electrical Stimulation (FES)
Comparator	• Each other

	• Usual care
Outcome	• Person/participant generic health-related quality of life • Carer generic health-related quality of life • Spasticity outcome measures • Physical function • Pain • Activities of daily living • Stroke-specific Patient-Reported Outcome Measures • Additional health care contacts • Hospitalisation • Stroke outcome – modified Rankin scale • Cost effectiveness data/resource use • Withdrawal due to adverse events
Study design	Randomised controlled trial
Timeframe	6 months
Additional information	Subgroup analyses for quantitative data: • Severity of spasticity (as measured by modified Ashworth scale: mild, moderate, severe, very severe) • Severity of stroke (NIHSS: mild, moderate, severe, very severe) • Time after stroke at the start of the trial (hyperacute, acute, subacute, chronic)

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