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Systematic review of adjunct therapies to improve outcomes following botulinum toxin injection for treatment of limb spasticity

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Abstract

Objective: To determine the quality of evidence from randomized controlled trials on the efficacy of adjunct therapies following botulinum toxin injections for limb spasticity.

Data sources: MEDLINE, EMBASE, CINAHL, and Cochrane Central Register of Controlled Trials electronic databases were searched for English language human studies from 1980 to 21 May 2015.

Study selection: Randomized controlled trials assessing adjunct therapies postbotulinum toxin injection for treatment of spasticity were included. Of the 268 studies screened, 17 met selection criteria.

Data extraction: Two reviewers independently assessed risk of bias using the Physiotherapy Evidence Database (PEDro) scale and graded according to Sackett's levels of evidence.

Data synthesis: Ten adjunct therapies were identified. Evidence suggests that adjunct use of electrical stimulation, modified constraint-induced movement therapy, physiotherapy (all Level 1), casting and dynamic splinting (both Level 2) result in improved Modified Ashworth Scale scores by at least 1 grade. There is Level 1 and 2 evidence that adjunct taping, segmental muscle vibration, cyclic functional electrical stimulation, and motorized arm ergometer may not improve outcomes compared with botulinum toxin injections alone. There is Level 1 evidence that casting is better than taping, taping is better than electrical stimulation and stretching, and extracorporeal shock wave therapy is better than electrical stimulation for outcomes including the Modified Ashworth Scale, range of motion and gait. All results are based on single studies.

Conclusion: There is high level evidence to suggest that adjunct therapies may improve outcomes following botulinum toxin injection. No results have been confirmed by independent replication. All interventions would benefit from further study.

Keywords

Muscle spasticity, botulinum toxins, adjunct therapy, electric stimulation therapy

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Introduction

Spasticity is a common consequence of upper motor neuron disorders including stroke, traumatic brain injury, spinal cord injury, multiple sclerosis, and cerebral palsy. Botulinum neurotoxin (BoNT) is a widely used and effective pharmacological treatment for focal muscle over-activity.[1,2]

Although multidisciplinary rehabilitation following BoNT treatment has been advocated,[1,3] the optimal elements of non-pharmacologic therapy for spasticity are not well-established. A wide variety of adjunct therapies can be used following BoNT injections. Kinnear et al.[4] performed a systematic review on this subject, but levels of evidence were not assigned to assist in guiding clinical decision making. Of the 11 studies that were included, the five that were pooled for meta-analysis were not sufficiently homogeneous in interventions (e.g. electrical stimulation parameters and dosing varied between studies) to lend importance to the results. Given the wide range of treatment options with varying levels of effectiveness and research quality, more information is required to help clinicians involved in spasticity management perform evidence-based practice.

The primary aim of this review is to determine the quality of evidence from randomized controlled trials (RCTs) on the efficacy of adjunct therapies following BoNT injections for limb spasticity resulting from various neurological conditions. In addition, we aimed to identify gaps in the evidence to help direct future efforts to areas of priority.

Methods

A systematic search strategy, developed by the College of Physicians and Surgeons of British Columbia librarians, was conducted to identify relevant studies published between 1980 and 21 May 2015 using electronic databases MEDLINE, EMBASE, CINAHL, and Cochrane Central Register of Controlled Trials. Reference lists of systematic reviews and included articles were manually scanned to expand the data set. The search was restricted to the English language. The search strategy was based on three key concepts: spasticity, BoNT, and RCTs. An example of the search strategy as applied in MEDLINE can be viewed in the Appendix (available online).

The inclusion criteria for studies in this systematic review were all RCTs comparing either: (1) BoNT alone with BoNT plus adjunct therapy, or (2) BoNT plus one adjunct therapy with BoNT plus another adjunct therapy. Participants were adults over the age of 18 with spasticity from various neurological conditions affecting the upper and/or lower limbs. The intervention, adjunct therapy, was any therapy that was administered in addition to the BoNT protocol with the intent of enhancing the effect of BoNT injections. BoNT injection could be of any dosage into any muscle group of the upper and/or lower limbs. Outcome measures had to be identified by the study authors as potential measures of efficacy of BoNT injections or BoNT injection plus adjunct therapies in adults with spasticity. When only an abstract was available, the study was excluded.

Two reviewers independently reviewed titles and abstracts of articles to determine eligibility for inclusion. Disagreement was resolved through consensus and if necessary, by third party resolution. Studies that clearly failed to meet the inclusion criteria were not reviewed further. Those that could not be excluded were retrieved and reviewed in full-text by the two reviewers. In all instances, differences of opinion were resolved by discussion. Studies that met criteria were retrieved and reviewed in detail.

Data were extracted from all included studies independently and in duplicate into excel spreadsheets, with the templates adapted from the Cochrane Collaboration.[5] Data included: description of participants (diagnosis, spasticity pattern), intervention (type, frequency, intensity, and duration of intervention), control (type of control, injection dose, dilution, muscle selection, and method of localization), outcome measures, duration of follow-up, and results.

Two reviewers assessed the methodological quality of the included studies independently using the Physiotherapy Evidence Database (PEDro) scale.[6] Consensus was sought via discussion, and a third reviewer was available if necessary. The PEDro scale is comprised of 11 yes or no quality

items, 10 of which are used to calculate the final PEDro score (0–10). Using a simplification of Sackett's levels of evidence that has been applied in the literature,[7] an RCT was considered to be Level 1 (higher quality) if it scored ⩾6 on the PEDro scale and Level 2 if it scored <6.

Owing to the clinically diverse nature of adjunct therapies utilized in the studies and differences in applications of similar adjunct therapies (e.g. differing dosing, timing, and stimulation variables in electrical stimulation therapies), meta-analysis was deemed inappropriate. Instead, descriptive comparisons are drawn below. The results of each intervention are outlined in the Appendix (Supplemental Table 2, available online). Within-group comparisons are not reported in this review, given that improvement in these cases could be from either the BoNT or the adjunct therapy. Details of BoNT injections are described in the Appendix (Supplemental Table 3, available online). Levels of evidence summaries are provided in Table 1. Unless otherwise stated, results are reported as mean ±SD.

Results

Search strategy

Figure 1 shows the flow of articles into the selected group.

Based on inclusion criteria, 17 studies were included.

Risk of bias in individual studies

The PEDro scores for all included studies are recorded in the Appendix (Supplemental Table 2, available online). Values ranged between two and eight, and the median PEDro score was six, indicating moderate methodological quality. Two studies[10,17] were double blinded, with sham control. However, the study by Bayram et al.[10] used no current with sham electrical stimulation. As a result, one point was deducted from PEDro scoring for blinding of participants in this study as it is expected that the participants would have been able to distinguish between the treatments. Therefore the only high quality (PEDro = 7) double-blind sham-controlled trial was by Karadag-Saygi et al.[17] on the adjunct intervention of kinesiotaping. The remaining studies were either single blinded ($N = 12$) or non-blinded ($N = 3$). Only the studies by Sun et al.[22] on modified constraint-induced movement therapy and Santamato et al.[14] on electrical stimulation were statistically powered.

Population

Supplemental Table 2 in the Appendix (available online) summarizes characteristics of included studies. The 17 studies included 422 participants. A total of 14 studies included participants at least six months post-stroke, two studies included participants with secondary progressive multiple sclerosis, and one study included mixed aetiologies. Seven studies examined spasticity of the upper limb, nine studies examined lower limb spasticity, and one study examined both upper and lower limb spasticity.

Controls

Seven studies compared the effects of BoNT plus adjunct therapy with BoNT alone. Only two studies attempted to include a placebo intervention. Karadag-Saygi et al.[17] compared BoNT plus kinesiotaping with BoNT plus sham taping, and Bayram et al.[10] compared BoNT plus electrical stimulation with BoNT with sham electrical stimulation. All other studies compared BoNT plus adjunct therapy with BoNT plus one or more other adjunct therapies, or with alternative controls such as task practice therapy or playing cards.

Interventions

A total of 10 different adjunct therapies were identified through the literature search: electrical stimulation, extracorporeal shock wave therapy, taping, casting, stretching, physiotherapy, segmental muscle vibration, dynamic splinting, modified constraint-induced movement therapy, and motorized arm ergometry.

All participants were treated with BoNT intramuscular injections. BoNT brands, injection techniques,

Table 1. Levels of evidence for adjunct treatments postBoNT injection in limb spasticity.

Levels of evidence	Studies	Recommendations
Electrical stimulation		
1	2 RCT[8,9]	Electrical stimulation of injected muscles in the upper or lower extremity (20 Hz, 0.2 ms, 50–90 mA), 30 minutes delivered three to six times daily over three days postBoNT injection, improves Modified Ashworth Scale postBoNT injection compared with BoNT alone.
1	1 RCT[9]	Electrical stimulation of upper extremity injected muscles (20 Hz, 0.2 ms, 50–90 mA), 30 minutes delivered three times daily over three days postBoNT injection, does not change upper limb position at rest, difficulty with cutting fingernails or putting arm through a sleeve, but does improve ease of hand hygiene.
2	1 RCT[10]	Electrical stimulation of lower extremity muscles (20 Hz, 0.2 ms, 50–90 mA), 30 minutes six times daily for three days with a lower dose of BoNT has the same effects as a higher dose of BoNT alone on outcome measures of Modified Ashworth Scale, 10-metre walking test, Clonus Score, Brace Wear Scale, and self-reported Global Assessment of Spasticity.
2	1 RCT[11]	Electrical stimulation of peroneal nerves at 4 Hz has better effect on CMAP postBoNT injections for spastic paraparesis compared with higher frequency electrical stimulation at 25 Hz; however, this was not accompanied by changes in Modified Ashworth Scale for either stimulation frequencies.
2	1 RCT[12]	Electrical stimulation of upper extremity injected muscles (4 Hz, 0.2 ms, intensity for visible muscle twitch), 30 minutes once daily for five days delivered immediately postinjection is better than electrical stimulation started one day postinjection for improving Modified Ashworth Scale and compound muscle action potential.
1	1 RCT[13]	Cyclic functional electrical stimulation of finger flexors/extensors/thenar muscles during task practice therapy, 60 minutes daily for 12 weeks does not improve upper extremity function measured with the 'How Well Scale' of Motor Activity Log –Observation, Action Research Arm Test, and Motor Activity Log – Self-Report compared with task practice therapy alone.
Extracorporeal shock wave therapy vs. electrical stimulation		
1	1 RCT[14]	Five days of extracorporeal shock wave therapy (7.5 Mz, 1000 impulses per muscle) once daily is better than electrical stimulation (5 Hz, 50–90 mA) twice daily for 30 minutes per session for improving Modified Ashworth Scale, Spasm Frequency Scale, and pain visual analogue scale when delivered immediately postBoNT injection of spastic finger flexors.
Taping vs. electrical stimulation vs. stretching		
1	1 RCT[15]	Spastic equinovarus foot taping for five days or electrical stimulation (5 Hz, intensity to patient tolerance) 30 minutes twice daily for five days are better than stretching 30 minutes twice daily for seven days with physiotherapist supervision for improving Modified Ashworth Scale, passive range of motion, gastrocnemius muscle action potential, and maximal ankle dorsiflexion during walking stance phase postBoNT injection. Results between taping and electrical stimulation groups were equivalent.
Casting vs. taping vs. stretching		
1	1 RCT[16]	Casting of the spastic equinovarus foot is better than stretching or taping for one week postBoNT injection for improving Modified Ashworth Scale, ankle passive range of motion, 6-minute walking test, and speed on 10-metre walking test. No differences were seen in strength of ankle dorsiflexors or Functional Ambulatory Category.

Table 1. (Continued)

Levels of evidence	Studies	Recommendations
Taping		
1	1 RCT[17]	Taping for two weeks postBoNT injection does not improve passive range of motion, Modified Ashworth Scale and gait parameters when compared with sham taping of the spastic equinovarus foot.
2	1 RCT[18]	Taping for three weeks postBoNT injection improves passive range of motion and Modified Ashworth Scale but not gait parameters when compared with BoNT alone in the spastic equinovarus foot.
1	2 RCT[15,16]	Taping for five to seven days is better than stretching 30 minutes twice daily for seven days for improving passive range of motion and gait parameters postBoNT injection.
Casting		
2	1 RCT[19]	Night-time casting with a made-to-measure rigid ankle–foot orthosis for a duration of four months postBoNT injection of the spastic equinus foot improves Modified Ashworth Scale and baropodometry outcome measures but not time on the 10-metre walking test.
Segmental muscle vibration		
1	1 RCT[20]	Low amplitude segmental muscle vibration to the rectus femoris postBoNT injection, delivered 30 minutes three times a week for four weeks, does not improve knee or ankle Modified Ashworth Scale, Fatigue Severity Scale, or Barthel Index compared with BoNT injection alone.
Motorized arm ergometer		
2	1 RCT[21]	Motorized arm ergometer 30 minutes three times a week for two months, does not improve Modified Ashworth Scale, goniometer range of motion, Rivermead Motor Stroke Assessment, and Motricity Index for the elbow or functional MRI postBoNT for upper extremity spasticity post stroke. There may be a better effect in individuals with residual motor function and worsening in individuals with no residual motor function
Modified constraint-induced movement therapy		
1	1 RCT[22]	Modified constraint-induced movement therapy two hours per day, three times per week over three months postBoNT injection helps improve: Modified Ashworth Scale of the elbows and fingers but not the wrist, scores on the Motor Activity Log and Action Research Arm Test, and global satisfaction in individuals post-stroke with a spastic upper extremity and some active wrist and finger extension.
Physiotherapy		
1	1 RCT[23]	Physiotherapy 40 minutes daily for 15 consecutive days following BoNT injection into the upper or lower extremities of individuals with secondary progressive multiple sclerosis improves Modified Ashworth Scale and visual analogue scale of self-reported satisfaction compared with BoNT alone.
Night-time dynamic splinting		
2	1 RCT[24]	Individuals with spastic elbow flexors post-stroke who can tolerate six to eight hours dynamic splinting per night for four months may have some improvements in active elbow extension and Modified Ashworth Scale compared with BoNT alone.

BoNT: botulinum neurotoxin; MRI: magnetic resonance imaging; RCT: randomized controlled trial; CMAP: compound muscle action potential.

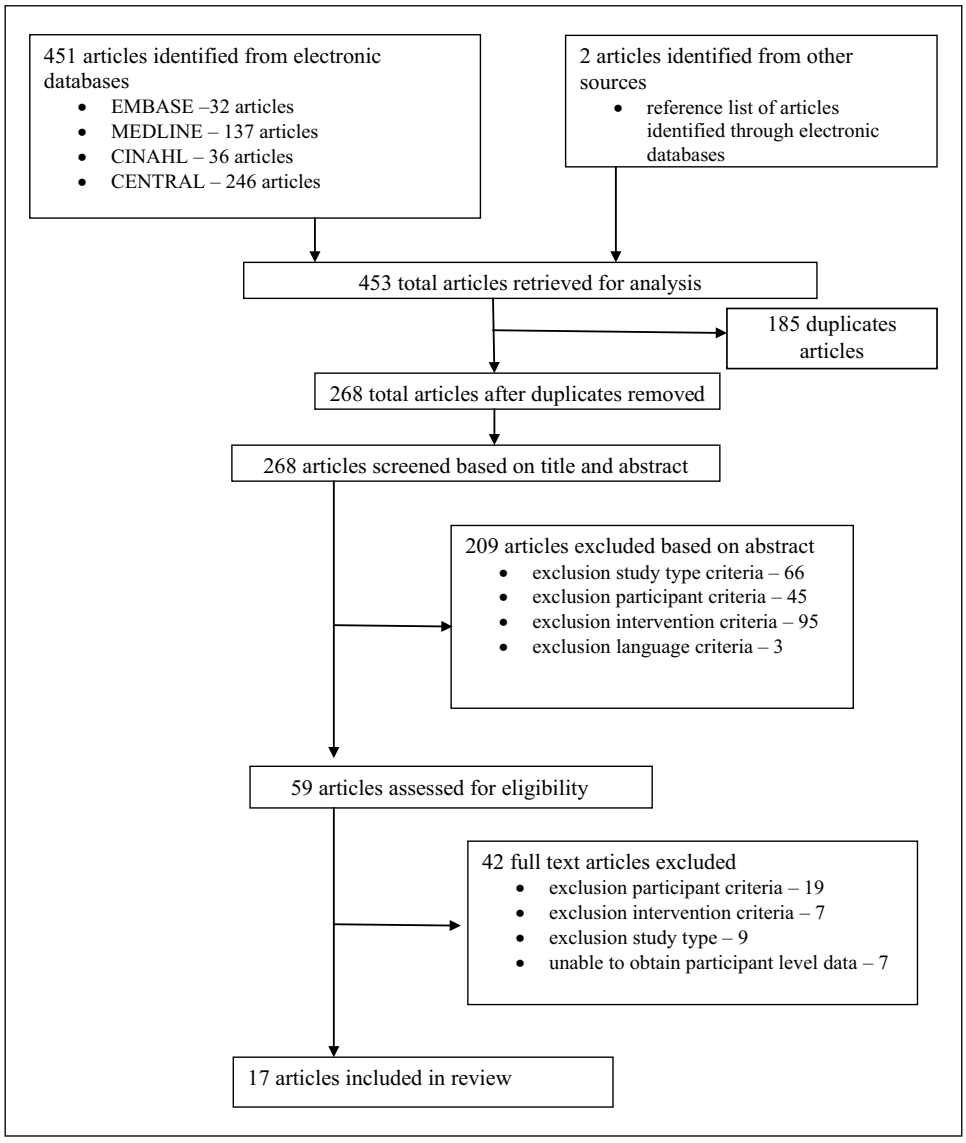

Figure 1. Study selection flowchart.

dilutions, doses, and target muscles injected are outlined in Supplemental Table 3 (Appendix, available online).

Electrical stimulation

With eight RCTs, electrical stimulation was the most frequently studied adjunct therapy. Only the study by Santamato et al.[14] was adequately statistically powered. All electrical stimulation studies stimulated motor points of injected muscles for elicitation of minimal to no muscle contraction, except for Frasson et al.,[11] where stimulation was applied to peroneal nerves. Variables for the intervention of electrical stimulation (frequency, current pulse duration, intensity) as well as duration of

treatment differed between the studies, therefore meta-analysis of results was not performed. Dosing ranged between 30 and 60 minutes per session, delivered between once daily to six times daily, for a duration of three days up to 12 weeks.

Four studies examined the effects of electrical stimulation after BoNT injection with controls of either BoNT alone,[8,9] sham electrical stimulation,[10] or the addition of task practice therapy to both treatment arms.[13]

Hesse et al.[8] found that the addition of electrical stimulation to BoNT decreased Modified Ashworth Scale scores more than with BoNT alone in lower limb spasticity. Hesse et al.[9] did not find differences in Modified Ashworth Scale, arm position at rest, ease of cutting fingernails, or putting the arm through a sleeve, however cleaning the palm was significantly easier in the electrical stimulation group. The study by Bayram et al.[10] on lower limb spasticity did not find differences in any outcome measures when comparing the addition of electrical stimulation to lower dose BoNT with sham electrical stimulation and higher dose BoNT.

Weber et al.[13] did not fully describe stimulation parameters. Task practice therapy was taught and standardized for the participants, a self-report diary was provided, and five additional hours with an occupational therapist were conducted to ensure participants could complete the programme independently. Compared with task therapy only, this high-quality RCT did not find a difference in outcome measures with the addition of cyclic electrical stimulation after BoNT injection.

Low frequency vs. high frequency electrical stimulation

Frasson et al.[11] studied the effect in individuals with spastic paraparesis from multiple aetiologies of low frequency (4 Hz) vs. high frequency (25 Hz) electrical stimulation of peroneal nerves. There were significant changes for compound muscle action potential percentage and amplitude for certain time points postinjection with low frequency electrical stimulation, and no changes with high frequency electrical stimulation. Electromyographic signs of denervation appeared earlier in stimulated muscles compared with non-stimulated muscles. Modified Ashworth Scale scores did not change in any of the participants throughout follow-up.

Immediate vs. delayed electrical stimulation

Picelli et al.[12] examined the effect on elbow flexor spasticity of electrical stimulation delivered over 30 minutes daily for three days vs. 60 minutes delivered immediately postinjection. The immediately delivered electrical stimulation protocol had a better effect compared with delayed electrical stimulation started one day postinjection. In both groups, Modified Ashworth Scale scores decreased significantly at four weeks follow-up.

Electrical stimulation vs. extracorporeal shock wave therapy

Santamato et al.[14] examined the effects of electrical stimulation compared with extracorporeal shock wave therapy postBoNT injection of spastic finger flexors. Both interventions were started immediately postinjection. This high-quality, adequately powered RCT found that both interventions led to improvements in Modified Ashworth Scale, spasm frequency scale, and pain visual analogue scale postinjections, with extracorporeal shock wave therapy showing significant benefits compared with electrical stimulation in all outcome measures at all time points.

Electrical stimulation vs. taping vs. stretching

Baricich et al.[15] studied the effect of electrical stimulation compared with taping and stretching started the same day after BoNT injections of the spastic equinovarus foot. Electrical stimulation was found to elicit earlier changes in gastrocnemius muscle action potentials compared with stretching post-BoNT injections. Taping and electrical stimulation had better outcomes than stretching at all time points, with no differences between taping and electrical stimulation groups.

Casting vs. taping vs. stretching

Carda et al.[16] studied the effects of casting vs. taping vs. stretching for one week following BoNT injection of the spastic equinovarus foot. After one week of the allocated intervention, all groups then received 30 minutes of gait training and 20 minutes of stretching daily for one week with a physiotherapist. Casting was better than taping or stretching for one week for improving Modified Ashworth Scale, ankle passive range of motion, 6-minute walking test, and speed on the 10-metre walking test. No differences were seen between groups in strength of ankle dorsiflexors and Functional Ambulation Category. The stretching group showed the least marked modifications in all parameters over all evaluations.

Taping

Two studies examined the effects of taping post BoNT injections compared with either sham taping[17] or a higher dose of BoNT alone[18] on the spastic equinovarus foot. The double blinded, high quality RCT by Karadag-Saydig et al.[17] taped for a duration of two weeks with similar BoNT protocols between groups. The single-blind RCT by Reiter et al.[18] taped for three weeks after a lower dose BoNT injection into the tibialis posterior alone compared with a higher dose BoNT injection into various ankle muscles (e.g. gastrocnemius, tibialis posterior, soleus) without taping. Karadag-Saygi et al.[17] demonstrated a greater improvement in ankle dorsiflexion passive range of motion after two weeks of taping, which did not persist on further follow-up, and had no significant differences in other outcome measures. The study by Reiter et al.[18] demonstrated an improvement in ankle position at rest, passive range of motion, and Modified Ashworth Scale, but not gait parameters in the higher dose BoNT group without taping compared with the taping group with lower dose BoNT.

Casting

Farina et al.[19] examined the nightly use of a made-to-measure rigid ankle foot orthosis compared with BoNT alone. Application of the cast took 15 minutes and the participants were provided with two half-hour instruction sessions on how to use the cast. Results were better for outcome measures of body structure and function (e.g. Modified Ashworth Scale, baropodometry), but not activity (10-metre walking test). Compliance with the orthosis was not reported.

Segmental muscle vibration

Paoloni et al.[20] studied the effect of adding segmental muscle vibration of the rectus femoris post-BoNT injection for stiff knee gait in participants with secondary progressive multiple sclerosis. This underpowered RCT did not show any differences between the two groups for all outcome measures on follow-up.

Motorized arm ergometer

Diserens et al.[21] looked at the effects of using a motorized arm ergometer postBoNT injection to the upper limb in individuals with spastic hemi-syndrome from chronic stroke. The paretic hand was strapped to the ergometer if there was insufficient power to grasp the handle. Sessions were supervised by a trained therapist. The control group played cards postBoNT injection. There were three months of no treatment between crossovers. No differences in any outcomes, including functional magnetic resonance imaging, were found between study arms. Subanalysis of four participants with residual motor activity in the arm showed that spasticity statistically improved in this group with arm ergometry, compared with the four participants without residual activity who showed worsening of their spasticity after use of the arm ergometer.

Modified constraint-induced movement therapy

One high-quality, adequately powered study by Sun et al.[22] examined the effects of modified constraint-induced movement therapy vs. conventional rehabilitation postBoNT injection on participants with chronic stroke and upper limb spasticity. Participants

had to be able to perform active extension >10° at the finger joints and >20° at the wrist prior to enrolment. The modified constraint-induced movement therapy group also had shaping, a behavioural contract, and a treatment diary. Shaping involved individualized task selection, graduated task difficulty and complexity, positive verbal feedback, and physical assistance with movements. A behavioural contract detailed what activities would be done with the restraint on and when the restraint should be removed for potentially unsafe situations. The participants were strongly encouraged to continue using their weaker upper limbs during activities throughout the day and while at home. At six months follow-up, there was an improvement in the primary outcome of Modified Ashworth Scale in the intervention compared with the control group for the elbows and fingers, but not wrist. Results were better for the intervention group in the Motor Activity Log, Action Research Arm Test, and patient global satisfaction outcome measures.

Physiotherapy

One high-quality study by Giovannelli et al.[23] examined the effects of physiotherapy postBoNT injection compared with BoNT alone in individuals with secondary progressive multiple sclerosis with focal spasticity of the upper and/or lower limbs. Two participants in the control group were lost to follow-up. Both Modified Ashworth Scale and visual analogue scale self-reported satisfaction were better postinjection in the group who received physiotherapy compared with BoNT alone. This study was limited by the lack of sham intervention in the control group, particularly given the subjective nature of the outcome measures.

Dynamic splinting

One study by Lai et al.[24] examined the addition of night-time dynamic splinting of the spastic elbow in individuals post-stroke postBoNT injection. Six participants were excluded from analysis owing to non-compliance with attending occupational therapy sessions; it is not stated how many were from the intervention vs. control groups. There were better active elbow extension and Modified Ashworth Scale scores in the intervention compared with control group on follow-up, although *P* values were not reported. Intention-to-treat analysis was not applied, which is of particular note owing to the drop-out rate.

Adverse events

Of the 17 studies included in this review, eight[11–13,15,19–21,24] did not report on adverse events. Transient pain at the injection site was the most common adverse event related to BoNT injections. The electrical stimulation study by Bayram et al.[10] reported that four participants in the control group experienced mild–moderate calf pain, which subsided within one to three days in all except one participant who had extended weakness, which caused an elevation of mean walking time at Week eight post injection. In the intervention group, there was one participant with muscle weakness that subsided in two weeks. Hesse et al.[8] reported bladder paresis requiring catheterization for 14 days in one electrical stimulation group participant. Carda et al.[16] reported that one participant in the taping group discontinued treatment because of pain, as well as one participant in the casting group.

Discussion

The lack of independent replication of RCT results to definitively support a specific adjunct therapy means that no single form of therapy combined with BoNT can yet be firmly supported. All interventions reviewed would benefit from further study.

When compared with BoNT injection alone, we found evidence suggesting that adjunct use of extracorporeal shock wave therapy, electrical stimulation, modified constraint-induced movement therapy, physiotherapy (all Level 1), casting, and dynamic splinting (both Level 2) result in improved Modified Ashworth Scale scores by at least one grade. There is Level 1 and 2 evidence that adjunct taping, segmental muscle vibration, cyclic functional electrical stimulation, and motorized arm ergometry postBoNT injections may not improve

outcomes compared with BoNT injections alone. There is Level 1 evidence suggesting that casting is better than taping, taping is similar to electrical stimulation, with both better than stretching, and extracorporeal shock wave therapy is better than electrical stimulation for outcomes including the Modified Ashworth Scale, passive range of motion and gait. All results are based on single RCTs. All but two studies (Santamato et al.[14] on electrical stimulation and Sun et al.[22] on modified constraint-induced movement therapy) were underpowered, so it is difficult to draw firm conclusions regarding the usefulness of therapies reviewed in this article. However, it is important for clinicians to be knowledgeable regarding the current levels of evidence relevant to their practice, even if independent replication of evidence is lacking. This review is also useful for investigators, as results highlight the need for future research to be conducted in this area. Recommendations for future studies are provided below.

With respect to electrical stimulation, given that each study used different dosing and stimulation parameters (e.g. timing, duration, frequency, intensity), further research on how electrical stimulation is best delivered with respect to these variables is needed, with full reporting of all variables. It appears that low-frequency electrical stimulation may be better than high-frequency electrical stimulation, and immediate electrical stimulation better than delayed electrical stimulation, although each of these findings are only supported by Level 2 RCTs. Some studies stimulated antagonist muscles as well as those injected with BoNT, whereas others stimulated only injected muscles. Whether electrical stimulation of antagonist muscles in addition to injected muscles improves outcomes is not yet known, and also merits further research.

With arm cycle ergometry, a potential confounding factor is the presence or absence of residual motor function in the affected arm. This must be taken into consideration in future studies.

Further research is required to determine whether taping postBoNT injection improves outcomes in the spastic equinovarus foot, as it may be that longer durations of taping (e.g. three vs. two weeks) have better effect.

Although stretching as an intervention had the least improvement in outcomes when compared with other therapies such as electrical stimulation and taping, there was no study that assessed stretching as the sole adjunct therapy. In comparative studies, results will be either equivalent or comparatively less effective, which does not mean that the less effective intervention does not improve outcomes. As stretching is a minimally invasive and low resource intervention that is commonly prescribed, it merits further research as an adjunct therapy.

The resources required for adjunct therapies should be clearly documented and considered in the design, reporting, and interpretation of all studies. For example, there is Level 1 evidence from two high-quality RCTs that taping is better than stretching. However, studies of taping included the need for taping to be checked and rearranged daily by a trained therapist, which may not be feasible in many clinical settings. Serial casting may be more effective than taping, however, the cast also needs to be changed twice per week and takes around 30 minutes to apply. Providing electrical stimulation on consecutive days postinjection also requires the use of a therapist or rehabilitation assistant, unless the individual purchases their own unit and is able to perform the procedure themselves or with help from caregivers. Similar resource requirements arise with other adjunct therapies described in this systematic review, particularly with physiotherapy, segmental muscle vibration, and modified constraint-induced movement therapy. Given the resource demands of these therapies, further research is needed to determine whether the gains outweigh the costs of these interventions.

Another challenge that arises in both clinical and research settings is the determination of goals for each individual and tailoring the therapy accordingly. The outcome measures used in the studies reviewed were highly variable, making analysis of pooled data difficult. Many studies used outcome measures that relate to body structure and function rather than activity and participation, which are domains that should be evaluated in studies of rehabilitation interventions. Future study designs should include outcome measures

that are validated and can be consistently reproduced by other investigators, and these should ideally address all domains of the International Classification of Functioning, Disability and Health.[25]

There was also variability in the BoNT injection techniques used, such as method of localization, dilution, and total dose. Previous RCTs have demonstrated that different methods of localization, such as manual needle placement vs. electromyography,[26] affect outcomes postBoNT injection, as does BoNT dilution.[27] These parameters should be replicated in future studies if possible to ensure consistency of results.

Almost half of the studies in this review did not report on adverse events. In the studies that did report adverse events, taping and casting were the adjunct therapies that led to discontinuation of treatment in a small number of participants owing to pain. Otherwise, adverse events were limited to postBoNT injection pain and transient muscle weakness, except for one electrical stimulation study where a participant with a history of ischemic stroke in the intervention group required catheterization for 14 days owing to bladder paresis. This may have been owing to effects of the BoNT alone, although electrical stimulation is thought to increase uptake of BoNT and it is yet unknown whether this could potentially lead to increased systemic as well as local effects. Therefore it is crucial for researchers to report on adverse events, as this information will guide future research efforts and clinical decision-making.

Study limitations include that the generalizability of these findings may be limited as many studies excluded those with previous BoNT injections. Therefore some results may not apply to those with a previous history of BoNT injections owing to denervation effects. Different pathologies considered in this systematic review might have influenced the differences in the results. Articles reviewed were limited to English and, while the search strategy to identify studies for this review was comprehensive, given the broad nature of the topic, it is possible that some studies may have been missed.

Clinical messages

- Adjunctive therapies such as electrical simulation, extracorporeal shock wave therapy, modified constraint-induced movement therapy, physiotherapy, casting, and dynamic splinting may improve spasticity outcomes, when used with BoNT injections for treatment of limb spasticity.
- Further research is needed to independently replicate these findings and to determine the cost-effectiveness of these interventions before they can be considered a standard of care.

Conflicts of interest

The authors have no conflict of interest with the contents of this systematic review.

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References

1. Esquenazi A, Novak I, Sheean G, Singer BJ and Ward AB. International consensus statement for the use of botulinum toxin treatment in adults and children with neurological impairments—introduction. *Eur J Neurol* 2010; 17(Suppl 2): 1–8.
2. Esquenazi A, Albanese A, Chancellor MB, et al. Evidence-based review and assessment of botulinum neurotoxin for the treatment of adult spasticity in the upper motor neuron syndrome. *Toxicon* 2013; 67: 115–128.
3. Turner-Stokes L and Ward AB. *Spasticity in adults: Management using botulinum toxin. National guidelines*. London: Royal College of Physicians, 2009.
4. Kinnear BZ, Lannin NA, Cusick A, Harvey LA and Rawicki B. Rehabilitation therapies after botulinum toxin-A injection to manage limb spasticity: A systematic review. *Phys Ther* 2014; 94(11): 1569–1581.
5. Higgins JPT and Green S. *Cochrane handbook for systematic reviews of interventions* Version 5.1.0 [updated March 2011], 2011. Available at: www.cochrane-handbook.org (accessed 18 September 2013).
6. Moseley AM, Herbert RD, Sherrington C and Maher CG. Evidence for physiotherapy practice: A survey of the Physiotherapy Evidence Database (PEDro). *Aust J Physiother* 2002; 48(1): 43–49.

7. Eng J, Teasell R, Miller W, et al. Spinal cord injury rehabilitation evidence: Method of the SCIRE systematic review. *Top Spinal Cord Inj Rehabil* 2007; 13(1): 1–10.
8. Hesse S, Jahnke MT, Luecke D and Mauritz KH. Short-term electrical stimulation enhances the effectiveness of botulinum toxin in the treatment of lower limb spasticity in hemiparetic patients. *Neurosci Lett* 1995; 201(1): 37–40.
9. Hesse S, Reiter F, Konrad M and Jahnke MT. 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. *Clin Rehabil* 1998; 12(5): 381–388.
10. Bayram S, Sivrioglu K, Karli N and Ozcan O. Low-dose botulinum toxin with short-term electrical stimulation in poststroke spastic drop foot. *Am J Phys Med Rehabil* 2006; 85(1): 75–81.
11. Frasson E, Priori A, Ruzzante B, Didonè G and Bertolasi L. Nerve stimulation boosts botulinum toxin action in spasticity. *Mov Disord* 2005; 20(5): 624–629.
12. Picelli A, Smania N, Storti I, et al. Immediate versus delayed electrical stimulation boosts botulinum toxin effect: A pilot study. *Mov Disord* 2011; 26(9): 1784–1785.
13. Weber DJ, Skidmore ER, Niyonkuru C, Chang C-L, Huber LM and Munin MC. Cyclic functional electrical stimulation does not enhance gains in hand grasp function when used as an adjunct to onabotulinumtoxinA and task practice therapy: A single-blind, randomized controlled pilot study. *Arch Phys Med Rehabil* 2010; 91(5): 679–686.
14. Santamato A, Notarnicola A, Panza F, et al. SBOTE study: Extracorporeal shock wave therapy versus electrical stimulation after botulinum toxin type a injection for post-stroke spasticity—a prospective randomized trial. *Ultrasound Med Biol* 2013; 39(2): 283–291.
15. Baricich A, Carda S, Bertoni M, Maderna L and Cisari C. A single-blinded, randomized pilot study of botulinum toxin type A combined with non-pharmacological treatment for spastic foot. *J Rehabil Med* 2008; 40(10): 870–872.
16. Carda S, Invernizzi M, Baricich A and Cisari C. Casting, taping or stretching after botulinum toxin type A for spastic equinus foot: A single-blind randomized trial on adult stroke patients. *Clin Rehabil* 2011; 25(12): 1119–1127.
17. Karadag-Saygi E, Cubukcu-Aydoseli K, Kablan N and Ofluoglu D. The role of kinesiotaping combined with botulinum toxin to reduce plantar flexors spasticity after stroke. *Top Stroke Rehabil* 2010; 17(4): 318–322.
18. Reiter F, Danni M, Lagalla G, Ceravolo G and Provinciali L. Low-dose botulinum toxin with ankle taping for the treatment of spastic equinovarus foot after stroke. *Arch Phys Med Rehabil* 1998; 79(5): 532–535.
19. Farina S, Migliorini C, Gandolfi M, et al. Combined effects of botulinum toxin and casting treatments on lower limb spasticity after stroke. *Funct Neurol* 2008; 23(2): 87–91.
20. Paoloni M, Giovannelli M, Mangone M, et al. Does giving segmental muscle vibration alter the response to botulinum toxin injections in the treatment of spasticity in people with multiple sclerosis? A single-blind randomized controlled trial. *Clin Rehabil* 2013; 27(9): 803–812.
21. Diserens K, Ruegg D, Kleiser R, et al. Effect of repetitive arm cycling following botulinum toxin injection for poststroke spasticity: Evidence from FMRI. *Neurorehabil Neural Repair* 2010; 24(8): 753–762.
22. Sun S-F, Hsu C-W, Sun H-P, Hwang C-W, Yang C-L and Wang J-L. Combined botulinum toxin type A with modified constraint-induced movement therapy for chronic stroke patients with upper extremity spasticity: A randomized controlled study. *Neurorehabil Neural Repair* 2010; 24(1): 34–41.
23. Giovannelli M, Borriello G, Castri P, Prosperini L and Pozzilli C. Early physiotherapy after injection of botulinum toxin increases the beneficial effects on spasticity in patients with multiple sclerosis. *Clin Rehabil* 2007; 21(4): 331–337.
24. Lai JM, Francisco GE and Willis FB. Dynamic splinting after treatment with botulinum toxin type-A: A randomized controlled pilot study. *Adv Ther* 2009; 26(2): 241–248.
25. World Health Organization. International Classification of Functioning, Disability and Health (ICF). Available at: http://www.who.int/classifications/icf/icf_more/en/ (accessed 27 March 2014).
26. Ploumis A, Varvarousis D, Konitsiotis S and Beris A. Effectiveness of botulinum toxin injection with and without needle electromyographic guidance for the treatment of spasticity in hemiplegic patients: A randomized controlled trial. *Disabil Rehabil* 2014; 36(4): 313–318.
27. Gracies JM, Lugassy M, Weisz DJ, Vecchio M, Flanagan S and Simpson DM. Botulinum toxin dilution and endplate targeting in spasticity: A double-blind controlled study. *Arch Phys Med Rehabil* 2009; 90(1): 9–16.e2.