
Botulinum Toxin in the Treatment of Upper and Lower Limb Spasticity Post Stroke

Robert Teasell MD, Norine Foley MSc, Katherine Salter BA, Sanjit Bhogal MSc.

Botulinum toxin is significantly associated with decreased spasticity, increased range of motion and improved upper extremity function.

Botulinum toxin in combination with electrical stimulation improves upper extremity function.

Deinnervation of the subscapularis muscle using botulinum toxin may reduce shoulder pain and improve passive range of motion, more so than deinnervation of the pectoralis major muscle.

Deinnervating lower extremity muscles with botulinum toxin reduces spasticity, but has not been shown to improve function.

Botulinum toxin in combination with electrical stimulation may improve spasticity and function.

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Contacts:

Dr. Robert Teasell
801 Commissioners
Road East

London, Ontario,
Canada

N6C 5J1

Phone:
519.685.4000

Web:
www.ebrsr.com

Email:
Robert.teasell@sjhc.london.on.ca

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1.0 Management of Spasticity

1.1 Introduction

Botulinum toxin (BT) is a neurotoxin, which works by weakening spastic muscles through selectively blocking the release of acetylcholine at the neuromuscular junction. The benefits of botulinum injections are generally dose-dependent and are realized within 3 to 7 days following injection. Two types of botulinum toxin (type A) are available- Botox and Dysport, although they are not bioequivalent. The dose equivalent is approximately 300-500 Units of Dysport equal 100 units of Botox (O'Brian 2002). Although BT has been shown to reduce spasticity following stroke, it remains unclear whether this results in functional improvements (Gallichio 2004). The advantages of BT include a lack of sensory disturbance and ability to target certain muscle groups. One of the advantages of botulinum is that it is safe to use on small, localized areas or muscles, such as those in the upper extremity. Unlike chemical neurolysis with either phenol or alcohol, botulinum toxin is not associated with skin sensory loss or dysesthesia (Suputtitada & Sunanwela 2005). Dynamic EMG studies can be helpful in determining which muscles should be injected (Bell and Williams 2003).

2.0 The Use of Botulinum Toxin in the Upper Extremity

2.1 Previous Reviews

The therapeutic effects of BT have been studied extensively in the upper

extremity. van Kuijk et al. (2002) reviewed 10 studies, (4 RCTs) and 6 uncontrolled studies evaluating spasticity in stroke patients by focal neuronal or neuromuscular blockade. The authors reported that botulinum toxin treatment was effective in reducing muscle tone (modified Ashworth Scale) and improving passive range of motion at all arm-hand levels in chronic patients for approximately 3-4 months. There was also preliminary evidence that BT treatment combined with electrical stimulation was beneficial. However, the authors concluded that the reductions in tone were not associated with improvements in functional abilities.

A meta-analysis authored by Francis et al. (2004) included the results from two RCTs (Bakheit et al. 2000, 2001), evaluating botulinum toxin on functional improvements. While previous individual RCTs have demonstrated a reduction in spasticity associated with treatment, unfortunately there has not also been a corresponding improvement in function. The authors attributed this lack of association to the effects of underpowered individual studies as well as to the choice of outcome(s) measure used, such as the Barthel Index which does not adequately capture gains that are specific to the upper extremity. The authors of this review pooled the data and assessed the effect on the arm section of the Barthel Index (dressing, grooming and eating) and reported a modest improvement following botulinum toxin. Pooling was only possible for two RCTs due to heterogeneity of interventions and outcomes.

2.2 Studies Evaluating BT in the Upper Extremity

Thirteen RCTs and six uncontrolled studies evaluating the effect of botulinum toxin on spasticity, were reviewed. The majority of the RCTs

compared either treatment with a single dose of BT, or differing doses of BT, to a placebo control. A single study compared two doses of BT without the inclusion of a non-treatment control (Fansisco et al. 2004). The results are presented in Table1.

Author/ Country PEDro Score	Methods	Outcomes
Bhakta et al. 1996 UK No Score	17 patients received a single course of intramuscular botulinum toxin to biceps brachii, flexor digitorum profundus, flexor digitorum superficialis and flexor carpi ulnaris.	Significant improvement in grading of biceps spasticity and forearm finger flexor spasticity were observed. Significant mean improvement of 17° for passive shoulder abduction or adduction, 17° for passive shoulder flexion and extension and 16° for passive elbow flexion and extension were noted. Significant mean improvement of 31° for passive wrist dorsiflexion and palmar flexion were observed. Hand hygiene improved in 14 of 17 patients. Shoulder pain improved in 6 or 9 patients and wrist pain improved in 5 of 6 patients.
Simpson et al. 1996 USA 8 (RCT)	A double blind, placebo controlled trial of 37 patients randomized to receive either a single treatment of either 75 units, 150 units or 300 units of total doses of BTX-A or placebo into the biceps, flexor carpi radialis and flexor carpi ulnaris muscles.	Treatment with 300-unit BTX-A dose resulted in clinical significant mean decrease in wrist flexor tone at 2, 4 and 6 weeks post-injection. BTX-A groups reported significant improvement on physician and patient Global Assessment of Response to Treatment at weeks 4 and 6 post-injection.
Smith et al. 2000 UK 7 (RCT)	Double blind placebo trial of 25 patients randomized to receive either 500 Mu, 1000 Mu or to receive 1500 Mu of botulinum toxin by intra-muscular injection or placebo consisting of an equal volume of sterile saline.	Combining data from active treatment, botulinum toxin showed significantly greater improvement in modified Ashworth scale at fingers, passive range of movement at the wrist, and finger curl distance at rest. Only significant difference between dose groups in favour of 1500 Mu for improved movement at the elbow.
Bakheit et al. 2000 UK 8 (RCT)	International, multi-center, randomized, double-blind placebo-controlled trial of 82 patients randomized to one of four groups (500 U of Dysport, 1000 U of Dysport, 1500 U of Dysport or placebo). Injections were made to the biceps brachii, flexor digitorum profundus and flexor digitorum superficialis, flexor carpi ulnaris and flexor carpi radialis muscles.	All 3 groups receiving Dysport showed significant reduction in MAS (Modified Ashworth Scale) scores in any joint at week 4 compared with placebo. At 16 weeks, the MAS scores were significantly reduced in the hemiparetic arm for all doses in the elbow and wrist and also in the fingers in the 1000 U Dysport group. No significant differences were found between groups on the Rivermead Motor Assessment, pain scores, or Barthel

		Index scores.
Lagalla et al. 2000 Italy No Score	34 stroke patients suffering from moderate to severe chronic spasticity received BTX-A injections every 3 to 5 months for 28 months and were observed for 3 years. Mean dose per session was 128 U. Patients also received physical therapy twice weekly.	Of the 28 patients who completed the trial, all received at least 6 injections. There was a significant decline in Ashworth scores after the first injection. However, there were no subsequent changes in scores. Passive and active ROM also improved significantly after the first treatment. Frenchay arm test scores improved in only 8 subjects.
Bakheit et al. 2001 UK 8 (RCT)	International, multi-center, randomized, double-blind placebo-controlled trial of 59 patients who received either placebo injections or a total of 1000 IU of BtxA (Dysport) into 5 muscles of the affected arm.	The group who received Dysport had a significant reduction in the summed Modified Ashworth Scale score at week 4 compared with the placebo group. The magnitude of benefit over the 16 week follow-up period was significantly reduced for the BTX-A group in the wrist and finger joints compared with the placebo group. No significant difference was noted between the groups in the joint ROM, muscle pain, goal-attainment or the Barthel Index scores at week 4 of the study. At week 16, the BTX-A group showed significantly greater improvement in elbow PROM.
Brashear et al. 2002 USA 7 (RCT)	126 stroke patients were randomized to receive a single injection of BTX-A (n=64) or placebo (n=64) (50 units injected in each of 4 wrist and finger muscles).	122 patients completed the study. The primary outcome was improvement in the 4-point Disability Assessment scores at 6 weeks (hygiene, dressing, pain and limb position). Six weeks after injection with BTX-A 83% of subjects reported at least a one-point improvement of DAS score compared to 53% of patients who were treated with placebo (p=0.007).
Francisco et al. 2002 USA 7 (RCT)	13 patients (10 strokes) with Modified Ashworth Scores (MAS) of 3 or 4 were randomized to receive either high volume BTX-A (50 units/1 mL saline:1.2 mL delivered per 4 muscles) or low volume BTX-A (100 units/1 mL saline delivered per 4 muscles). On average, patients in the high volume group received 417 units BTX-A compared to patients in the low volume group (432 units).	Assessments were completed at 4, 8 and 12 weeks post injection. MAS scores of both wrist and finger flexors were assessed. While MAS scores decreased significantly in both treatment groups, there were no differences between the low and high volume BTX-A regimens.
Pandyan et al. 2002 UK No Score	14 stroke patients with elbow flexor spasticity received 3 injections of botulinum toxin Type A (BTX-A) into the m.biceps brachii, m.branchioradialis and m.flexor digitorum longus (mean dose 70U, 56.5 U and 83.3 U respectively). Assessments were made before and 4 weeks after treatment. They included the modified Ashworth Scale (MAS), grip strength and upper limb function (Action Research Arm	There was a significant improvement in upper limb function (P<0.05) as measured by the ARAT.

	TEST (ARAT)), and strength at the elbow (isometric).	
Bakheit et al. 2004 UK No Score	An open label study in which 51 patients with established post-stroke upper limb spasticity received 1000 units of BtxA (Dysport) into five muscles of the affected arm. Treatment was repeated every 12, 16, or 20 weeks as clinically indicated. Each patient received a total of three treatment cycles. Efficacy of treatment was assessed using the Modified Ashworth Scale. Patients were assessed on study entry and on week 4 and 12 of each treatment cycle for all safety and efficacy parameters. Blood samples for BtxA antibody assay were taken at baseline and on completion of the trial.	41 subjects completed all 3 treatment cycles. Improvement from the cycle one baseline was observed in all the outcome measures. 100% of subjects achieved at least a 1- point decrease on MAS scores in at least 1 joint. By the end of the 3 rd cycle, 98% had achieved a 1-point reduction. 90% of subjects who completed the 3 cycles reported that the treatment had been beneficial. Mild to moderately severe treatment related adverse events were reported in 24% of cases. No BtxA antibodies were detected
Brashear et al. 2004 USA 7 (RCT)	15 stroke patients were randomized to receive a single Botox type B injection (10,000U) in the elbow, wrist, finger and thumb (n=10) or placebo (n=5). Measures were recorded at 2, 4, 8, 12 and 16 weeks.	There was no significant decrease in muscle tone in the elbow, wrist, or finger. A decrease in Ashworth scale scores was observed at the wrist at week 2 in the treatment group. Improvement was also observed at week 4 for the elbow (p=.039), wrist (p=.002), finger (p=.001) and thumb (p=.002) in the treatment gr. Improvements were not sustained.
Gordon et al. 2004 USA No Score	Additional component of study by Brashear et al. 2002. 111 patients who completed the study entered into an open label study of BTX-A and received up to four treatments. The mean dose was 220U. The longest interval between cycles was 24 weeks.	Compared to baseline values from the double-blind portion of the study, there were significant improvements in each of the four domains of the Disability Assessment Scale. There were also improvements in Modified Ashworth Scores.
Childers et al. 2004 USA 7 (RCT)	91 patients were randomized to 4 groups: (1) 90U Botox type A; (2) 180U Botox; (3) 360U Botox; (4) placebo. Efficacy outcome measures were completed for the 4 groups as follows: (1) n=16; (2) n=15; (3) n=18; (4) n=18.	A dose-dependent response in muscle tone was generally observed in tone reduction in the wrist (p<.03), elbow (p<.04, and finger (p<.04), but not in pain, FIM scores, or SF-36 scores.
Suputtitada & Suwanwela 2005 Thailand 6 (RCT)	Patients received either a placebo (n=15) or one of three doses of Dysport (350 U n=15, 500 U n=15, 1000 U n=15) into five muscles of affected arm by anatomical and electromyography guidance. Efficacy was assessed throughout the 6-month study period by the Modified Ashworth Scale (MAS), the Action Research Arm Test (ARA),	All doses of Dysport studied showed a significant reduction from baseline of muscle tone and pain compared to placebo. However, the effect of functional disability was best at a dose of 500 U and the peak improvement was at week 8 after injection. A dose of 1000 U Dysport produced such an excess degree of muscle weakening that the number of randomized patients was reduced to five. BI

	the Barthel Index (BI) and the Visual Analogue Pain Scale (VAS).	and ARA of all patients were decrease after injection. No other adverse event was considered related to the study medication.
Slawek et al. 2005 Poland No Score	Open-label study of 21 stroke patients with onset of symptoms from 3 months to less than 3 years. Patients received an average dose of botulinum toxin-A of 255 U, based on individual spasticity. Outcome assessed included Modified Ashworth scores, finger flexion scale, nine-hole peg test, Motor Assessment Scale, assessed up to week 16.	There were statistically significant improvements in baselines scores to week 16 for MAS (elbow and wrist), Bhahkta finger scale in passive movements and muscle tone analysis. The only significant result for active movement analysis was MAS (arm). Pain was present only in 11 patients and did not significantly improve following treatment. Individualized BTX-A injection regimens may be an effective, reversible and safe new treatment option for patients with spasticity. Nevertheless, functional improvement may be reached only in selected patients.
Jahangir et al. 2007 Malaysia 6 (RCT)	27 patients, at least 3 months following stroke, with focal spasticity of the wrist and fingers were randomized to receive a single injection of 40 U of botulinum toxin (Botox) or placebo. 20 U were injected into the wrist and finger flexors. All subjects received physical therapy for 1 hour, twice a week for 3 months. Assessments were performed at baseline and 1 and 3 months after injection and included the Modified Ashworth Scale (MAS) Barthel Index (BI) and EQ-5D and EQ VAS for quality of life.	At the end of 3 months there were significant improvements favouring the Botox group in terms of MAS score of both the wrist and finger, but no significant differences on any of the other outcomes assessed No serious Botox related adverse effects were reported.
Bhakta et al. 2008 UK 9 (RCT)	Additional results from 2000 study evaluating the impact of associated reactions on activities of daily living. Associated reactions were measured using hand dynamometry. The effort used was measured using maximum voluntary grip in the unaffected arm. Measurements were recorded at 2 pre-treatment and 3 post-intervention times. Activities that patients felt caused associated reactions and activities that were affected by associated reactions were recorded.	Peak associated reactions force was reduced at week 6 with botulinum toxin A compared with placebo (mean group difference 19.0 N; 95% confidence interval (CI): 7.2, 30.9; $p < 0.01$) and week 2 ($p = 0.005$), with the effect wearing off by week 12 ($p = 0.09$). 31 patients noted associated reactions on a regular basis and 24 said that these movements interfered with daily activities. Ten of 12 patients receiving botulinum toxin A and 2 of 12 receiving placebo reported reduction in interference with daily activities ($p = 0.02$)
Kanovsky et al. 2009 Germany 8 (RCT)	148 chronic stroke patients from 23 sites in 3 European countries with wrist and finger flexor spasticity and with at least moderate disability in their principal therapeutic target of the Disability Assessment Scale (DAS) were treated either with NT 201 (Xeomin) (median, 320 U) or placebo and followed up for up to 20 weeks. Outcomes assessed included the	A significantly higher proportion of patients treated with NT 201 had improved by at least 1 point on the Ashworth Scale score on the wrist flexors, compared with the placebo group at the end of 20 weeks (39.7% vs. 19.2%, $p=0.007$). The proportion of responders for all other muscle groups (clenched fist, thumb-in-palm, flexed elbow and pronated forearm) was significant greater for patients in the active drug group, at 4

	Ashworth Scale, DAS, Carer Burden Scale and the global assessment of benefit, as identified by the investigators, carers and patients.	weeks. On all of the other outcomes assessed, patients in the active drug group fared better than patients in the control group on at one assessment point.
Simpson et al. 2009 USA 8 (RCT)	60 subjects with upper-limb spasticity due to stroke or traumatic brain injury (TBI) were randomized to 1 of 3 groups: (1) intramuscular BoNT plus oral placebo; (2) oral tizanidine (TZD) plus intramuscular placebo; (3) intramuscular placebo plus oral placebo. Wrist flexors were systematically injected, while other upper limb muscles were injected as per investigator judgment (total maximum dose: 500 U). The study duration was 22-24 weeks. The primary outcome was the difference in change in wrist flexor modified Ashworth score (MAS) at 6 weeks. Other outcome measures included adverse events (AE).	At 6 weeks the mean changes from baseline in wrist flexor tone scores were: BoNT: -1.32, TZD: -0.22, placebo: -0.68. BoNT produced significantly greater reductions compared with either placebo or TZD. There were more adverse events associated with TDZ compared with BoNT
McCroory et al. 2009 Australia 9 (RCT)	96 patients an average of 5.9 years post stroke were randomized to receive either 500-1,000U botulinum toxin type A or placebo into the affected distal upper limb muscles on 2 occasions, 12 weeks apart. Assessment was undertaken at baseline, 8, 12, 20 and 24 weeks. The primary outcome measure was the Assessment of Quality of Life scale (AQoL) assessed at week 20. Secondary outcome assessments included Goal Attainment Scaling (GAS), pain, mood, global benefit, Modified Ashworth Scale (MAS), disability and carer burden.	There were no significant between group differences in AQoL change scores. There were no other significant differences in pain, mood, disability or carer burden. However, patients treated with botulinum toxin type A had significantly greater reduction in spasticity (MAS) ($p < 0.001$), higher GAS scores ($p < 0.01$) and greater global benefit ($p < 0.01$).
Meythaler et al. 2009 USA 6 (RCT)	21 subjects with stroke onset more than 6 months with tone greater than 3 on the Ashworth Scale for 2 joints in the involved upper extremity were randomized in a crossover trial to receive either 100 U BTX-A combined with a defined therapy program or placebo injection combined with a therapy program in two 12-week sessions. The primary functional outcome measure was the Motor Activity Log (MAL), assessed at baseline and at the end of treatment. Subjects were also assessed on physiologic measures including tone (Ashworth Scale), range of motion, and motor strength.	The use of BTX-A combined with therapy as compared with therapy only improved the functional status of the subjects on the MAL Quality of Movement subscale ($P=.0180$). There was a trend toward significance in the Amount of Use subscale ($P=.0605$). After each 12-week period, tone had largely returned to baseline ($P>.05$).

Turner-Stokes et al. 2010 UK 9 (RCT)	Additional analysis from McCrory et al. 2009. Main outcome measures were: individualized goal attainment and its relationship with spasticity and other person-centred measures - pain, mood, quality of life and global benefit.	Goal-attainment scaling outcome were highly correlated with reduction in spasticity ($\rho=0.36$, $p=0.001$) and global benefit ($\rho=0.45$, $p<0.001$), but not with other outcome measures. Goals related to passive tasks were more often achieved than those reflecting active function.
Sun et al. 2010 Taiwan 6 (RCT)	32 patients (≥ 1 year after stroke) with ability to actively extend >10 degrees at metacarpophalangeal and interphalangeal joints and 20 degrees at wrist of the affected upper limb were randomized to receive BtxA + modified constraint-induced movement therapy (CIMT) (combination group) (n=16) or BtxA + conventional rehabilitation (control group) (n=16) for 2 hours/day, 3 days/week for 3 months. The primary outcome assessed spasticity on the Modified Ashworth Scale (MAS) at 6 months. Secondary outcomes assessed real-world arm function (Motor Activity Log), laboratory motor activity (Action Research Arm Test), and patients' global satisfaction.	The combination group showed significantly greater improvements in elbow, wrist, and finger spasticity ($P = .019$, $P = .019$, and $P < .001$, respectively), affected upper extremity real-world arm function ($P < .001$) and laboratory motor activity ($P < .001$) than the control group at 6-month post injection. Patients reported considerable satisfaction and no serious adverse events occurred.
Bensmail et al. 2010 France No Score	15 outpatients with spastic hemiparesis and 9 healthy controls were included in this single-site, open-labeled study of Botulinum toxin (Botox) with dosages specific to each participant. The trajectories of reaching movements were recorded, and kinematic variables were computed. A clinical evaluation included the Motor Activity Log, the Action Research Arm Test (ARAT), and the Box and Block Test (BBT). Patients were assessed before, 1 month after a first (M1), and 1 month after a second BTI (M4, at 4 months) in proximal and distal muscles.	Significant differences were found between hemiparetic patients and healthy participants for all kinematic parameters. All parameters tended to improve after BT. This effect was significant for velocity and smoothness. Functional scores also tended to improve. Improvements were greater at M4 than at M1, although the differences were not significant. There were no significant improvements from baseline to follow-up on any of the functional assessments.
Kaji et al. 2010a) Japan 9 (RCT)	109 subjects with upper limb spasticity following chronic stroke were randomized to receive a single treatment with lower-dose (120–150 U)(n=21) or placebo (n=11) or higher dose (200–240 U) (n=51) BoNTA or placebo (n=26). The tone of the wrist flexor was assessed at baseline and at weeks 0, 1, 4, 6, 8 and 12 using the Modified Ashworth Scale (MAS) for wrist, finger, thumb and disability in activities of daily living (ADL) was rated using the 4-point Disability Assessment Scale (DAS).	Higher dose BoNTA was associated with greater reductions in MAS and DAS scores associated with limb positioning compared with lower dose or placebo at 12 weeks. There were no differences in the number of adverse events reported among the treatment or placebo groups.

<p>Cousins et al. 2010 UK 5 (RCT)</p>	<p>30 subjects following stroke within the previous 3 weeks with impaired grasping ability were randomized to receive a single injection of either one-quarter, or half standard dose botulinum toxin, or placebo (saline) to prevent the development of spasticity. Arm function, active and passive movement, and spasticity at elbow and wrist were recorded at baseline, and at 4, 8, 12 and 20 weeks post intervention. A pre-planned subgroup analysis included only subjects with no arm function at baseline (Action Research Arm Test score = 0).</p>	<p>Arm function, assessed using the ARAT improved in all three groups between baseline and week 20, but there were no significant differences among groups. In the subgroup analysis restricted to subjects without arm function at baseline, there were no significant differences among groups except for the active range of elbow flexion, which was greater in the ¼ dose group compared with the other 2 groups.</p>
<p>Shaw et al. 2011 UK 8 (RCT)</p>	<p>333 patients with at least 1 month post stroke with upper limb spasticity and reduced arm function were randomized to receive injection(s) with 100 – 200 U botulinum toxin type A plus a 4-week therapy program (n=170) or a therapy program alone (n=163). Repeat injection(s) and therapy were available at 3, 6, and 9 months. The primary outcome was successful outcome defined as either a 3-point gain on the Action Research Arm Test (ARAT) for those with baseline scores of 0-3, a gain of at least 6 points for those with baseline scores of 4-51, and a final ARAT score of 57 for those with baseline scores of 52-57 at 1 month. Secondary outcomes included measures of impairment, activity limitation, and pain at 1, 3, and 12 months.</p>	<p>There was no significant difference in the percentage of patients who has achieved a successful outcome: 25% of patients in the treatment group had achieved a successful outcomes compared with 19.5% of patients in the control group; P=0.232. Significant differences in favor of the intervention group were seen in muscle tone at 1 month; upper limb strength at 3 months; basic arm functional tasks (hand hygiene, facilitation of dressing) at 1, 3, and 12 months; and pain at 12 months.</p>
<p>Kanovsky et al. 2011 Czech Republic 8 (RCT)</p>	<p>Patients from 2009 study were invited to participate in an extension of the study. 145 patients received up to 5 additional sets of NT 201 injections for an open-label extension period of up to 69 weeks</p>	<p>Mean cumulative dose of NT 201 was 1120 U. The proportion of treatment responders (≥1-point improvement on the Ashworth scale) for flexors of wrist, elbow, finger, and thumb, and forearm pronator ranged from 49% to 80%. The proportion of treatment responders (≥1-point improvement on the Disability Assessment Scale) ranged from 43% to 56%. The majority of investigators, patients and caregivers rated NT 201 efficacy as very good or good (56-84%). Adverse events considered treatment-related occurred in 11% of patients. Formation of neutralizing antibodies was not observed in any patient after repeated treatments.</p>

Discussion

Assessing the effectiveness of botulinum toxin in the treatment of

upper limb spasticity was difficult owing to the broad range of doses and types of agents administered. Among the RCTs reviewed, many assessed the between a single dose, administered to several sites, of botulinum toxin A as either Dysport®, Botox® or Xeomin® vs. placebo. A single trial assessed the benefit of BT-type B (Brashear et al. 2004-10,000 U BT-B). The dose equivalent is approximately 300-500 Units of Dysport equal 100 units of Botox (O'Brian 2002). Among these trials, the results were ambiguous. The greatest benefit appeared to be realized in the patients who received Botox (Brashear et al. 2002) who had reductions in tone and also experienced improvement in functional outcome. Patients treated with BT-B (MyoBloc) appeared to have the poorest response to treatment (Brashear et al. 2004). One trial, the most methodically rigorous (McCrory et al. 2009) evaluated the effectiveness of 2 doses of Botox, given 12 weeks apart, compared with placebo. The most recent trial (Shaw

et al. 2011) failed to find a benefit of treatment with BT-A on function, assessed by the Action Research Arm Test, although spasticity was significantly reduced as was pain at one-year following injection.

Several trials assessed the effect of several doses of botulinum toxin compared with placebo (Bakheit et al. 2000, Simpson et al. 1996, Smith et al. 2000, Childers et al. 2004, Suputtitada & Suwanwela 2005). Due to the small sample sizes, many of the authors of these studies grouped the treatments together and compared the effects with the placebo. This approach presented difficulties when attempting to determine if escalating doses were associated with greater reductions in spasticity. Generally all doses of BT resulted in reduction in muscle tone; however, increasingly higher doses were associated with muscle weakening.

A summary of the results from the RCTs, all of good quality, is presented in Table 2.

Table 2. Summary of Botulinum Toxin Injection and Spasticity in the Treatment of Upper Extremity Post Stroke

Author/ PEDro Score	n	Intervention	Main Outcome(s) Result
Kaji et al. 2010 9	109	120 U Botox vs. placebo & 200 U Botox vs. placebo	Modified Asworth Scale (+ hi dose Botox vs. placebo, - low dose Botox vs. placebo) Disability Assessment Scale (+ both groups)
McCrory et al. 2009 9	96	500-1,000U of Dysport vs. placebo x 2 occasions	The Assessment of Quality of Life scale (- at week 20)
Shaw et al. 2011	333	100-200 U Dysport + 4 weeks therapy vs. therapy only	ARAT scores (-) Modified Ashworth Scale (+)
Kanovsky et al.	148	Median of 320 U Zeomin vs. placebo	Ashworth Scale scores (-/+)

2009 8 (RCT)			
Bakheit et al. 2000 8	82	500 U of Dysport vs. 1000 U of Dysport vs. 1500 U of Dysport vs. placebo	Modified Ashworth Scale (+ for all three groups at wk 4 and week 16 in the elbow and wrist and in the fingers in the 1000U group compared to placebo group) Rivermead Motor Assessment (- at 4 and 16 weeks)
Bakheit et al. 2001 8	59	Total of 1000 IU of BtxA (Dysport) into 5 muscles of the affected arm vs. placebo injections	Summed Modified Ashworth Scale score (+ at week 4) Magnitude of benefit in wrist and finger joints (+ over 16 wk follow-up period) Joint ROM (- at wk 4) Muscle pain (- at wk 4) Goal-attainment (- at wk 4) Barthel Index (- at wk 4) Elbow PROM (+ at 16 wks)
Simpson et al. 1996 8	37	Single treatment of 75 units vs. 150 units vs. 300 units of BTX-A or placebo	Decrease in wrist flexor tone (+ in 300 BTX-A group at 2,4 and 6 wks post-injection) Global Assessment of Response to Treatment (+ with all BTX-A groups at 4 and 6 wks post-injection)
Simpson et al. 2009 8	60	Up to 500 U of BT-X vs tizanidine vs. placebo	Decrease in wrist flexor tone (+ at 6 weeks-favouring BT-X)
Bhakta et al. 2000, 2008 7	40	Total of 1000 IU Dysport (n=20) vs. placebo (n=20) divided between elbow, wrist, and finger flexors.	Disability (+ at 2 & 6 weeks) Caregiver burden (+ at 2, 6 & 12 weeks) MAS (finger) (+ at 2,6 & 12 weeks) MAS (elbow) (+ at 2 weeks) Pain (-) Associated reactions (+)
Brashear et al. 2002 7	126	Injection of botulinum toxin A (50 units) vs. placebo	Disability Assessment scores (+ at 6 weeks)
Smith et al. 2000 7	25	500 units vs. 1000 units vs. 1500 units of botulinum toxin or placebo	Modified Ashworth Scale at fingers (+ for all botulinum groups) Passive range of movement at wrist (+ for all botulinum groups) Finger curl distance at rest (+ for all botulinum groups) Only significant difference between dose groups was seen in improved movement at

			the elbow (+ 1500 Mu group)
Francisco et al. 2004 7	13 (10 stroke)	High volume BTX-A (50 units/1 mL saline:1.2 mL delivered per 4 muscles) vs. low volume BTX-A (100 units/1 mL saline)	Modified Ashworth Scale (-at 4, 8 and 12 weeks post injection)
Brasher et al. 2004 7	15	10000 U of BTX-B or placebo	Modified Ashworth scale (+ at week 2, - at weeks 4, 8, 12, and 16) Global Assessment of Change (-)
Childers et al. 2004 7	91	Up to 2 treatments of placebo, or 90, 180, or 360U of BTX.	Muscle tone (+ at weeks 1-6) FIM (-) SF-36 (-)
Meythaler et al. 2009 6	21	100 U Botox + therapy vs. saline + therapy	Motor Activity Log (Quality of Use) (+) Motor Activity Log (Amount of Use) (-) Asworth Scale (-)
Sun et al. 2010 6	32	1,000 U Dysport + mCIMT vs. 1,000 U Dysport + conventional rehab	MAS (+) Motor Activity Log (amount of use) (+)
Jahangir et al. 2007 6	27	50 U Botox vs. placebo	Modified Ashworth Scale (+ at 3 months) Barthel Index (-) EQ-5D (-)
Suputtitad & Suwanwela 2005 6	60	Single dose of either placebo or one of 3 doses of BTX-A (350, 500 or 1,000U)	Modified Ashworth scale (+ in 500 and 1,000 U groups) ARAT (+ at 8 and 24 weeks 500 U) BI (+ at 8 and 24 weeks 500 U)

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups

Conclusion Regarding Botulinum Toxin Injection in the Upper Extremity

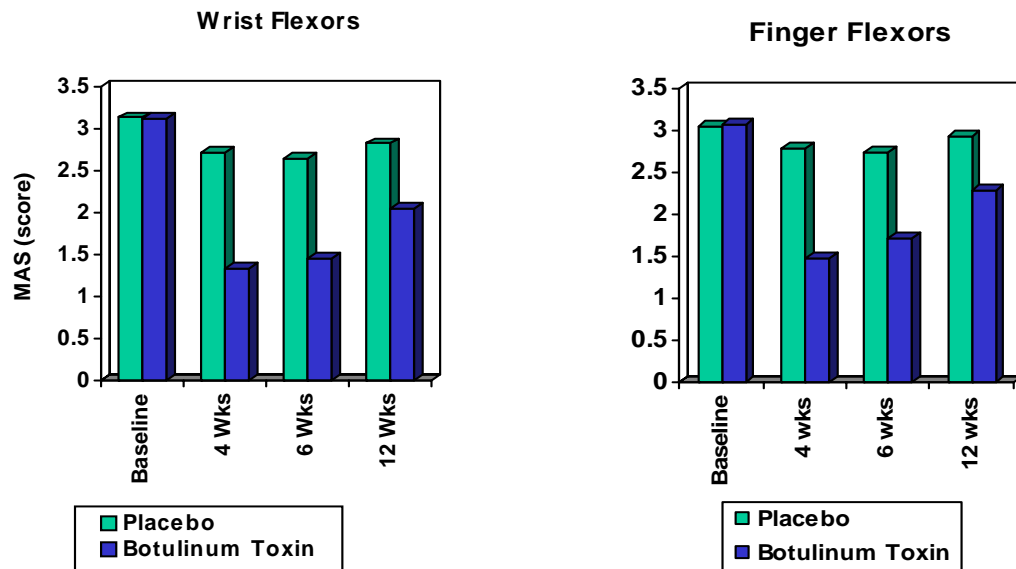
There is strong (Level Ia) that treatment with BT alone or in combination with therapy significantly decreases spasticity in the upper extremity in stroke survivors. However, it is not clear that the improvements are

sustained, nor is there strong evidence that they are associated with improved function and quality of life.

Botulinum toxin is significantly associated with decreased spasticity, increased range of motion and improved upper extremity function.

Figure 1. Changes in Wrist and Finger Flexor Muscle Tone with Botulinum Toxin (Brashear et al. 2002)

A randomized, double-blind, placebo controlled, multi-center trial investigated the efficiency and safety of one-time injections of botulinum toxin A in 126 subjects with increased flexor tone in the wrist and fingers after a stroke. Muscle tone was measured with the use of the Ashworth Scale. Scores range from 0 (no disability) to 4 (rigid flexion).



MAS(score) is short for Modified Ashworth Scale. Scores for the wrist were statistically significant ($p < 0.001$) at 4, 6, and 12 weeks follow-up. Ashworth Scale scores for the fingers were also statistically significant ($p < 0.001$) at 4, 6, and 12 weeks follow-up.

2.3 Electrical Stimulation Combined with Botulinum Toxin Injection in the Upper Extremity

A single study evaluated the efficacy of botulinum toxin injection combined with electrical stimulation. The results are presented in Tables 3 and 4.

Table 3. Electrical Stimulation Combined with Botulinum Toxin Injection in the Upper Extremity

Author/ Country Pedro Score	Methods	Outcomes
Hesse et al. 1998 Germany 7 (RCT)	A placebo controlled trial of 24 patients randomized to one of four groups: 1000unit BTX-A + electrical stimulation (Group A); 1000 units of BTX-A (Group B); Placebo + electrical stimulation (Group C); and Placebo (Group D). Intra-muscular injection of either BTX-A or placebo into six upper limb flexors. Electrical stimulation of the injected muscles with surface electrodes, was conducted three times, 1/2 hr each day for three days (Group A and C).	Significant muscle tone reduction of the elbow joint was most prominent for Group A. Group A experienced fewer difficulties while cleaning the palm of the hand, when compared to Group B and Group D. Patients in the BTX-A groups experienced fewer difficulties when putting the involved arm through a sleeve, compared to patients in groups C & D.

Discussion

A single trial evaluated the effect of botulinum toxin combined with electrical stimulation (Hesse et al. 1998). Although the sample size

was small, there was a reduction in tone in the elbow among patients in the main treatment group. Patients in this group also demonstrated improved performance on certain activities of daily living.

Table 4. Summary of Combined Therapy with Botulinum Toxin Injection in the Upper Extremity

Author/ PEDro Score	N	Intervention	Main Outcome(s) Result
Hesse et al. 1998 7 (RCT)	24	1000unit Btx A + electrical stimulation (Group A) vs. 1000 units of Btx A (Group B) vs. Placebo + electrical stimulation (Group C) vs. and Placebo (Group D).	Muscle Tone Reduction (- elbow joint for group A) Reduction in difficulties while cleaning palm (+ group A compared to group B and D) Difficulties putting arm through a sleeve (+ reduction between botulinum groups and placebo)

- Indicates non-statistically significant differences between treatment groups

+ Indicates statistically significant differences between treatment groups

Conclusions Regarding Treatment of Spasticity: Botulinum Toxin Injections

There is moderate (Level 1b) evidence that electrical stimulation combined with Botulinum Toxin injection is associated with reductions in muscle tone.

Botulinum toxin in combination with electrical stimulation improves upper extremity function.

subluxation (Crossens-Sills and Schenkman 1985, Moskowitz et al. 1969b, Savage and Robertson 1982, Shai et al. 1984), shoulder contractures or restricted shoulder range of motion (Bloch and Bayer 1978, Braun et al. 1981, Fugl-Meyer et al. 1975, Crossens-Sills and Schenkman 1985, Hakuno et al. 1984, Risk et al. 1984) and spasticity, particularly of the subscapularis and pectoralis muscles (Braun et al. 1981, Caldwell et al. 1969, Moskowitz 1969a, 1969b). Other suggested causes of shoulder pain include reflex sympathetic dystrophy or injury to the rotator cuff musculotendinous unit.

3.0 Hemiplegic Shoulder

3.1 Causes of Hemiplegic Shoulder Pain

Although many etiologies have been proposed for hemiplegic shoulder pain, increasingly it appears to be a consequence of spasticity and the sustained hemiplegic posture. Shoulder pain may be more common among patients with neglect following stroke (Kaplan 1995). Factors most frequently associated with shoulder pain are shoulder (glenohumeral)

3.2 Management of the Painful Hemiplegic Shoulder

Management of the painful hemiplegic shoulder, once the condition has developed, is difficult and response to treatment is frequently unsatisfactory (Risk et al. 1984). The best treatment approach has not been definitely established, in part, due to the uncertainty of the etiology of the pain.

As a result, a wide variety of treatments have been used, with varying degrees of success (Snels et al. 2002). Ideally, measures should be taken immediately following stroke to minimize the potential for the development of shoulder pain. Early passive shoulder range of motion, and supporting and protecting the involved shoulder, in the initial flaccid stage are regarded as important steps to reduce the development of shoulder pain.

3.3 Botulinum Toxin as Treatment For Muscle Imbalance

Subscapularis spasticity is characterized by shoulder range of motion being most limited with pain being reproduced on external rotation. This appears to correlate well with hemiplegic shoulder pain that is now thought to be a consequence of spastic muscle imbalance about the shoulder in many cases. Pectoralis muscle spasticity, characterized by limitation of range and pain on shoulder abduction, is seen to a lesser extent, causing a similar muscle imbalance. Intra-articular injections of steroids, botulinum toxin and other agents have been used in an effort to treat spastic muscles, redress the imbalance and to relieve hemiplegic shoulder pain.

Table 5. Injections for Muscle Imbalance in Hemiplegic Shoulder

Author, Year Country PEDro Score	Methods	Outcomes
Hecht 1995 No Score	Prospective study of 20 patients receiving botulinum toxin muscle blocks to the subscapular and pectoralis major musculature.	85% benefited from subscapularis block, and 55% benefited from pectoralis major block and 45% showed improved active ROM.
Bhakta et al. 1996 UK No Score	17 patients received a single course of intramuscular botulinum toxin to biceps brachii, flexor digitorum profundus, flexor digitorum superficialis and flexor carpi ulnaris.	Shoulder pain improved in 6 of 9 patients with shoulder pain.
Yelnik et al. 2007 France 7 (RCT)	20 hemiplegic patients with upper limb spasticity due to stroke were randomly assigned to receive either one injection of Botulinum toxin A (BT-A; 500 units) (n=10) or placebo (n=10) in the subscapularis muscle. Non-standardized physical therapy was given to both groups on weekdays. Pain was measured using a 10-point visual analogue scale.	Pain decreased from 7.5 to 1.5 by week 4 in the treatment group and from 5.5 to 4 in the control group (p=0.025). There was also significant improvement in lateral rotation (mean 12.5% vs. -2.5%, p=0.018), but not for change in abduction observed in the treatment group (70% vs. 72.5%).
Kong et al. 2007 Singapore 8 (RCT)	17 patients recruited from an outpatient clinic with spastic shoulder pain resulting from a stroke that occurred more than 3 months later were randomized to receive a single injection of 500 U of Dysport (n=8) or saline placebo (n=9), injected into the pectoralis major and biceps brachii. Pain was the primary outcome assessed on a 10 point VAS at 4 weeks following treatment. Muscle tone and	At week 4 there was no significant difference in the resolution of shoulder pain between the groups. (Dysport: median VAS decreased from 6 to 4, placebo: decreased from 6 to 3). Subjects who received Dysport showed significantly greater improvements in median shoulder adductor and elbow flexor Ashworth Scale scores than placebo at week 4 but not at week 8 and 12.

	passive range of shoulder abduction were also assessed at weeks 4, 8 and 12.	
Marco et al. 2007 Spain 8 (RCT)	31 patients with moderate to severe spastic shoulder pain, 3 or more months post stroke, admitted for inpatient rehabilitation were randomized to receive treatment with either TENS (short pulses of high frequency and low intensity for 6 weeks) + 500 U of Dysport injected into 4 sites of the pectoralis major muscle of the paretic side under EMG guidance (n=16), or TENS + placebo (n=15). Pain was assessed on a 100 point VAS at 1 week, 1, 3 and 6 months. Other outcomes assessed included spasticity (MAS) and shoulder range of motion (flexion, abduction, and external rotation)	Pain was reduced significantly more among patients in the treatment group by the end of 6 months (76.4 to 30.1 vs. 70.1 to 48.3, time x treatment interaction p = 0.035). The degree of external rotation was also increased significantly more among patients in the treatment group (7.9 to 38.9 vs. 6.7 to 19.3, group x time interaction, p=0.041). There were no other statistically significant differences between the groups.
De Boer et al. 2008 The Netherlands 6 (RCT)	22 stroke patients with spastic hemiplegia, substantial shoulder pain and reduced external rotation of the humerus were randomized to receive a single injection of either botulinum toxin A BT-A (2x50 units) or placebo applied to the subscapular muscle at two locations. Pain was scored on a 100 mm vertical Visual Analogue Scale (VAS); external rotation was recorded by means of electronic goniometry. Assessments were carried out at 0 (baseline), 6 and 12 weeks	While pain decreased over time in both groups, there was no significant treatment effect of BT-A. Similarly, external rotation improved significantly over time with no between group difference.
Lim et al. 2008 South Korea 9 (RCT)	29 stroke patients with shoulder pain were randomized to receive intramuscular injections of i) Botulinum toxin (BT-A) (100 U total) during one session to the infraspinatus, pectoralis and subscapularis muscles in conjunction with an intraarticular injection of normal saline to painful shoulder joint (n=16), or an intraarticular injection of triamcinolone acetonide (TA) (40 mg) and an intramuscular injection of normal saline to the same muscles. Outcome measures were pain (measured using a numeric rating scale), physician's global rating scale, shoulder range of motion (ROM) in 4 directions, arm function measured using Fugl-Meyer score, and spasticity measured using the modified Ashworth scale. Measurements were made at baseline and 2, 6, and 12 weeks after injection.	At 12 weeks after treatment mean decrease in pain was 4.2 in the BT-A group and 2.5 in the TA-treated group (p=0.051), and improvements in overall ROM were 82.9 degrees versus 51.8 degrees in these groups (p=0.059). There were no significant differences between the 2 groups in terms of improvement in physician global rating, Fugl-Meyer score or modified Ashworth scales.

Pedreira et al. 2008 Brazil No Score	In an open label study, 15 patients with spastic hemiparesis secondary to stroke received a single injection of BT-A (average dose 280 IU). Assessments were performed at 1, 2 and 4 months after treatments and included pain (0-10 visual analog scale) and goniometry (abduction, extension, flexion and rotation). All subjects received physical therapy.	The mean pain score was reduced non-significantly over the study period (from 8 to 6); however, there was a significant improvement in flexion and rotation.
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Discussion

Six RCTs, all of good quality assessed the efficacy of botulinum toxin in the treatment of hemiplegic shoulder. The subscapularis muscle was the most common injection site. The inclusion criteria were generally strict which resulted in small sample sizes, and suggests that the trials may not have been adequately powered. The heterogeneity of treatments and doses hinder the process of formulating conclusions. The two trials that demonstrated a benefit of treatment in

terms of pain reduction (Marco et al. 2007, Yelnik et al. 2007) used either a higher dose of Botox or added treatment with TENS. In the single trial that compared triamcinolone acetonide with botulinum toxin are difficult to interpret since subjects in each group improved (Lim et al. 2008). Despite a lack of statistical significance, the authors of this trial suggested that treatment with Botulinum toxin was still superior and the effects longer lasting. The results from these trials are summarized below.

Table 6. Summary of RCTs Evaluating Botulinum Toxin

Study/PEDro	n	Interventions	Outcome
Lim et al. 2008 9	29	triamcinolone acetonide (40 mg) vs. 100 Botox-A	Pain (-) Range of Motion (-)
Kong et al. 2007 8	17	500 U Dysport vs. placebo	Pain (-) Modified Ashworth Score (-) Range of motion (-)
Marco et al. 2007 8	31	TENS + 500 U Dysport vs. TENS + placebo	Pain (+) Modified Ashworth Score (-) Range of Motion (+/-)
Yelnik et al. 2007 7	20	500 U Botox vs. placebo	Pain (+) Range of Motion (+/-)
De Boer et al. 2008 6	22	100 U Botox vs. placebo	Pain (-) Range of motion (-)

Conclusions Regarding Motor Block for Muscle Imbalance

There is conflicting (Level 4) evidence that botulinum toxin injected into the subscapularis muscle reduces spastic

shoulder pain or improves passive range of motion of the hemiplegic shoulder.

There is moderate (Level 1b) evidence that intra-articular steroid injections do

not improve either pain or passive range of motion associated with the hemiplegic shoulder.

Deinnervation of the subscapularis muscle using botulinum toxin may reduce shoulder pain and improve passive range of motion, more so than deinervation of the pectoralis major muscle.

4.0 The Use of Botulinum Toxin in the Lower Extremity

Although not as well studied as the use of botulinum toxin for the treatment of spasticity in the upper extremity, several RCTs have evaluated the efficacy of BT in the lower extremity. The treatment contrasts varied considerably between studies, which included: BT vs. placebo, BT vs. phenol and different dosing levels of BT. The results are presented in Table 7.

Table 7. Injection of Botulinum Toxin in the Lower Extremity

Author, Year Country PEDro Score	Methods	Outcomes
Burbaud et al. 1996 France 7 (RCT)	In a double-blinded, placebo-controlled trial, 23 adult hemiparetic stroke patients with ankle plantar flexor and foot invertor spasticity received 1 injection of botulinum toxin (BTX) and one of placebo in random, one at day 0 and the other at day 90. Patients were examined at day 0, 30, 90 and 120. Patients were assessed on the Ashworth scale, Fugl-Meyer Scale, gait velocity and a self-report of treatment efficacy.	Patients reported subjected improvement in foot spasticity after BTX but not after placebo injection. Significant changes noted on the Ashworth scale values for ankle extensors and invertors and for active dorsiflexion after BTX injection. BTX was less effective in patients with longer duration of spasticity.
Childers et al. 1996 USA 7 (RCT)	Double blind trial of 17 patients randomized to either Group 1 receiving BTX-A at mid belly of the gastrocnemius or to Group 2 receiving BTX-A at the proximal portion of muscle located distal to the popliteal fossa. A placebo was injected at the alternative site in both groups.	No significant differences were noted between the two treatments on any of the outcome measures.
Hesse et al. 1996 Germany No Score	12 patients were injected with 400 U botulinum toxin A into the soleus and tibialis posterior muscles and both heads of the gastrocnemius muscle.	9 of 12 patients improved with reduction of spasticity, improved gait ability and more normal temporal pattern of muscle activity with a prominent reduction of the premature activity of the plantar flexors. Significant improvement in gait velocity, stride length, and cadence was observed.
Kirazli et al. 1998 Turkey 8 (RCT)	Double blind trial of 20 patients randomized to receive either 400 units of botulinum toxin Type A into the calf muscles or to receive a tibial nerve blockage with 3 ml of 5% phenol.	Significant improvement for dorsiflexion and eversion for BTX-A observed at week 2 and 4. Significantly better Global Assessment scores at weeks 2, 4, 6, 8 for BTX-A but no significant difference between groups at week 12.
Reiter et al. 1998	Single blind trial of 18 patients randomized to receive either EMG-	Group A showed greater gains in dorsiflexion at rest and after passive mobilization.

Italy 5 (RCT)	guided injection of 190 to 320U of BTA diluted with saline to a concentration of 5U/0.1mL in 3 to 5 muscles (group A) or to receive a fixed doses or 100U of BTA into two points of tibialis posterior muscle alone followed by ankle-foot taping (group B).	Benefits of treatment persisted in 7 group A patients at 3 months whereas it vanished in 6 group B patients. Gait velocity showed an average increase of 17% in group A and 23 % in group B. Step length increased by an average of 21% in group A and 29% in group B.
On et al. 1999 Turkey 5 (RCT)	Patients with ankle plantar flexor and foot invertor spasticity secondary to stroke and who demonstrate severe spasticity that did not respond to conventional treatment were randomized to receive either a single treatment of BTX-A or 3 ml of 5% phenol. Patients were evaluated by using the Ashworth scale, and electrophysiologic studies measured the amplitudes of the Achilles tendon response (ART), M response, H reflex response and maximum H:M ratio and Achilles tendon response to H response ration from the soleus muscle at baseline and at weeks 2, 4 and 12.	Both BTX-A and phenol treatments caused a reduction in plantar flexor spasticity as assessed by the Ashworth scale, however decrease more significant at weeks 2 and 4 in the BTX-A group. Reduction in ATR after BTX-A was significantly greater than decrease noted in the phenol group. Decrease in M-response and H reflex amplitude was greater in the phenol group than the BTX-A group ART:H ratio reduced in the BTX group at weeks 2 and 4 but significantly increased in the phenol group at all visits.
Pittock et al. 2003 8 (RCT)	In a double-blind, placebo-controlled, dose-ranging study, 234 patients with hemiparesis with spastic equinovarus deformity of the ankle after stroke were randomized to one of 4 treatment groups: 500 units of Dysport; 1000 units of Dysport; 1500 units of Dysport and placebo. Patients were assessed every 4 weeks over a 12-week period.	Distance covered during 2-minute walking test significantly increased in each group, but there were no differences between groups. Significant improvement in calf spasticity, limp pain reduction in use of walking was noted in the Dysport groups relative to the control group.
Mancini et al. 2005 Italy 6 (RCT)	45 patients with chronic stroke and lower-limb spasticity were randomized to receive one of 3 injection of Botox: i) low dose,ii) medium dose and iii) high dose. Evaluations included Modified Ashworth Scale, Medical Research Council Scale and gait velocity, as well as a visual analogue scale (VAS) for gait function and pain and were conducted at baseline, week 4 and 4 months.	Groups 1, 2 and 3 received a total Botox dose of 167 U, 322 U and 540 U, respectively. All groups had improved by 4 weeks, but patients in groups 2 and 3 only retained the beneficial effects. Patients in group 3 reported more adverse effects.
Caty et al. 2008 Belgium No Score	20 chronic hemiparetic poststroke patients with stiff knee gait and ability to walk on a treadmill received a single injection of botulinum toxin (BT) BT was injected into several spastic muscles: the rectus femoris (200 U), semitendinosus (100 U) and triceps surae (200 U). Asworth scale scores were assessed before and 2 months after the injection.	BT injection was associated with reduced rectus femoris muscle tone (median value of 2 [1 to 2.5] to 0 [0 to 1]; p<0.001), and reduced semitendinosus muscle tone (1 [1 to 1.5] to 1 [0 to 1]; p<0.001).

Kaji et al. 2010b) Japan 9 (RCT)	120 patients from 19 medical institutions with lower limb spasticity following stroke > 6 months previously were randomized to a single treatment of 300 U BoNTA or placebo. Assessments were conducted bi-weekly from baseline to 12 weeks following treatment and included MAS of the ankle flexor, gait pattern scale using the Physician Rating Scale (-1 to 9/limb), Gait speed (10-m timed walk) and clinical global impression (-5 to +5).	There was a significant mean reduction in MAS scores at weeks 4, 6 and 8 in the treatment group compared with the control group; however, there were no significant differences between groups at week 10 or 12. Significant improvement in the Clinicians Global Impression was noted by the investigator at weeks 4, 6 and 8 (p = 0.016-0.048), but not by the patient or physical/occupational therapist. There were no other significant differences between groups.
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Discussion

Studies evaluated a variety of interventions and outcomes, making conclusions difficult. Only three RCTs compared the effects of BTx to a placebo (Burdaud et al. 1996, Pittock et al. 2003, Kaji et al. 2010b). All reported an improvement in spasticity, but not function (Figure 2). Two

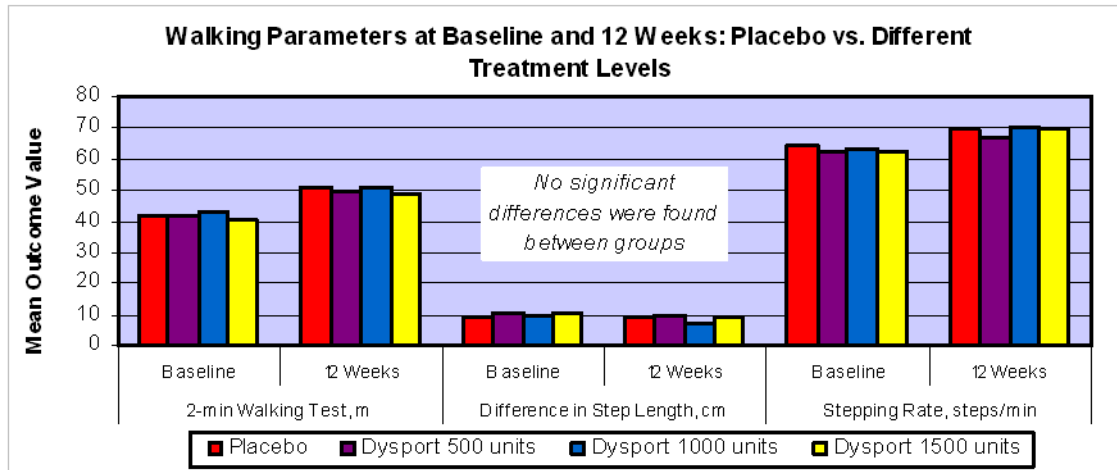
studies compared BTx injection to a phenol block (Kirazli et al. 1998, On et al. 1999), with mixed results in terms of measures of spasticity, while function was not evaluated. Mancini et al. (2005) compared different levels of dosing and reported that all levels were associated with a significant reduction of spasticity.

Table 8. Summary of RCTs evaluating the Effectiveness of Botulinum Toxin (BTx)

Author/ PEDro Score	Intervention (n)	Improvement in Spasticity	Improvement in Function
Kaji et al. 2010b) 9	BTx vs. placebo (120)	+ (Weeks 4,6,8) - (Weeks 10, 12)	-
Pittock et al. 2003 8	BT x (3 dosing levels vs. placebo) (234)	+	-
Kirazli et al. 1998 8	BTx vs. phenol (20)	+ (Weeks 2-4) - (Weeks 8-12)	N/A
Burbaud et al. 1996 7	BTx vs. placebo (23)	+	-
Childers et al. 1996 7	BTx at 2 different sites (21)	-	-
Mancini et al. 2005 6	BTx (low vs. med. vs. high dose)(45)	+ (all levels)	+
On et al. 1999 5	BTx vs. phenol (20)	+	N/A
Reiter et al. 1998 5	BTx (one vs. four muscles) (18)	+	N/A

Figure 2. 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. (Pittock et al. 2003)

234 stroke patients with hemiparesis and spastic equinovarus deformity of the ankle were randomized to one of 4 treatment groups: 500 units of Dysport; 1000 units of Dysport; 1500 units of Dysport and placebo. Patients were assessed every 4 weeks over a 12-week period.



Distance covered during the 2-minute walking test significantly increased in each group, but there were no between-groups differences. Significant improvement in calf Spasticity and limb pain reduction in use of walking was noted in the Dysport groups relative to the control group.

Conclusions Regarding Botulinum Toxin in the Lower Extremity

There is strong (Level 1a) evidence that deinnervating muscles, in the lower extremity, with Botulinum toxin reduces spasticity.

There is conflicting (Level 4) evidence whether such deinnervation improves functional outcomes.

Deinnervating lower extremity muscles with botulinum toxin reduces spasticity, but has not been shown to improve function.

4.1 Electrical Stimulation Combined with Botulinum Toxin Injection in the Lower Extremity

Three studies evaluated the efficacy of botulinum toxin injection combined with electrical stimulation. The results are presented in Tables 9 and 10.

Table 9. Electrical Stimulation Combined with Botulinum Toxin Injection in the Lower Extremity

Author, Year Country PEDro Score	Methods	Outcomes
Johnson et al. 2002/2004 UK 6 (RCT)	21 ambulatory adults within 1 year after stroke with a spastic drop foot were randomized to receive normal physiotherapy + a single Botox injection (Dysport) into the medial and lateral heads of the gastrocnemius (200U each) and tibialis posterior (400U each) muscles and FES, daily x 12 weeks or to physiotherapy alone. The main outcome measures included: walking speed, Physiological Cost Index, Modified Ashworth Scale, Rivermead Motor Assessment, and Medical Outcomes Study 36-Item Short-Form Health Survey.	Walking speed increased over 12 weeks in both control (P=.020) and treatment groups (nonstimulated, P=.004; stimulated, P=.042). The baseline corrected (analysis of covariance) increase in mean walking speed at 12 weeks, relative to controls, was .04m/s without stimulation, and .09m/s with stimulation.
Bayram et al. 2006 Turkey 6 (RCT)	12 chronic stroke patients with spastic drop foot were randomly assigned to receive low-dose (100 units) botulinum toxin (BT) injection to the posterior tibial muscle in combination with short-term electrical stimulation (n = 6) or high dose BT injections in equal doses to the posterior tibial, soleus, medial, and lateral gastrocnemius muscles (n=6). Evaluations included resting position angle, active and passive ankle range of motion, Modified Ashworth Scale, time walking 10 m, clonus score, Brace Wear Scale, and Global Assessment of Spasticity Scale and were conducted at baseline and 2, 4, 8, and 12 wks after the treatment.	No significant difference was found between the study groups after treatment. There was significant within group improvement in all study parameters in both groups. Improvement in spasticity following high dose BT treatment was maintained for a longer period of time; however, functional improvement and patient satisfaction were sustained until the end of the study in both groups.
Baricich et al. 2008 Italy 5 (RCT)	24 chronic stroke patients received 500 IU of Dysport into the gastrocnemius muscle and were then randomized to one of 3 additional therapy groups: taping (maintained for 5 days), electrical stimulation (30 min, 5x/week) or stretching (30 min x 7 days). Subjects were evaluated before treatment (t0), and at 10 (t1), 20 (t2) and 90 (t3) days after treatment. Outcome measures were: Modified Ashworth Scale (MAS); passive range of motion (PROM) at the ankle;	Mean MAS scores were lowest in the ES group at t1. The taping and electrical stimulation groups performed better in all outcome measures at t3. The taping group performed better mainly for maximum ankle dorsiflexion angle in stance. The stretching group showed a less durable result, with some worsening at the t3 evaluation compared with the assessment performed before treatment.

	measurement of muscle action potential at the gastrocnemius medialis; and measurement of maximum ankle dorsiflexion angle in stance using gait analysis.	
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Discussion

Bayram et al. (2006) evaluated the effects of 2 treatments simultaneously (BT + FES) but did not use a factorial design and the sample size was very small (n=12). Therefore the effect of two levels of BT treatment was impossible to distinguish. Johnson et

al. (2002) reported that a combination of BT and FES resulted in improvements in both spasticity and function compared to physical therapy alone. Baricich et al. (2008) reported that a combination of BT and FES resulted in improvements in both spasticity and function compared to physical therapy alone.

Table 10. RCTs Examining Botulinum Toxin and FES on the Lower Extremity

Author/ PEDro Score	Intervention (n)	Improvement in Spasticity	Improvement in Function
Johnson et al. 2002/2004 6	BT+ FES vs. Physiotherapy (21)	+	+
Bayram et al. 2006 6	Low-dose BT + FES vs. high dose BT +sham FES (12)	-	-
Baricich et al. 2008 5	BT +taping vs. BT+ electrical stimulation vs. BT + stretching	+ (taping)	+ (taping & es)

Conclusions

There is conflicting (Level 4) evidence that botulinum toxin in combination with electrical stimulation reduces spasticity and improves function.

Botulinum toxin in combination with electrical stimulation may improve spasticity and function.

Summary

- 1. There is strong (Level 1a) evidence that BT used either alone or in combination with therapy, significantly decreases spasticity in the upper extremity of stroke survivors. However, it is not clear that the improvements are sustained, nor is there strong evidence that they are associated with improved function and quality of life.**
- 2. There is conflicting (Level 4) evidence that botulinum toxin injected into the subscapularis muscle reduces spastic shoulder pain or improves passive range of motion of the hemiplegic shoulder.**
- 3. There is moderate (Level 1b) evidence that intra-articular steroid injections do not improve either pain or passive range of motion associated with the hemiplegic shoulder.**
- 4. There is strong (Level 1a) evidence that deinnervating muscles with BT reduces spasticity in the lower extremity. However, there is conflicting (Level 4) evidence as to whether deinnervation improves functional outcome.**
- 5. There is strong (Level 1a) evidence that electrical stimulation, combined with BT can reduce spasticity, both in the upper and lower limbs. However, there is conflicting (Level 4) evidence that a reduction in tone can help to improve functional outcome.**

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