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Critically Appraised Topic (CAT)

Title timing of treatment and prognostic factors

Determining the effectiveness of Botulinum Toxin-A injection combined with upper extremity rehabilitation in improving function in patients with post-stroke spasticity.

Author, Contact Information, Date

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CAT Question

How effective is Botulinum Toxin-A combined with upper extremity rehabilitation in improving function in patients with post-stroke spasticity?

Background: Stroke is the second leading cause of mortality and disease burden in adults over 60 years of age (Demetrios et al., 2013; zit. nach WHO, 2003). Approximately one-third of stroke patients develop spasticity, and of these one-third may require treatment with BoNT-A (Royal College of Physicians, 2009). Having the necessary knowledge to determine who can best benefit from this treatment can therefore have an impact on the quality of life of a potentially large patient group. While the evidence is now clear that BoNT-A decreases spasticity and increases range of motion in combination with an upper extremity therapy program; the literature and national guidelines are unclear rearding improvement in upper extremity function (Foley, 2013; Liepert, 2012; Royal College of Physicians 2009). The Deutsche Gesellschaft für Neurologie state that *some* patients have improved active function following treatment (2012). While the Canadian guidelines state that improvements in range of motion and spasticity do not necessarily result in better upper extremity function (Foley, 2013). The British National Guidelines describe the physiological theory behind potential gains in function: *In some instances the treatment of spasticity may unmask voluntary muscle movement allowing the individual to manage active functional tasks that they were previously unable to perform. More often, however, the underlying weakness of the limb precludes the return to active function (*Royal College of Physicians, 2009). All 3 guidelines recommend a multidisciplinary approach with individualized goals and treatment which can include pain relief, improved range of limb movement, ease of care and, and active or passive functional gain (Foley, 2013; Liepert, 2012; Royal College of Physicians, 2009). Further research is recommended by all authors to further define treatment protocols and patient groups who could benefit from BoNT-A injections combined with a therapy program.
A literature search was completed to determine if further research has been conducted in the past 4 years to gain further insight into prognosis and treatment of this patient group in regards to potential for gains in function.

Summary of Results from the Reviewed Studies

The literature from 2010 onwards supports the guideline statements that BoNT-A combined with upper extremity therapy does improve function in some patients.Foley et al. (2013) state that moderate treatment effect was found for combined therapy and BoNT-A injections and it may improve passive function more than active function. Demetrios et al. (2013) state that there is low level evidence for the effectiveness of outpatient multidisciplinary rehabilitation in improving active function and impairments following Botulunum Toxin A injection for upper limb spasticity in adults with chronic stroke. There is low quality evidence that high intensity training of the affected limb

with mCIMT following Botulinum Toxin A injections improved spasticity, active upper limb function, and achieved high satisfaction in persons with residual motor function, with benefits maintained up to six months. They also state that there is very low quality' evidence that a higher intensity programme of occupational therapy with additional dynamic elbow splinting assisted in maintaining active range of movement at the elbow. And lastly that there is no evidence that task-practice therapy with cyclic FES was superior to task-practice therapy only in improving spasticity or tone and upper limb motor function. The authors suggest future research to include patient's personal goals to determine the effectiveness of multidisciplinary treatment in the clinical setting. This is addressed by Jost et al. (2014), in their open-label post-marketing surveillance prospective study. In a pool of 409 patients from Germany and Austria; 84% of the goals that were set together by the patient and physician were achieved. The authors state that improvement in spasticity translates into meaningful improvement in patient-centred outcomes and that Dysport treatment is effective and well-tolerated. The authors noted a trend that more „passive function" goals were set for persons in later stages post-stroke such as dressing and personal hygiene. Similary, Shaw et al. (2010) conducted a multicentre trial which determined combined therapy and BoNT-A provide enhanced improvement of basic upper limb functional tasks and reduce pain at 12 months. It should be noted that both groups did improve in terms of upper extremity function at 12 months. Further research is also emphasized by all authors.

Summary of the Praxis Relevant Implications and Recommendations

The literature tends to support the use of BoNT-A for functional gains, however passive functional gains are more likely than active functional gains in chronic patients. Functional gains could be expected in patients who are still in the recovery phase following stroke, and that these could potentially be optimized with BoNT-A treatment. The literature reinforces the need for individualized goal-setting in clinical practice with a combined injection and therapy treatment program for optimal results. In regards to therapy interventions, mCIMT is likely superior to neurodevelopmental theory. It can be due to the high intensity of the program which was also cited it as important factor for effective combined therapy and elbow splinting following BoNT-A injection to maintain active range of movement. The RCT BoTULS study not only supported patients with spasticity can benefit from a combination of boNT-A and therapy for functional gain, but that patients also benefit from a stand-alone therapy program. The gains were mostly in terms of basic upper limb functional tasks and pain reduction. I think these results underline the importance that gains can be made, but dramatic results are not to be expected.

Search Strategy for the CAT (including key words, synonyms)

Patient/Client/Group: adults with post-stroke spasticity

Intervention: Botulinum Toxin A injection(s) in the shoulder, elbow, wrist, and/or hand with concurrent upper extremity rehabilitation.

Comparison: Standard upper extremity rehabilitation (occupational and/or physical therapy)

Outcome/s: Improved function interpreted as decreased activity limitations and/or participation restrictions.

Referral Databanks, Websites, and Journals

Search for: „Botulinum“ *and* „stroke“ *and* („upper extremity“ *or* „therapy“ *or* „rehabilitation“ or „spasticity“)

Databanks: Google scholar, OTDBase, Pedro, Cochrane, Medline, National Guidelines Clearinghouse, UK Guidelines: National Electronic Library for Health, Clinical Guidelines Database.

Search Strategy: once 3 national guidelines from 2010 were found for managing post-stroke spasticity; the focus was to find reviews or multi-centre studies which would have been published from 2010 onwards.

Inclusion Critieria

- Multi-centre trials prospective studies, randomized controlled trials, systematic reviews, and meta-analyses published from 2010 onward.
- Study Population: Adults with post-stroke spasticity.
- Outcome measures reflect improvement in function at the level of activity and/or participation.

Exclusion Criteria

- Studies addressing the pediatric population.
- Studies adressing spasticity that was not stroke-induced.
- Studies which assess only contracture, tone or pain management (impairment).

Summary of Studies

	Study 1	**Study 2**	**Study 3**	**Study 4**
Author(s) Year	Demetrios, M., Khan, F., Turner-Stokes, L., Brand, C., & McSweeney, S. (2013)	Foley, N., Pereira, S., Salter, K., Fernandez, M.M., Speechly, M., Sequeira, K., Miller, T., & Teasell, R. (2013)	Jost, W.H., Hefter, H., Reissig, A., Kollewe, K., & Wissel, J. (2014)	Shaw, L., Rodgers, H., Price, C., van Wijk, F., Shackley, P., Steen, N., Barnes, M., Ford, G., & Graham, L. (2010)
Study Design	Systematic Review (3 RCTS included)	Systematic Review and Meta-Analysis	Open-label, Multi-center Prospective Study	Open-label, Multi-center, Randomised controlled trial

Subjects/ Participants	91 Adults with post-stroke spasticity (US and Taiwan)	1000 Adults with post-stroke spasticity	409 Adults with post-stroke spasticity (Austria and Germany)	332 adults with moderate-to-severe post-stroke spasticity
Intervention(s)	**Lai (2009)** – Botulinum Injection & dynamic elbow splinting & occupational therapy **Sun (2010) –** Botulinum injection & mCIMT **Weber (2010) -** Botulinum injection & task-practice therapy & FES	Botulinum toxin injection with 'standard' therapy (4 studies) and 'additional' therapy (12 studies)	Botulinum toxin A injection with physiotherapy and/or occupational therapy	Botulinum toxin A injection with a 4-week upper limb therapy program (one hour 2x/week) and daily home program. Repeated therapy and injection possible every 3 months to max. 12 months.
Comparison - Intervention	**Lai (2009) –** Botulinum injection & occupational therapy **Sun (2010) –** Botulinum injection & Neurodevelopmental therapy (NDT) **Weber (2010) –** Botulinum injection & task-practice therapy	'Standard' therapy(physical and/or occupational therapy). Description is vague.	None	Upper limb therapy program (one hour 2x/week) and home program
Measurements Assessments	**Lai (2009)** – ROM und MAS **Sun (2010)** – MAS, MAL, AOU, QOM, ARAT, Patient satisfaction scale. **Weber (2010)** - MAL-O, ARAT, MAL-SR.	Information extracted from: FIM, Barthel, MAL, Frenchay Arm Test, ARAT, DAS, Rivermead Motor Assessment, Motor Assessment Scale and applied to ICF model	Goal-attainment criteria, satisfaction and effectiveness rating scale (patient and physician perspective)	Barthel ADL, Oxford Handicap Scale, SIS, EQ-5D, upper limb functional activity questions, MAS, Motricity Index, Grip Strength, ARAT, Nine-Hole Peg Test, Upper-limb Pain Scale, COPM
Results	**Lai (2009) –** Very low quality evidence that a higher intensity Occupational therapy program with dynamic splinting of the elbow and botulinum injections assists in maintaining active range of movement at the elbow compared to the control group. **Sun (2010)** – Low quality evidence that mCIMT & Botulinum Injections (compared with NDT) improved spasticity, active upper limb function, high patient satisfaction and benefits maintained at 6 months. **Weber (2010)** – No evidence that FES with therapy was better than therapy alone following botulinum injection for improving spasticity, tone, nor upper limb function.	Moderate treatment effect. Treatment with Botulinum toxin A injection may improve passive function more than active function.	High goal achivement, satisfaction and effectiveness rating (over 84% in all categories). Improvement in spasticity translates into meaningful improvement in patient-centred outcomes and that Dysport is effective and well-tolerated.	Both groups improved in terms of upper extremity function at 12 months. Injections may enhance improvement of basic upper limb functional tasks and reduce pain at 12 months.

CAT Author's Summary of the Study Results and Conclusion

The literature from 2010 onwards supports the guideline statements that BoNT-A combined with upper extremity therapy does improve function in some patients; and some authors provide further insight from the perspective of larger scale studies and reviews.
Foley et al. (2013) combined the results from 16 studies to determine that BoNT-A treatment does improve function post-stroke in their Systematic Review and Meta-Analysis. Evidence for moderate treatment effect was found with large result ranges between studies. The authors suggest that outcome selection influenced the results. Size effects were small when motor activity and activities of daily living were assessed, while size effects were larger for assessments of spasticity. This implies that treatement with Botulinum Toxin A may improve passive function more than active function. The timing of the final outcome (12-24 weeks), doses of Botulinum Toxin A (75-500 units), and outcomes measures (see „Interventions“) were variable in all of the studies. 4 studies assessed level of activity, 1 study assessed participation (quality of life), and the remaining 11 assessed at the level of body function and structures. Only two of the 16 studies fit the criteria for adequate methodological quality (Jaded Scale). 6 of the studies had positive results (indicating improvement), 8 had negative results (no difference with control group), and 2 did not report an activity-related outcomes. Some studies actually indicated a deterioration in activity-level for some individuals. Therefore the positive conclusions of the authors are to be interpreted with caution.
Demetrios et al. (2013) are the most critical in regards to results, following a strict GRADE analysis according to the Cochrane Collaboration Guidelines. The authors state that there is low level evidence for the effectiveness of outpatient multidisciplinary rehabilitation in improving active function and impairments following Botulunum Toxin A injection for upper limb spasticity in adults with chronic stroke. 3 studies were included in the analysis and the following was determined by the review authors:

- There is low quality evidence that high intensity training of the affected limb with mCIMT following Botulinum Toxin A injections, compared with a lower intensity neurodevelopmental therapy programme (following injection), improved spasticity (one MAS point) and active upper limb function (ARAT and MAL) and achieved high satisfaction in persons with residual motor function, with benefits maintained up to six months (Sun 2010).
- There is very low quality' evidence that a higher intensity programme of occupational therapy with additional dynamic elbow splinting (following Botulinum Toxin A injection) assisted in maintaining active range of movement at the elbow in the short-term, compared with occupational therapy only following injection (Lai 2009).
- There is no evidence that task-practice therapy with cyclic FES was superior to task-practice therapy only in improving spasticity or tone (MAS) and upper limb motor function (MAL-Observation, ARAT, and MAL-Self Report) in people with residual motor function, at 12 weeks (Weber 2010).

The evidence for CIMT after BoNT for post-stroke upper limb spasticity, in improving active upper limb function in this review (Sun 2010), is also supported by one cohort study and in another long-term study indicating improvement at 24 weeks and one year (Levy 2007; Wolf, 2006; cited in Demetrios et al., 2013). However, evidence for improvement in active upper limb function after BoNT is supported by a few studies (Rousseaux 2002; Slawek 2005; cited in Demetrios et al., 2013) but not by others (Elia 2009; Shaw 2011; Sheean 2001; cited in Demetrios et al., 2013).
The authors found insufficient evidence for the optimal type and intensity of MD rehabilitation programmes following BoNT for upper and lower limb spasticity, consistent with the current body of literature.The authors suggest to include „real-world“ factors in future research including patient's personal goals and more ecological assessment tools to better determine the effectiveness of multidisciplinary treatment in the clinical setting.

This is addressed by Jost et al. (2014), in their open-label post-marketing surveillance prospective study. In a pool of 409 patients from 85 clinics in Germany and Austria; 84% of the goals that were set together by the patient and physician were achieved. 87% of patients and 86.7% of physicians were satisfied with the results. The therapy goal of pain reduction was achieved in 94.7% of patients, tone reduction was achieved in 94.3%, improvement in administering physio- or occupational therapy was achieved in 93.0%, facilitation of care/hygiene was improved in 89.9%, and improvement in arm mobility was achieved
in 89.2%. The authors state that improvement in spasticity translates into meaningful improvement in patient-centred outcomes and that Dysport treatment is effective and well-tolerated. The authors comment that the patients who achieved goals in terms of „improvement of arm mobility" were a small portion of the group who were mainly in the early stages of treatment post-stroke. The authors noted a trend that more „passive function" goals were set for persons in later stages post-stroke such as dressing and personal hygiene.
Response to treatment was reported as rapid with results noted in most patients at 4 weeks (intermediary visit).
Similary, Shaw et al. (2010) conducted a multicentre trial also in a clinical setting with a large pool of patients. The trial was an RCT and the therapy program was structured with numerous outcome measeures. They concluded that combining botulinum toxin Type A injections with an upper limb therapy program to treat spasticity did not enhance improvement in function compared to an upper limb therapy program when measured at one-month with the ARAT scale (primary outcome measure). However, the combined treatment provided better improvement of muscle tone at 1 month, upper limb strength at 3 months, upper limb functional activities related to undertaking basic functional tasks (at 1,3, and 12 months), and reduced upper limb pain significantly at 12 months. The authors emphasize the importance of setting realistic goals for treatment; and then determining if botulinum toxin A can help the patient reach these goals. They state that the injections combined with therapy may not achieve *enhanced* improvement in active upper limb function. However, it may provide enhanced improvement of basic upper limb functional tasks and reduce pain at 12 months. It should be noted that both groups did improve in terms of upper extremity function at 12 months.
Further research is also emphasized; as they state that the relationship between spasticity and functional limitation is not yet clearly defined and studies are needed to improve measurement of spasticity and upper limb joint movement for clinical practice. Optimal dosage and patterns of injections as well as the efficacy of repeat injection also need to be defined.

Implications for Practice

The literature tends to support the use of BoNT-A for functional gains, however passive functional gains are more likely than active functional gains in chronic patients. Functional gains could be expected in patients who are still in the recovery phase following stroke, and that these could potentially be optimized with BoNT-A treatment. Further research in this area could potentially benefit a large group of patients.
The overwhelmingly positive gains reported in the Jost et al. (2014) article used goal-attainment as their primary outcome; which reinforces the need for individualized goal-setting in clinical practice for optimal results. Furthermore it supports the importance of a combined injection and therapy treatment program to achieve those goals. This echoes the current evidence for multidisciplinary treatment following BonT-A injection cited in the guidelines, and described as „low-level" evidence-based in the Cochrane Review (Foley et al., 2013).
When selecting a therapy intervention following BoNT-A injection for my patients, one should take into consideration that an mCIMT proved better than a neurodevelopmental approach for improving active upper limb function and achieving high satisfaction in person with residual motor

function (and benefits up to 6 months) (Demetrios et al, 2013), keeping in mind that the evidence is considered low quality. A high intensity program seemed to be a recurring theme where Demetrios et al. (2013) cited it as effective in combined therapy and elbow splinting following BoNT-A injection to maintain active range of movement.
The RCT BoTULS study (largest undertaken to date) not only supported patients with spasticity can benefit from a combination of boNT-A and therapy for functional gain, but that patients also benefit from a stand-alone therapy program. Both groups improved with a structured, moderately-intensive therapy program (spanning 4 weeks) which more reflects the every day clinical setting that I am in. The enhanced gains with BoNT-A therapy were mostly in terms of basic upper limb functional tasks and pain reduction. What was most remarkable was that approximately 70% of patients had no function at the beginning of the trial and achieved gains. Perhaps the specific, structured nature of the task-oriented therapy program also had an impact on positive results. Obtaining a copy of their program structure would be interesting to further investigate the constructs of an effective therapy program.
All in all, I think these results underline the importance that gains can be made, but dramatic results are not to be expected. This is important to share with patients who are still in search of an elusive „cure“ for their spasticity and concurrent underlying muscle weakness.

Critical Analysis of a Review / Meta-Analysis

Reference

Demetrios ,M., Khan, F., Turner-Stokes, L., Brand, C., & McSweeney, S. (2013). Multidisciplinary rehabilitation following botulinum toxin and other focal intramuscular treatment for post-stroke spasticity (Review). *Cochrane Database of Systematic Reviews, 6*, 1-40. doi: 10.1002/14651858.CD009689.pub2

Goal / Purpose / Question

To assess the effectiveness of multidisciplinary rehabilitation, following BoNT and other focal intramuscular treatments such as phenol, in improving activity limitations and other outcomes in adults and children with post-stroke spasticity. To explore what settings, types and intensities of rehabilitation programmes are effective.
No studies involving the lower extremity nor children were included in the 3 studies which met the rigorous quality criteria. Therefore this Systematic Review met the CAT criteria.

Review / Meta-analysis Design

The authors cast a broad search strategy to collect 877 randomised controlled trials from the following databases: Cochrane Stroke Group Trials Register (February 2012), the Cochrane Central Register of Controlled Trials MEDLINE, EMBASE, CINAHL, AMED, LILACS, PEDro, REHABDATA and OpenGrey. Additional sources included trial registries, reference lists, handsearched journals in an effort to identify all relevant studies. Once carefully scrutinized, ***only 3 met the following critieria***:

Included trials: RCTs that assessed the effectiveness of MD rehabilitation programmes following BoNT or other focal intramuscular treatment for upper limb or lower limb post-stroke spasticity, or both, with either routinely available local services or lower levels of intervention; or studies that compared MD rehabilitation programmes in different settings, of different types or at different intensities.

Excluded trials: RCTs that assessed the effectiveness of unidisciplinary therapy (e.g. Physiotherapy) or a single modality (e.g. splinting).

Primary outcome measures: validated measures of *activity level* (active and passive function) according to the World Health Organization's International Classification of Functioning, Disability and Health.

Secondary outcome measures: symptoms, impairments, participation, QoL, impact on caregivers and adverse events.

Subject Setting

The 3 RCTs took place in an ambulatory setting where the adult subjects with chronic stroke received a multidsiciplinary rehabilitation program following Botulinum Toxin injections for upper limb spasticity. All three were single-centre trials, 2 of which were completed in the US, and one in Taiwan. All 3 studies had small sample sizes and were considered underpowered by the review authors.

Description of Study Subjects

91 subjects were enrolled in the three studies, of which 82 were included in the analyses (9 drop-outs).

Inclusion criteria for the studies were varied: chronic stroke was defined as greater than six months by Lai (2009) and Sun (2010) while Weber (2010) defined it as over one year following the event. Weber (2010) included persons with TBI in the control group; however they were matched with the treatment group for

cognitive deficits and neurological impairments and all subjects in the treatment group had had a stroke. Moderate or severe upper limb spasticity were defined differently: Modified Ashworth Scale (MAS) ≥ 2 by Lai (2009) and Weber (2010) versus MAS ≥ 3 by Sun (2010). Sun (2010) and Weber (2010) included participants with voluntary upper limb motor activity relying on different criteria for inclusion. Sun's criteria: 10 ° active extension at metacarpophalyngeal and interphalyngeal joints and 20 ° at the wrist. Weber's criteria: the Chedoke McMaster Assessment of hand impairment score of ≥ 2 with ability to do at least 1 of the following stage-3 tasks: active wrist extension greater than half range; active finger/wrist flexion greater than half range; or actively touch thumb to index finger when the hand was placed in supination with thumb fully extended. Lai (2009) focused on elbow spasticity and included participants with range of movement deficits greater than 24% in elbow extension, with no criteria reflecting whether they had functional or non-functional upper limbs.

Intervention(s)

The multidisciplinary programs were diverse and varied in terms of approach, use of modalities as well as frequency and intensity.

Lai (2009): 36 participants received occupational (including manual therapy) and dynamic elbow splinting (vs. occupational therapy alone) following Botulinum Toxin A injections. All participants in received two hours of occupational therapy weekly for 16 weeks. The intervention group additionally had education in using the EED (dynamic elbow splint worn 6-8 hours during sleep) and visits to adjust the device every two weeks.

Sun (2010): 32 participants were divided into two groups to compare modified constraint induced movement therapy (mCIMT) with neurodevelopmental therapy following botulinum Toxin A injections. All participants had 1 hour of occupational therapy and 1hour of physiotherapy three times a week for 3 months. The mCIMT group had a higher intensity of upper limb training since the non-affected limb was restrained for at least five hours per day.

Weber (2010): 23 participants were divided into two groups to compare task-practice therapy (incorporating occupational therapy sessions and a home exercise programme) with cyclic functional electrical stimulation (FES) to facilitate grasp and release versus task-practice therapy *only* following Botulinum Toxin A injection. The control group received six one-hour sessions and the intervention group received seven one-hour sessions of occupational therapy over 12 weeks. All participants were required to do a one-hour daily task practice home exercise programme, during which the intervention group also wore the cyclic FES device.

Outcome Measures:

Lai (2009): Primary outcome: Impairment - mean % change in active range of movement elbow extension and Modified Ashworth Scale (MAS) elbow flexors before and 14 weeks after injection. No outcomes of activity limitations (active or passive upper limb function).

Sun (2010): Primary outcome: impairment - MAS

Secondary outcomes: activity limitation: Motor Activity Log (MAL) amount of use (AOU) and quality of movement (QOM) (questionnaire for patient self report), Action Research Arm Test (ARAT)
Other: patient's global satisfaction with treatment (7-point scale) and adverse events
Time points: before injection, 1, 3 and 6 months.

Weber (2010):Primary outcome: activity limitation: How Well Scale of MAL-Observation (MAL-O).

Secondary outcomes: activity limitation: ARAT, MAL-Self-Report (MAL-SR)
Time points: baseline (2 weeks prior) and 6 and 12 weeks after injection.

Review / Meta-Analysis Method(s)

Combining Results was done qualitatively due to the limited number of studies with clinical, methodoligcal and statistical heterogeniety. Outcome time points, assessment scales, and intervention programs were all different. The review authors independently selected the trials, extracted data, and assessed methodological quality using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) to provide a qualitative synthesis of 'best evidence'. The reviewers graded all three articles as having a high risk of bias and were graded as 'low quality' based on the criteria (underpowered). Lai (2009) and Weber (2010) both acknowledge that the small sample size in their RCT was not adequate to power statistical analysis of variance, meaning that the results must be interpreted with caution.

Review / Meta-Analysis Results

The following was determined by the review authors:

1) There is low quality evidence that high intensity training of the affected limb with mCIMT following Botulinum Toxin A injections, compared with a lower intensity neurodevelopmental therapy programme (following injection), improved spasticity (one MAS point) and active upper limb function (ARAT and MAL) and achieved high satisfaction in persons with residual motor function, with benefits maintained up to six months (Sun 2010).
2) There is very low quality evidence that a higher intensity programme of occupational therapy with additional EED (following Botulinum Toxin A injection) assisted in maintaining active range of movement at the elbow in the short-term, compared with occupational therapy only following injection (Lai 2009).
3) There is no evidence that task-practice therapy with cyclic FES was superior to task-practice therapy only in improving spasticity or tone (MAS) and upper limb motor function (MAL-Observation, ARAT, and MAL-Self Report) in people with residual motor function, at 12 weeks (Weber 2010).

Authors' Conclusion(s)

The authors state that at best there is 'low level' evidence for the effectiveness of outpatient multidisciplinary rehabilitation in improving active function and impairments following Botulunum Toxin A injection for upper limb spasticity in adults with chronic stroke. Further trials are recommended to build evidence, particularly in determining the effect of multidisciplinary rehabilitation on 'passive function' (caring for the affected limb), caregiver burden, and the individual's priority goals for treatment as these were not addressed. Further research is also needed to determine optimal types (modalities, therapy approaches, settings) and intensities of therapy for improving activity (active and passive function) in adults and children with post-stroke spasticity, in the short and longer term as these factors remain unclear.

The authors found insufficient evidence for the optimal type and intensity of MD rehabilitation programmes following BoNT for upper and lower limb spasticity, consistent with the current body of literature. Thus, recommendations advocating integrated multidisciplinary rehabilitation programmes following focal spasticity management are based on expert opinion only.

In regards to CIMT: The evidence for CIMT after BoNT for post-stroke upper limb spasticity, in improving active upper limb function in this review (Sun 2010), is also supported by one cohort study and in another long-term study indicating improvement at 24 weeks and one year (Levy 2007; Wolf, 2006; cited in Demetrios et al., 2013). However, evidence for improvement in active upper limb function after BoNT is supported by a few studies (Rousseaux 2002; Slawek 2005; cited in Demetrios et al., 2013) but not by others (Elia 2009; Shaw 2011; Sheean 2001; cited in Demetrios et al., 2013).

Validity of Review / Meta-Analysis

The authors present quite a long list of limitations affecting the quality of evidence in this review and its' validity:

- The authors find a discrepancy between the emerging evidence for the effectiveness of BoNT (Botulinum Toxin A) in stroke - which is an improvement of passive function and achieving individual goals - (Turner-Stokes 2010c) compared to the studies reviewed. Two of the studies (Sun 2010; Weber 2010) addressed active function in the minority subset of patients with residual upper limb function, for which this is a realistic goal. However stroke survivors have varied clinical presentations, while the inclusion criteria of the reviewed studies was quite strict in regards to residual upper motor activity. Therefore, this evidence cannot be generalised to the heterogeneous stroke population.
- Only generic description of the treatment programs were available, which makes it difficult to apply the protocols in a real-world setting even if one has patients who match the description of the study subjects.
- The subjects were assessed at different time points which makes it difficult to use the information to determine the optimal treatment program length.
- Attrition rates were moderate to high which can further decrease the quality of results which were already low quality.
- Thought the positive results regarding mCIMT training support the current literature regarding this treatment approach, the optimal protocol for mCIMT training for stroke survivors with spasticity is yet to be determined.
- Difference in age and etiology in baseline groups. Weber (2010) included patients with TBI in the control group (39%). Even if they were matched for level of function and cognition, there was no subgroup analysis for TBI vs. Stroke which could also affect the quality of the already low-quality results.
- Inconsistent terminology and definitions for 'spasticity' affecting interpretation of results.
- Inadequate allocation concealment (Lai 2009;Weber 2010).
- High risk of performance bias due to non-blinding of treating therapists and participants (all studies).
- Small sample sizes and underpowered studies. Recruitment from single-centre trials with strict inclusion and exclusion criteria can be limiting.
- difficulty controlling for personal factors such as patient motivation and self-efficacy, and activity level outside of therapy programmes (not assessed in any of the studies).

Personal Conclusion / Interpretation

The authors of the Cochrane review were very rigorous and meticulous in regards to analysing the quality of the studies and present the results with caution in regards to intepreting them for everday practice. Despite this, the authors recommend a multidisciplinary approach to treatment which reiterates expert consensus. They describe the optimal therapy approach remains a „black box" which I find appropriate since so many protocols (or lack of), patient factors, therapy approaches, and modality use come into play that broad, sweeping recommendations for a patient group is certainly not possible following such a review. The authors suggest to include „real-world" factors in future research including patient's personal goals and more ecological assessment tools to better determine the effectiveness of multidisciplinary treatment in the clinical setting. This is addressed by Jost et al. (2014), and addressed in the CAT text.

Critical Analysis of a Review / Meta-Analysis

Reference

Foley, N., Pereira, S., Salter, K., Fernandez, M.M., Speechley, M., Sequeira, K., Miller, T., & Teasell, R.(2013). Treatment with Botulinum Toxin Improves Upper-Extremity Function Post Stroke: A Systematic Review and Meta-Analysis. *Archives of Physical Medicine and Rehabilitation*, 94, 977-989.

Goal / Purpose / Question

To examine whether treatment with botulinum toxin type A (BTX-A) is associated with improvements in activity capacity or performance associated with poststroke spasticity in the upper extremity.

Review / Meta-analysis Design

Systematic Review *and* Meta-analysis. Included: English randomised controlled trials, dating from 1985-2011, that compare injection of Botulinum Toxin A with a placebo or non-pharmacological treatment. Of the 436 articles initally identified, 16 were included in the review. 10 contained data which was combinable for a meta-analysis (1000 subjects). The methodological quality of the RCTs was evaluated using the Jaded Scale.

Subject Setting

The setting was not specified. Some studies included traumatic brain injury patients (<40% of total). Variable doses of Botulinum Toxin A, variable stages of recovery (subacute and chronic) and variable performance levels were described in the heterogeneous mix of studies.

Description of Study Subjects

Adults recovering from a first stroke or subsequent one presenting with moderate to severe spasticitiy (minimum 60% of total sample). Inclusion criteria was generally a Modified Ashworth Scale of 2 or more in at least two joints. Exclusion criteria across all studies included fixed contracture and previous treatment for spasticity. Subjects received injection(s) to the shoulder, elbow, wrist and/or finger compared to a placebo or non-pharmacological treatment followed by an assessment of activity performance or capacity. Average time from stroke in subjects ranged from less than a year to 91 months.

Intervention(s)

Intervention Group: Botolinum Toxin A injection (location and dose based on clinical judgement) in combination with „standard“ therapy in 4 studies and „additional“ therapy in 12 other studies which was poorly described by the authors.

Comparison Group: The comparison-intervention was standard therapy, which included occupational and/or physical therapy (no details of intensity or therapeutic interventions provided by authors).

Outcomes Measures: were described in terms of *activity capacity* or *performance* and were assessed at the level of *1) body function/structure*, *2) activities*, and *3) participation* based on ICF categorization. The studies used different assessments including the: FIM, Barthel, Motor Activity Log, Frenchay Arm Test, Action Research Arm Test, Disability Assessment Scale, and the arm subscale of the a) Rivermead Motor Assessment, b) Motor Assessment Scale.

Review / Meta-Analysis Method(s)

The results were categorized together according to the ICF model to pool more data for analysis, but the authors mention that they could not be translated into clinically meaningful units as a result. The details of the statistics provided by the original authors were also variable, affecting the precision of the reported effect sizes and results of the meta-analysis.

Review / Meta-Analysis Results

The timing of the final outcome (12-24 weeks), doses of Botulinum Toxin A (75-500 units), and outcomes measures (see „Interventions“) were variable in all of the studies. 4 studies assessed level of activity, 1 study assessed participation (quality of life), and the remaining 11 assessed at the level of body function and structures. Only two of the 16 studies fit the criteria for adequate methodological quality (Jaded Scale). 6 of the studies had positive results (indicating improvement), 8 had negative results (no difference with control group), and 2 did not report an activity-related outcomes. Some studies actually indicated a deterioration in activity-level for some individuals.

Authors' Conclusion(s)

Evidence for moderate treatment effect was found with large result ranges between studies. The authors suggest that outcome selection influenced the results. Size effects were small when motor activity and activities of daily living were assessed, while size effects were larger for assessments of spasticitiy. This implies that treatement with Botulinum Toxin A may improve passive function more than active function.

Validity of Review / Meta-Analysis

Combining assessments which are validated for completey different levels and categories of performance resulted in a general statement that a moderate treatment effect was found at the cost of clinically meaningful units. The authors combined the studies since one theory as to why some RCTS did not indicate any effectiveness was that the studies were underpowered.

The authors of this review argue that the Disability Assessment Scale is the best assessment as it was constructed to evaluate upper extremity function following Botulinum Toxin injection. The authors argue that the FIM and Barthel are least effective since they also address many other domains of life including communication, cognition, and mobility.

They also explain the negative results from RCTs with the hypothesis that underlying muscle weakness and dexterity play a larger role than spasticity for upper extremity movement for some patients. Furthermore, some patients have learned new patterns of movement with spastic arm postures, which is no longer possible following injection.

The authors also indicate that they included studies where the baseline functional data was not always provided.

Personal Conclusion / Interpretation

The Disability Assessment Scale may indicate the best results, but passive function is the principal therapeutic target of the scale (hygiene, dressing, limb posture, and pain subsets) which does not, in my opinion, indicate improvement of activities of daily living for many patients. Patients with mild spasticity were *not* included in the study, which excludes an entire group who could potentially benefit and provide positive results. I thinks another weakness of this study is that they do not describe the concurrent therapy program; neither type, frequency, nor intensity. Some RCTs have indicated that the intensity can

have an effect on recovery; a factor ignored by the authors. I find that the authors combined too many variables; chronicity, dosing regimes, injection sites, concurrent therapy, outcomes selected, and timing of assessment of draw any relevant conclusions. Lastly, they did not exclude studies which did not have adequate methodological quality according to the Jaded Scale; certainly affecting the quality of conclusions. On a positive note, I find that allowing physician judgement for dosage and selection of muscles as well as variable therapy intensity reflects the heterogeniety (and reality) of clinical practice.

Critical Analysis of a Quantitative Study

Reference

Jost, W.H., Hefter, H., Reissig, A., Kollewe, K., Wissel, J. (2014). Efficacy and safety of botulinum toxin type A (Dysport) for the treatment of post-stroke arm spasticity: Results of the German–Austrian open-label post-marketing surveillance prospective study. *Journal of the Neurological Sciences,* 337, 86-90.

Goal / Purpose / Question

To evaluate the safety and efficacy of current practice in the treatment of patients with post-stroke arm spasticity in Germany and Austria.

Quantitative Study Design

Design: prospective open-label non-interventional multi-center post-marketing surveillance study. One treatment cycle of Dysport treatment was assessed. There was a baseline functional assessment at the time of injection, 4 weeks (optional), and at 12 weeks. Only subjects who attended all 3 appointments were included in the statistical analysis. Patients and Physicians were not blinded as the study was designed for a „real-world" evaluation of everyday practice.

Subject Setting

409 patients in an outpatient setting at 85 centers in Austria and Germany were assessed. No further details are provided.

Description of Study Subjects

The average time post-stroke was 7 months for the 409 patients. 307 patients attended all 3 appointments and their information was included in the final statistical analysis. 334 patients continued another round of Dysport treatment at 12 weeks. 43.6% of the 75 patients who declined treatment at 12 weeks did so because they were still benefitting from their desired effect.

The subjects were all over 18 and had spasticity due to an apoplexie. They were scheduled to receive treatment or had already received treatment. Subjects with fixed contractures were excluded.

Intervention(s)

Intervention Group: Client-centred goals were set by the physician and subject at the time of injection. The study protocol described 5 patterns of spasticity and related Dysport treatment recommendations; however muscle evaluation and treatment dosing was left ultimately to the physician's discretion. 93.8% received physiotherapy and 56.4% received occupational therapy concurrently.

Control Group: There was no comparison group as the goal of the study was to determine the effectiveness of Dysport treatment and therapy in the real-world setting.

Methodology

Response to treatment was based on whether or not the patients met their treatment goals following injection of Dysport into the shoulder, elbow, wrist, and/or hand in combination with therapy. Goal-attainment criteria were set, as well as a satisfaction and effectiveness rating scale which the subject and the physician responded to separately. The goals were selected by the patient and the physician in

collaboration at the first appointment. They included: tone reduction, improvement of mobility, pain reduction, facilitation of care/hygiene, support of physiotherapy and occupational therapy, and individual functional gain. A descriptive scale was used divided into 4 categories: „Goal achieved", „Good Goal Achieved", „Best Goal Achieved", „No Goal Achieved".

Results

84% of the goals were achieved; 87% of subjects and 86.7% of physicians were satisfied with the results. The therapy goal of pain reduction was achieved in 94.7% of patients, tone reduction was achieved in 94.3%, improvement in administering physio- or occupational therapy was achieved in 93.0%, facilitation of care/hygiene was improved in 89.9%, and improvement in arm mobility was achieved in 89.2%.

Authors' Conclusion(s)

The authors state that improvement in spasticity translates into meaningful improvement in patient-centred outcomes and that Dysport treatment is effective and well-tolerated. The authors comment that the patients who achieved goals in terms of „improvement of arm mobility" were a small portion of the group who were mainly in the early stages of treatment post-stroke. The authors noted a trend that more „passive function" goals were set for persons in later stages post-stroke such as dressing and personal hygiene. Response to treatment was reported as rapid with results noted in most patients at 4 weeks (intermediary visit).

Study Validity

The authors state that severity of spasticity was not statistically analysed as a factor which could influence results. There is no information as to how closely the physicians' adhered to the spasticity treatment guidelines, so they cannot make the correlation between results and spasticity guidelines. However, they argue is that the bottom line is whether or not the patient achieved goals, which was the case.

Personal Conclusion / Interpretation

Though the goal of the study was to analyse treatment effect in the clinical everyday setting; I found that including subjects who had already received Dysport treatment could confound the results since the cumulative effect of treatment was not taken into account.
The intensity of therapy was not mentioned, nor were the rehabilitation goals. It would have been interesting to have included this aspect to gain further insight into the effectiveness of combined therapy and Dysport treatment. A goal category was „improvement in administering physiotherapy or occupational therapy" which I found unusual. While the goal of therapy is not to administer it more easily, but to achieve goals in function and everyday living! „Improvement in physiotherapy or occupational therapy" would make more sense; and I wonder if perhaps it was a translation error.
Lastly the goal categories are not a validated scale such as the „Goal Achievement Scale". There is no option between „no goal achieved" and „goal achieved" but the authors later discuss how some goals were partially achieved. The descriptors are confusing for me, and could have been confusing for the subjects as well.
In general, the study is interesting because it addresses therapy and Dysport treatment effect in everyday practice in a client-centred structure which is relevant to my current practice.

Critical Analysis of a Quantitative Study

Reference

Shaw, L., Rodgers, H., Price, C., Van Wijck, F., Shackley, P., Steen, N., Barnes, M., Ford, G., & Graham, L. (2010). BoTULS: a multicentre randomised controlled trial to evaluate the clinical effectiveness and cost-effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A, *Health Technology Assessment,*14(26), 1-158. DOI: 10.3310/hta14260

Goal / Purpose / Question

The study evaluated the clinical effectiveness and cost-effectiveness of botulinum toxin type A plus an upper limb therapy programme in the treatment of post-stroke upper limb spasticity.

Quantitative Study Design

A multicentre open-label parallel-group randomised controlled trial and economic evaluation. The economic evaluation results will be excluded from the critical analysis since the information does not address the goal of this CAT.

Subject Setting

The setting ecompassed twelve stroke services in northern England linked with the International Centre for Neurorehabilitation, Newcastle upon Tyne. Referrals were received from all stages of the rehabilitation continuum-of-care: stroke units, outpatient clinics, day hospitals, community, rehabilitation teams, stroke clubs and day centres.

Description of Study Subjects

332 adult patients with moderate/severe upper limb spasticity at the shoulder, elbow, wrist or hand and reduced upper limb function due to stroke more than 1 month previously were enrolled in the trial between July 2005 and March 2008. 208 (62%) participants were randomised before July 2007 and entered the trial for 12 months. The remaining 125 (38%) participants were followed for 3 months.

Inclusion Criteria: Spasticity at the elbow must be moderate with a measure of >2 on the Modified Ashworth Scale and/or spasticity must be present in the wrist, fingers, and/or shoulder (no defined scale value). Reduced upper limb function (ARAT score from 0-56). Ability to comply with the requirements of the protocol and upper limb therapy program.

Exclusion Criteria: Significant cognitive or speech impairment which impeded the ability to perform the ARAT. Other upper limb impairment (eg. Arthritis, frozen shoulder). Evidence of fixed contracture. Pregnancy or lactating. Other diagnosis likely to interfere with treatment (eg. Blindness, malignancy). Other diagnosis which causes spasticity. Contraindications to intramuscular injection or Botulinum Toxin type A. Injection of Botulinum in the arm in the last 3 months. Previous enrolment in this study.

Recruitment: Patients were recruited in the rehabiliation centres and stroke units. Further recruitment was done with flyers and advertising at stroke clubs and day centres.

Randomisation: was computerized with the central independent web-based randomisation service from the Clinical Trials Unit, Newcastle University. Participants were first stratified according to research site and level of upper limb function (3 groups: ARAT score 0-3; 4-28; or 29-56). Then they were randomised to intervention or to control in a 1:1 ratio using permuted block sequences. Randomisation groups were well matched in regards to demography, stroke characteristics and comorbidity.

Withdrawal: There were 9 deaths and 12 withdrawals.

Intervention(s)

Intervention Group: received botulinum toxin type A injection(s) (DysportR) combined with a standardized 4-week upper limb therapy program (one hour twice a week). Participants were clinically reassessed at 3, 6 and 9 months to determine the need for repeat botulinum toxin type A injection(s) and/or therapy. This means that some patients received one round of Dysport injections & therapy while others received up to 4 rounds.

Control Group: The control group received the upper limb therapy program (one hour twice a week).

The Upper limb therapy program: was divided into two standardized menus and a home program. The first menu was for subjects with no active function (ARAT score 0-3) and focussed on maintaining range of motion, encouraging active-assisted upper limb movement in the context of functional activities, hand hygiene, and positioning.

The second menu had been previously piloted in a study. It was constructed for subjects with some retained upper limb movement. Following stretching of soft tissues, the program focussed on task-oriented practice aimed at patient-centred goals. The goals were measured by the COPM.

The menus were standardized in terms of: category of tasks, number and order of repetitions, and feedback provided. Within this framework, the clinician had the freedom to tailor the activities to the level of the patient. All clinicans were trained in the use and application of this protocol.

A written home program based on the face-to-face therapy program was given to each patient to carry out daily at home independently or with a caregiver. The subjects were encouraged to continue the proram daily after the 4 week program.

If the patient was already receiving therapy, then the program was given in that setting (eg. Stroke unit, at home) and services were coordinated between the study clinician and regular treating clinician (patient continue concurrent treatment).

All participants were eligible for a repeat 4-week therapy program at 3,6, and 9 months.

Botulinum Injections: The physicians selected the muscles and dosages based on National Health Service Guidelines: „The management of adults with spasticity using botulinum toxin: a guide to clinical practice."

Study Method

Patients and therapists were not blinded (no placebo injection). However, the assessing clinicians who evaluated the patient at 1, 3, and 12 months were blinded.

Each outcome assessment consisted of 2 phases. Stage 1: a postal questionnaire including the Barthel ADL Index, Oxford Handicap Scale, Stroke Impact Scale, EQ-5D, upper limb functional activity questions, and resource utilisation. Stage 2: assessment of upper limb impairment and function with the Modified Ashworth Scale, Motricity Index, Grip Strength, ARAT, Nine-Hole Peg Test, and upper limb pain. The patient was also interviewed to seek information about the participant's experience and views of he study treatment. The Stage 1 questionnaire was reviewed at this time to make sure it was fully completed.

The COPM was re-evaluated only at the one month mark.

Interpretation of assessments: A successful outcome at one month was defined as either 1) A change of 3 or more points on the ARAT for participants whose baseline score was 0-3, 2) a change of six or more points on the ARAT for participants whose baseline score was between 4 and 51, and 3) a final ARAT score of 57 for a participant whose baseline was 52-56. This was considered the primary outcome while all other outcome measures were grouped as secondary.

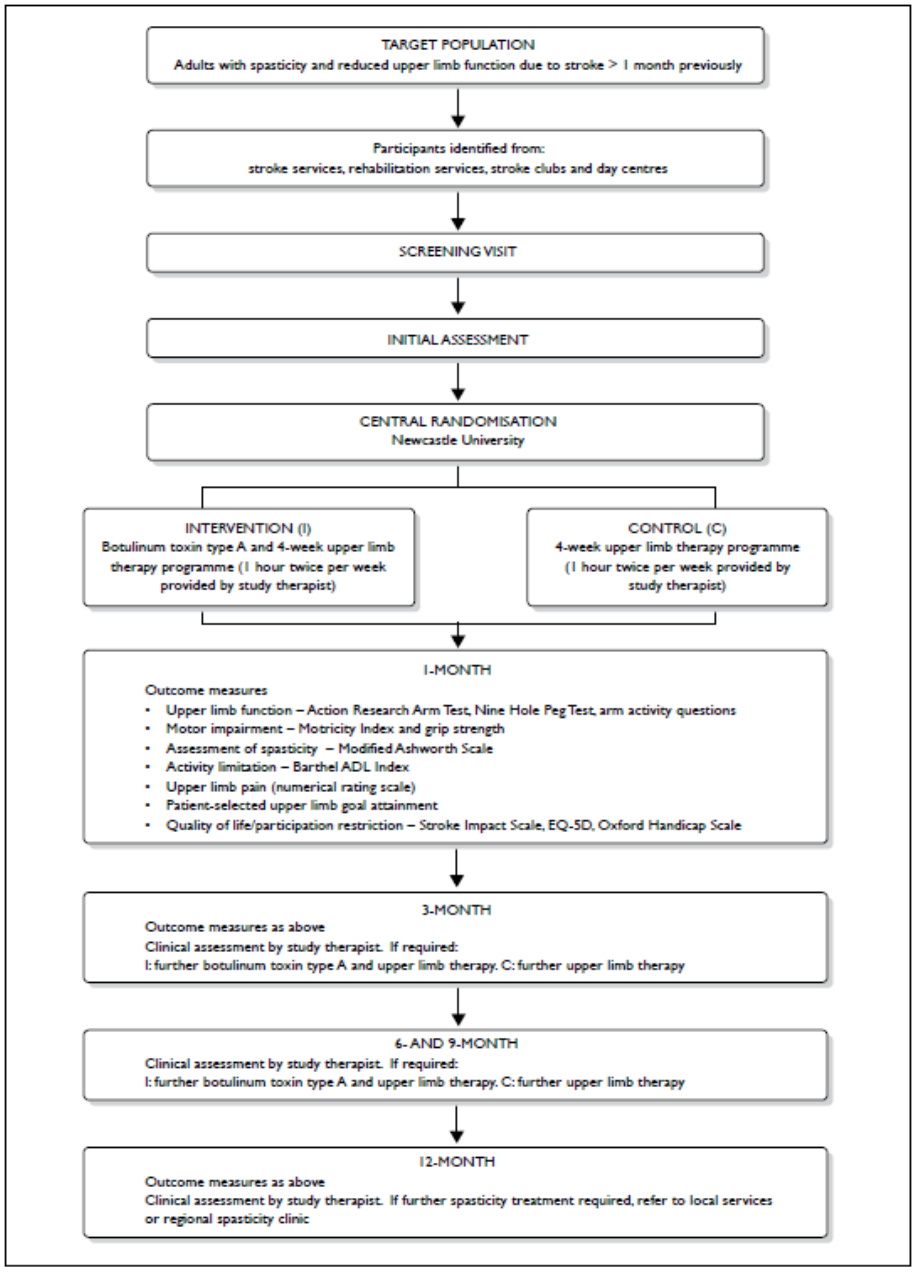
An important secondary outcome was comparing the proportion of participants in each randomisation subgroup who improved by one point or more on the baseline score of the „basic upper limb functional

activities questions“. This allowed comparison with previous trials.

Statistical change in score in any of the other secondary outcome measures was considered a key find.

The subgroups for analysis were: 1) subjects who had within the past year vs. those > 1 year post-stroke; 2) subjects with no initial upper limb activity (ARAT 0-3) vs. participants with some initial upper limb activity (ARAT 4-56).

Statistical Analysis: For the primary outcome, Fisher's exact test and an interval estimate of the intervention in the form of a 95% confidence interval for the relative risk was calculated. Secondary outcomes providing binary data were compared using Fischer's Test or Chi-squared analysis. Secondary outcomes providing continuous or ordinal data were analysed with the Whitney-Mann U-Test.



Results

21 Tables are included in the detailed results analysis which spans 29 pages in the study article. Due to the volume of results; only the main outcomes will be highlighted and the author of the CAT encourages readers to consult the original text for further clarification.

Primary Outcome Measure: A change in ARAT score (improved arm function) was not significantly different between the control and intervention group at 1, 3, and 12 months. On a positive note, there was improvement in both groups: 19.5% in the control group and 25.1% in the intervention group already at one month. The improvement in the control group was higher than anticipated at 24.2% at 3 months and 29.3% at 12 month. This improvment may reflect the effectiveness of a repetitive task-specific upper limb therapy program regardless of concurrent botulinum toxin injection.

Secondary Outcome Measures:
Spasticity: at the elbow was decreased in the intervention group by an average of one point on the Modified Ashworth Scale (vs. zero in the control group). No difference in spasticity was seen at 3 or 12 months.

Basic functional activities: Subjects in the intervention group were more likely to complete basic functional activities (eg. dress a sleeve, open hand to clean palm or cut fingernails) at one and three months. Again, improvement was observed in both groups: 75.7% in the intervention group at 1 month vs. 63.2% in the control; 71.8% at 3 months vs. 58.2% in the control group. Improvement was sustained in the intervention group for more passive functional activities at 12 months: opening the hand for cutting the nails and cleaning the palm, but not for other activities.

Pain: An average improvement of 2 points on a 10-point severity scale was measured in the intervention group at 12 months (vs. no improvement in the control group). No significant differences were seen at 1 or 3 months.

Statistically significant differences in favour of the intervention group were measured with several other assessment scales, however the differences were small and are not necessarily clinically relevant. They include:
At 3 months - change in upper limb function (ARAT – primary outcome measure), pain (EQ-5D), and participation restriction (Oxford Handicap Scale)
At 12 months – anxiety/depression (EQ-5D), and participation restriction (Oxford Handicap Scale).

No differences were found in grip strength, dexterity nor the Barthel ADL Index.

There were no differences between the groups for achieving patient-selected goals (COPM). The Table below illustrates, however, that both groups improved.

TABLE 12 Canadian Occupation Performance Measure (COPM) scores

	Control ($n = 145$)	Intervention ($n = 155$)	p-value
Baseline performance: median (IQR)	1.7 (1.0 to 2.8)	2.0 (1.0 to 3.0)	0.143
Post-treatment performance: median (IQR)	4.7 (3.1 to 6.7)	4.8 (3.4 to 6.0)	0.985
Change in performance: median (IQR)	2.3 (1.3 to 4.0)	2.3 (1.2 to 3.8)	0.535
Baseline satisfaction: median (IQR)	1.6 (1.0 to 2.8)	2.0 (1.0 to 3.3)	0.152
Post-treatment satisfaction: median (IQR)	4.8 (3.0 to 6.8)	4.8 (3.5 to 6.2)	0.792
Change in satisfaction: median (IQR)	2.4 (1.0 to 4.4)	2.3 (1.0 to 4.0)	0.342

In regards to the subgroups (patients grouped into 3 levels of functional use of the upper limb), there was no significant difference in regards to achieving better success on the primary outcome measure (change in ARAT score).

Authors' Conclusion(s)

Combining botulinum toxin Type A injections with an upper limb therapy program to treat spasticity did not enhance improvement in function compared to an upper limb therapy program when measured at one-month with the ARAT scale (primary outcome measure). However, the combined treatment provided better improvement of muscle tone at 1 month, upper limb strength at 3 months, upper limb functional activities related to undertaking basic functional tasks (at 1,3, and 12 months), and reduced upper limb pain significantly at 12 months.

The authors emphasize the importance of setting realistic goals for treatment; and then determining if botulinum toxin A can help the patient reach these goals. They state that the injections combined with therapy may not achieve *enhanced* improvement in active upper limb function. However, it may provide enhanced improvement of basic upper limb functional tasks and reduce pain at 12 months. It should be noted that both groups did improve in terms of upper extremity function at 12 months.

Further research is also emphasized; as they state that the relationship between spasticity and functional limitation is not yet clearly defined and studies are needed to improve measurement of spasticity and upper limb joint movement for clinical practice. Optimal dosage and patterns of injections as well as the efficacy of repeat injection also need to be defined.

A national register system is also recommended by the authors to record the clinical details of patients receiving botulinum toxin treatment, with their goals and outcomes to better structure future RCTs to capture the patient group that would benefit from this treatment.

Study Validity

The authors identify several elements in the RCT that could influence the validity and quality of the RCT.

- The authors state that to-date no functional assessment exists that is appropriate for the entire spectrum on stroke patients. They believe that the ARAT is not relevant for patients with no active movement at baseline (ARAT 0-3); which was 67.4% of the control group and 77.2% of the intervention group! They explain that the original inclusion criteria required subjects to have upper extremity movement, however the inclusion criteria was broadened due to recruitment difficulties without modifying the primary outcome measure.
- Only 57% of subjects were reevaluated at 12 months. Those recruited after July 2007 were followed only for 3 months because the study was behind schedule due to recruitment difficulties. Therefore the authors may have missed an important treatment effect due to the greatly reduced sample size at this stage. Sustained benefit in terms of upper extremity function may have not been demonstrated at 12 months because a large portion of participants did not receive 3-monthly repeat injections.
- The relation between spasticity and motor weakness and their influence on function remains a debated topic. What is understood is that a botulinum toxin dose that is too weak will not improve function while the muscles will remain too spastic, and a dose that is too strong can result in reduced active upper limb function due to excessive muscle weakness. While the dosing guidelines are open to clinical reasoning and error, it can be that some subjects received sub-optimal dosing which would ultimately affect results.
- The relative improvement of „specific upper limb activities „but not necessarily the ARAT score demonstrates that the trial reflects a combination of improvement in both passive and/or active function vs. only active function (ARAT).
- The timing of assessment in relation to injection was less than optimal. The 1 month evaluation is when the injection is at its peak, but only in the first cycle of treatment, while the 6 and 12 month evaluation is timed when the injection is wearing off. It would have benn practical for further assessment to evaluate peak effect for repeated injection (at 4, 7, and 10 months). However this did not fit the resource limitations and participant burden.
- Patients were not blinded (no placebo injection).
- Inclusion of the COPM was in recognition that improvement in patient-selected goals may provide a more meaningful treatment evaluation than standard outcome measures, however the goals set may or may not have been realistic and achievable.
- There is as of yet, no validated measure of spasticity for the shoulder, wrist, or fingers exists. Therefore severity and improvement could not be objectively rated (missing potential improvements). The MAS is validated for the elbow, but is in fact a measure of tone and not spasticity.
- A strength supporting the validity of the study is the quality of the data. Follow-up levels were high and there were low levels of missing data.

Personal Conclusion / Interpretation

The fact that the study is the largest RCT to date over a long period of time, with so many outcome measures gives me a certain confidence in applying the results in my daily practice.

The evidence-based standardized & structured therapy and home program with two menus (low upper extremity function, and moderate/high extremity function) piqued my interest. Especially since lasting improvement was noted in in *both* groups (those who received therapy alone or therapy & botulinum toxin

injections). I have contacted the authors for a copy of the therapy program which was validated in a pilot project as well as this RCT.
I was suprised to see such improvement in a group who predominantly had no or very little active movement (ARAT 0-3). I think the take-home message is that the injections are not a magic bullet to dramatically improve function, however gains are possible at every level of baseline function, whether passive and/or active. Individual patient goal-setting is essential for such success as well (COPM).
The choice of outcome measures did not seem adequate sometimes. For example, if most patients couldn't complete the nine-hole peg test, then why include it? The authors identify this problem with the ARAT as well. I think that they could have reconsidered their primary outcome measure. Luckily they included many secondary outcome measures which nonetheless captured improvement in function and reduction in pain.
I found the timing of the assessments were not optimal. I would like to know what functional gains are made when the injection is at its peak effect in the second, third, or fourth cycle. For example, spasticity was decreased by one point on the MAS at one month (peak effect), but not at 3 and 12. What impact does this have on the patient's function and independence? What happened in between these points of time? Furthermore, most patients did not receive repeated cycles, so most patients at 12 months had received no therapy for 8 months, while others were on their 4 th round of injections and therapy; but they were all grouped together in the intervention group. I feel that I don't know what I could recommend to my patients in terms of *length of time* for repeating injections and commitment to an intensive therapy program.
The authors took a humanistic approach by administering botulinum toxin A to 4 persons in the control group at one month and 8 persons at 3 months due to an „unacceptable degree of spasticity“. They chose to follow the National Guidelines for spasticity management over study protocol; however that certainly could have confounded the results since the patient data remained in the control group information pool.
I also found it interesting that botulinum injection seems to be a standard treatment in this healthcare network, as 67 of the control group were referred for botulinum toxin injections after the 12 month study trial. This gives me impetus to refer my patients to a specialist for evaluation, as a large number of patients with upper extremity spasticity seem to benefit from this treatment combination.

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Appendix A : Text Abbreviations

AOU	Amount of Use
ARAT	Action Research Arm Test
BoNT-A	Botulinum Toxin-A
COPM	Canadian Occupational Performance Measure
DAS	Disability Assessment Scale
EQ-5D	European Quality of Life – 5 Dimensions
FIM	Functional Independence Measure
MAL	Motor Activity Log
MAL-O	Motor Activity Log – Observational
MAS	Modified Ashworth Scale
MAL – SR	Motor Activity Log – Self-Report
QOM	Quality of Movement
SIS	Stroke Impact Scale