

# Does Spasticity Reduction by Botulinum Toxin Type A Improve Upper Limb Functionality in Adult Post-Stroke Patients? A Systematic Review of Relevant Studies

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## Abstract

**Objective:** Botulinum toxin type A (BTX-A) use reduces upper limb (UL) spasticity in stroke patients, but the effects on functional recovery remain uncertain. The aim of present review was to ascertain if the reduction of spasticity by use of BTX-A was linked to a functional gain of UL or in activity of daily living in post-stroke patients.

**Data source:** Search of relevant studies was conducted on MEDLINE, the Cochrane Central Register of Controlled Trials and EMBASE (1995 to July 2012).

**Study selection:** Only randomized studies (RT) treating patients with UL post-stroke spasticity by BTX-A injection were included. Prospective open label, case series, cohort studies and case reports were excluded.

**Data synthesis:** Thirty-four RTs were individuated, but only 16 were considered in the analysis. Trials varied widely in methodological design and measures used in assessing UL ability. Benefit in UL functional recovery was reported in 13 studies, but only in six the result was significant.

**Conclusion:** some oriented-focused movements of UL unequivocally improve after reduced spasticity by BTX-A treatment, but evidence that arm functionality in adult post-stroke patients significantly benefit from this intervention is still doubt. No improvement in global functionality of activity daily living was observed.

**Keyword:** Botulinum toxin; Spasticity; Stroke; Upper limb; Functionality

## Introduction

Spasticity is a common disabling disorder that occurs from 17 to 43% in patients with stroke affecting both the upper and the lower limb [1-4]. If left untreated, it can hamper functional outcome by promoting persistent abnormal posture that in turn produces muscular-tendon contractures and bone deformity. Several functional limitations arise from spasticity including impaired movement, hygiene, self-care, poor self-esteem, body image, pain and pressure ulcers that increase carer burden. Furthermore, patients with severe spasticity can develop poor social participation and quality of life (QOL) [5]. Because of these concerns and related high social costs [6], many therapeutic strategies have been proposed for the treatment of this disorder including surgical, medical and rehabilitative procedures. Among these, botulinum toxin type A (BTX-A) is became the first line to treat focal/multifocal spasticity, in the clinical practice. There is now, a well-established body of evidence demonstrating the effectiveness of BTX-A for post-stroke spasticity reduction both in the upper and the lower limb [7-18]. Nevertheless, its impact on motor performance and functional outcome remains controversial [19,20]. In particular, the effect of reduced spasticity on upper limb ability recovery after stroke is unclear. The central thread in treating spasticity is the assumption that it contributes to the limitation of activities, and that its reduction will bring about an improvement in function. The aim of present review was to ascertain if the reduction of spasticity by use of BTX-A was linked to a functional gain in upper limb or in activity of daily living in post-stroke patients. Therefore, relevant studies addressing upper limb (UL) spasticity reduction and functional improvement after BTX-A treatment in adult post-stroke patients were reviewed.

## Method

Search of relevant studies was conducted on MEDLINE (from 1995 to July 2012), the Cochrane Central Register of Controlled Trials and EMBASE (1995 to July 2012). Search terms varied slightly across databases but included: "cerebrovascular accident" or "stroke" and the terms "botulinum toxin", "spasticity" as either MeSH terms, key words, or subject headings. Only randomized studies (RT) treating patients with UL post-stroke spasticity by BTX-A injection were included. Studies of treatment for both lower and/or UL spasticity were included if the results for patients with UL spasticity were reported separately. Prospective open label, case series, cohort studies and case reports were excluded. Furthermore, because confounding results, RTs were also excluded whether: i) post-stroke spasticity was treated by different serotype neurotoxin; ii) botulinum toxin was given early after the stroke, before clinical evidence of severe spasticity was established; iii) mixed sample of subjects with spasticity secondary to stroke or other neurological disorders was enrolled; iv) spasticity followed a non-

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stroke etiology (e.g., multiple sclerosis, cerebral palsy and brain injury); v) trials focused BTX-A action on different disorders other than spasticity in post-stroke patients including its effect on painful spastic shoulder, and on physiological aspects of spasticity; vi) BTX-A dilution and endplate-targeting in single spastic muscle were investigated.

According to Food Drug Administration (FDA), the BTX-A drug formulations were defined onabotulinumtoxinA, abobotulinumtoxinA, and incobotulinumtoxinA, commercially marketed as Botox, Dysport and Xeomin, respectively. However due to common commercially BTXA denomination in clinical practice, neurotoxin was defined thorough the text, accordingly.

## Results

Thirty-four RTs were individuated. Of these, 17 were excluded due to exclusion criteria: i) one trial in which post stroke spasticity was treated by botulinum toxin type B (rimabotulinumtoxinB) [21]; ii) three trial that evaluated the effect of BTX-A given early post stroke before clinically evident spasticity [22-24]; iii) one trial that studied the effect of BTX-A dilution and endplate-targeting in sole spastic biceps [25]; iv) five trials enrolling mixed sample of subjects with spasticity secondary to brain injury, multiple sclerosis other than stroke [9,26-29]; v) six studies focusing the effect of BTX-A on the reduction of pain associated to spastic shoulder [30-35] and one trial that investigated the effects of BTX-A on associated reactions of spasticity [36]. The remaining 17 RTs were included [11,13,37-51]. Since one study reported secondary analysis of finding previously published, both were considered as single study, leaving 16 RTs in the analysis [13,47]. Of these, 13 were randomized, double blind, placebo controlled studies, 2 were RCT without placebo group, and one trial had a randomized, cross-over, placebo method design (Figure 1). Two RCT had an additional follow-up lasting 42 and 69 weeks, respectively [41,45,52,53]. Both focused safety and efficacy of BTX-A and were published as open-label studies. All included studies are described in Table 1. Trials varied in methodological quality, size, time from stroke onset, muscles injected,

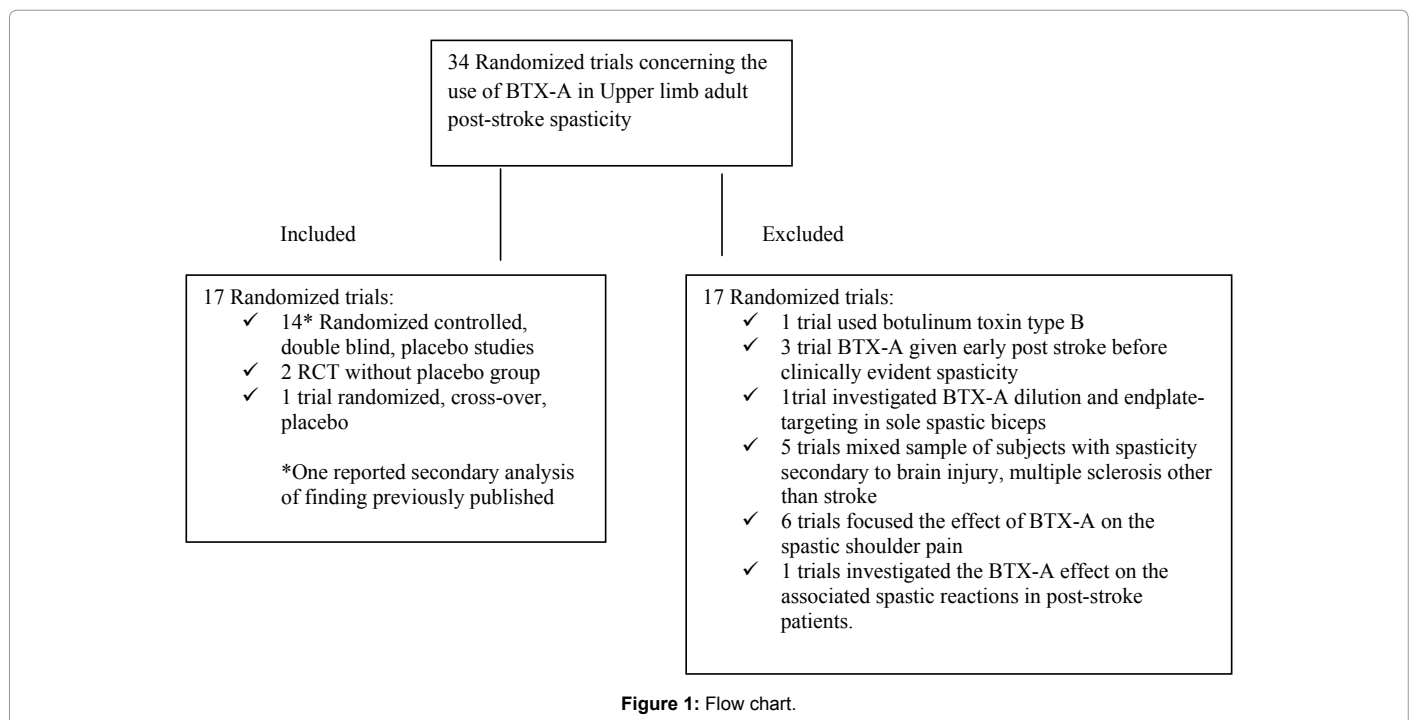
dose of botulinum toxin delivered and outcome measures used. Eight, 7 and 1 RTs used abobotulinumtoxinA (Dysport), onabotulinumtoxinA (Botox), incobotulinumtoxinA (Xeomin) formulations, respectively. No head to head trial comparing directly the efficacy of neurotoxins was performed.

## Associated treatments

Additional treatments including electrical stimulation (ES) and rehabilitative strategies associated to BTX-A injection were present in 4 trials. Of these, one study investigated BTX-A plus ES compared to solely ES. The remaining three studies concerned BTX-A and physiotherapy strategies: one described the effect of combined BTX-A plus modified constraint induced therapy (mCIT) compared to BTX-A plus conventional physiotherapy [48], one study in which BTX-A plus physical therapy was compared to placebo plus physical therapy [51], and one study without placebo group that compared BTX-A plus standardized physiotherapy to group with solely standardized therapy [49,50]. In six studies, it was commonly noted that all participants received or continued a physical rehabilitation program, but the content of this was not described [38,40-44].

## Spasticity and BTX-A dose

Measurement of spasticity is a challenge because of the complex multifaceted definition, and no tool covers all aspects of the definition. So far, spasticity quantification remains based on subjective measurements and no instrumental technique has been widely used in clinical practice. Ashworth Scale (AS) and modified Ashworth Scale (MAS) were used in 12 and 4 trials, respectively. Spasticity reduction was the primary outcome measure in 12 studies. Of these, one trial focused as primary outcome both the reduction of spasticity and the quality of life [13]. Spasticity resulted homogenous across the studies as MAS or AS  $\geq 2$  was considered in inclusion criteria for all enrolled patients. Three trials included subjects with spasticity  $\geq 3$  to MAS or AS [38,46,48].



**Figure 1:** Flow chart.

Study	Patients, (M, F), mean age; time after stroke	BTX type; dose, area, additional intervention	muscles	Spasticity scale	UL functional measures	Other measures	Spasticity reduction	Functional gain of UL	Description of results/ adverse events
Simpson [37] RP, DB, PC, multicentre	37 pts (16 M, 21 F); 9 (75 MU), 9 (150 MU), 9 (300 MU), 10 ( placebo); mean age 59±12 yrs; mean time from stroke onset 37 (9-133) months	BTX-A (Botox) 75, 150, 300 MU; elbow, wrist	BB, FCR, FCU by EMG guidance	AS ≥ 2 , Global Assessment of Spasticity Scale§ <sup>1</sup>	FIM, Fugl-Meyer Scale, motor task/ function rating scale	caregiver dependency scale, function and pain assessment, Rand 36-Item Health Survey	Significant reduction of spasticity for elbow and wrist in patients treated with 300 MU	negative	No improvement on the FIM, Fugl-Meyer, caregiver dependency, function and pain assessment, motor/ function task rating scale, or the Rand 36-Item Health Survey. Significant improvement on physicians and patients global assessment in the high- and low-dose groups at 4 and 6 wks.
Hesse [38] RC, DB, PC single centre	24 pts (19 M, 5 F); 6 BTX, 6 BTX + ES, 6 ES + placebo, 6 placebo; mean age 52.3 yrs; mean post-stroke time interval was 7.45 months	BTX-A (Dysport) 1000 MU; elbow, wrist, finger flexors, electrical stimulation	BB, B, FCR, FCU, FDS, FDP by EMG guidance	MAS ≥ 3	Evaluation of 3 activities of daily living* <sup>1</sup>	Global pain assessment	Significant reduction of spasticity in BTX + ES, particularly of the elbow and wrist joint. No difference in other groups	partial positive	Only activity in cleaning the palm of affected hand improved significantly in BTX + ES group
Bakheit [39] RC, DB, PC multicentre	82 pts (51 M, 31 F); 22 (500 MU), 22 (1000 MU), 19 (1500 MU), 19 Placebo; mean age 52.5 yrs; 3 months after stroke	BTX-A (Dysport) 500, 1000, 1500 MU; elbow, wrist, finger flexors	BB, FDP, FDS, FCR, FCU by anatomical landmark	MAS ≥ 2 Effective and safe dose (end-point)	RMA Scale (arm section), BI, ADL, evaluation of 3 activities of daily living* <sup>1</sup>	ROM, pain scale £	Significant decreases in MAS (any joint) at wk 4 with all BTX-A doses vs placebo. Decreased MAS score over 16 wks for elbow and wrist in all BTX groups and fingers in 1000 MU group.	positive	no significant differences between the groups in ROM, pain, RMA Scale, BI for activities of daily living. Subjective caregiving scale not analyzed, but BTX-A treated patients showed improvement extending the elbow to put the affected arm into a garment sleeve or to open the hand for cleaning the palm or for cutting the fingernails.
Bhakta [40], RP, DB, PC single center	40 pts (23 M, 17 F); 20 (1000 MU) 20 placebo; mean age 60.2 yrs; mean time from stroke onset 3 yrs	BTX-A (Dysport) 1000 MU; elbow, wrist, finger flexors; physiotherapy	BB, B, FDP, FDS, FCU by anatomical landmark	MAS ≥ 2	PDS* <sup>5</sup> and CBS§ <sup>3</sup> (primary outcome)	MRC, MVG, ROM, pain	significant improvements in finger flexor spasticity with BTX-A vs placebo at wk 2, 6, and 12 ( $P = 0.001$ , $P = 0.001$ , and $P = 0.006$ ); significant reduction of elbow spasticity at 2 wks. <i>Decreased grip strength in BTX group compared with placebo at wk 6.</i>	positive	Improvement of disability ( 8 of 17 patients in the BT-A group ) in cleaning the palm, putting the arm through sleeves, doing home physiotherapy exercises and cleaning armpit at 2 and 6 wks. Significant reductions in carer burden with BTX-A vs placebo at wk 2, 6, and 12 ( $P = 0.011$ , $P = 0.005$ , and $P = 0.027$ , respectively); no improvement in pain. Active ROM negative, passive shoulder and elbow ROM improved in BTX, but not significantly. Significant improvement in wrist ROM at 2 and 12 wks post-treatment

Bakheit [11], RC, BD, PC multicenter	59 pts (26 M, 33 F); 27 BTX-A: mean age 64.1±13.2; 32 placebo: mean age 67±11.1; at least 3 months after stroke	BTX-A (Dysport) 1000 MU; elbow, wrist and finger flexors	BB, FDS, FDP, FCU, FCR by anatomical landmark	MAS ≥ 2 Effective and safe of single dose at 4 wks (end-point)	BI, GAS* <sup>3</sup> , evaluation of 3 activities of daily living* <sup>1</sup>	ROM, pain score, GAB§ <sup>4</sup>	Significant reduction in MAS at 4 wk in any joints (P= 0.004).	positive	No significant difference in BI score or the number of goals attained but significant improvement in GAB . Less difficult in extending the elbow to put the affected arm into a garment sleeve or to open the hand for cleaning the palm or for cutting the fingernails at 4 weeks after the BTX injections but statistical analysis was not performed. Improved passive range of movement at the elbow over 16 wk in BTX group compared with placebo. No significant difference in pain and active ROM
Brashear [41], RC, DB, PC multicenter	126 pts (63 M, 53F); 64 BTX-A, 62 placebo; mean age 60.5 yrs; 6 months elapsed from stroke	BTX-A (Botox) 221.3±18.8 MU; wrist, finger flexors	FCR, FCU, FDS, FDP, FPL and thumb muscles; modality of injection not reported.	AS ≥ 2	DAS* <sup>2</sup> (primary outcome)	global assessment scale§ <sup>2</sup>	Significant reduction of spasticity	positive	Improvements in DAS (pain, dressing, hygiene, cosmesis), physician and patient/caregiver global assessment. Eighty-three percent of BTX group had at least a one-point improvement in the score on the DAS in one or more of these areas, as compared with 53% of subjects who received placebo (P=0.007)
Childers [42] RC, DB, PC multicenter	91 pts; (60 M, 31 F); 21 BTX-A (90 MU), 23 BTX-A (180 MU), 21 BTX-A (360 MU), 26 (placebo); mean age 60 yrs; time from stroke onset 25.8 months (range 0.9 –226.9)	BTX-A (Botox) 90,180, 360 MU; wrist, elbow and finger flexors	BB, FCU, FCR, FDS, FDP by EMG guidance	MAS ≥ 2	FIM, 5-point assessment of functional disability	global assessments scale § <sup>2</sup> , pain, SF-36,	Significant reduction spasticity in all BTX groups . High BTX pts showed more reduction of spastic wrist at all of the visits through week 12.	negative	No significant differences in functional disability, and composite FIM scores were detected between treatment groups. No significant differences in intensity of pain. The SF-36, detected significant improvement only in patients in the 90U BTX group at week 6 on the social functioning section.
Suputtitada et al. [43] RC, DB, PC single center	50 pts (26 M, 24 F); 15 BTX-A (350 MU), 15 BTX-A (500 MU), 5 (stopped) BTX-A (1000 MU), 15 placebo; mean age 55.2±8.9 yrs in PC group, 46.5±8.5, 53±18.6, and 59.8±9.1 yrs for BTX-A groups, mean time from stroke onset 8.5 months	BTX-A (Dysport) 350, 500, 1000 MU; elbow, wrist, and finger flexors; full program rehabilitation <sup>c</sup> therapy of the upper limb 3 days per week	BB, FCU, FCR, FDS, FDP by EMG guidance	MAS 4 End-point 1-The lowest effective dose of BTX, 2-onset and duration of BTX effect 3-hand function	ARAT* <sup>7</sup> , BI,	Pain (VAS)	Significant reduction of spasticity in 350 and 500 MU BTX-A group at 2 and 8 wks. Reduction of pain	positive effect for 350 and 500 MU BTX-A group (significant increase in ARAT at 8 and 24 wks)	Mean ARAT and BI increased during the first 8 weeks and then became rather stable throughout the 6-month study period in the 350 and 500 U group. Too much weakness in treated arm and reduced ARAT and BI for 1000 MU BTX-A subjects.
Jahangir et al. [44] RC, DB, PC single center	52 pts (33 M, 19 F); 27 BTX-A, 25 placebo; mean age 60.6 yrs; at least 1 year elapsed from stroke	BTX-A (Botox) 80 MU; wrist and finger flexors; regular physiotherapy session	FCR, FCU, FDS, FDP, modality of injection not reported.	MAS ≥ 2	BI§	EQ-5D and EQ VAS	Decreased spasticity at wrist and fingers compared with placebo at 1 and 12 week	negative	Although there was an improvement in the measures of global function and quality of life in the BTX-A group compared to baseline, there was no significant improvement in between the two groups

<p>Kanovský P [45] RC, DB, PC multicenter</p>	<p>148 pts (77 M, 71 F) 73 BTX-A, 75 placebo; mean age 55.6 (12.1) yrs; mean time from stroke onset 55 (48.7) months</p>	<p>BTX-A (Xeomin); mean dose 307 (80-435) MU; elbow, wrist, finger flexors; physical and occupational therapy <sup>c</sup></p>	<p>BB, B, FCR, FRU, FDS, FDP, PQ, PT, thumb flexor. Pronators and thumb flexors were injected on the investigator's clinical judgment by EMG or nerve stimulation</p>	<p>AS ≥ 2</p>	<p>DAS*<sup>2</sup></p>	<p>GAB§<sup>4</sup>, CBS§<sup>3</sup></p>	<p>Significant reduction of spasticity in wrist and finger flexors at 4 wks for BTX-A group</p>	<p>positive</p>	<p>Significant improvement in individual's DAS domains for BTX-A group: hygiene (weeks 2, 4, and 8; P &lt; 0.05), dressing (week 2; P = 0.003); limb position (weeks 2, 4, and 8; P &lt; 0.009); and pain (weeks 2 and 4; P &lt; 0.04). Significant improvement global assessment of efficacy and CBS</p>
<p>Meythaler JM [46] DB, CO, PC single center</p>	<p>21 pts (15 M, 6 F); 11 BTX-A plus physiotherapy; 10 PC plus physiotherapy; mean age 53.33±14.8 yrs (range, 21–79); at least 6 months from stroke onset</p>	<p>BTX-A (Botox) 300-400 MU; elbow, wrist; occupational therapy <sup>a</sup> and a focused neuro- developmental therapy <sup>b</sup></p>	<p>Elbow flexors, FRC, FRC by EMG guidance</p>	<p>AS ≥ 3 (primary outcome)</p>	<p>The primary functional outcome measure was the MAL*<sup>6</sup>, Klein-Bell Activities of Daily Living Scale, BI</p>	<p>MOS-36 Item Short-Form Health Status Survey, ROM, motor and grip strength, pain</p>	<p>Significant reduction of spasticity in BTX-A group combined with therapy</p>	<p>positive</p>	<p>The use of BTX-A combined with therapy as compared with therapy only improved the functional status of the subjects on the MAL QOM subscale (P=0.018, t test) and showed a trend toward significance in the AOU subscale. In a crossover analysis for the randomized trial, there was a clear advantage of BTX-A combined with therapy over the placebo-controlled therapy (P=0.0605, ANOVA). No significant improvement in ROM, strength, pain, Klein-Bell Activities of daily living, BI and MOS-36</p>
<p>Mc Crory et al. [13] RC, DB, PC multicenter</p>	<p>96 pts (58 M, 38 F); 54 BTX, 42 placebo; mean age 59.5 yrs (58.4±14.6 and 59.7 ±12.2 in BTX-A and PC group, respectively); mean time elapsed from stroke 5.9 ± 10.5 yrs</p>	<p>BTX-A (Dysport) 750-1000 MU; wrist, elbow and finger flexors;</p>	<p>BB, B, BR, T, FCR, FCU, FDS, FDP, thumb flexors; EMG or nerve/muscle stimulation were all at the clinicians' discretion.</p>	<p>MAS ≥ 2 (primary end-point)</p>	<p>GAS*<sup>3</sup>, PDS*<sup>5</sup>, MMAS,</p>	<p>AQoL, (primary outcome), pain (100 point VAS), mood, GAB§<sup>4</sup>, CBS§<sup>3</sup></p>	<p>Significant reduction of spasticity in BTX group at all visits</p>	<p>positive</p>	<p>Significant improvement in GAS score at week 20 for BTX-A (p &lt; 0.01). No difference between groups in PDS, CBS, AQoL, pain, mood, MMAS. At wk 8, the chosen item from the patient disability rating scale (PFOM) was improved from baseline in 20/54 (37%) of the BTX-A group compared with only 6/38 (15%) of the placebo group (p = 0.02). A significantly higher proportion of both patients and investigators reported a benefit from treatment in the BTX-A group compared with the placebo group.</p>
<p>Tuner-Stokes [47]</p>	<p>secondary analysis of previous study (Mc Crory et al.)</p>							<p>positive</p>	<p>A significant treatment effect was observed with respect to GAS. Continued improvement in goal attainment between wks 8 and 20. Goal- scaling outcome T-scores were highly correlated with reduction in spasticity and global benefit. There were no significant associations with changes in pain, mood, or quality of life, nor with overall patient disability or carer burden.</p>

Sun SF [48], RC, observer-blinded trial; single center	29 pts (24 M, 5 F), 15 BTX-A + mCIT, 14 pts BTX-A + conventional physiotherapy; mean age 58.7 ± 9.9 and 61.5 ± 9.4 yrs in experimental and control group, respectively; mean time from stroke onset 2.9 yrs	BTX-A (Dysport) 1000 MU; mCI and conventional physiotherapy & elbow, wrist and finger flexors	BB, FCR, FCU, FDP, FDS by anatomical landmarks	MAS ≥ 3 (primary outcome)	MAL* <sup>6</sup> , ARAT* <sup>7</sup> (secondary outcome)	Patients' Global Satisfaction § <sup>8</sup>	significant improvement in spasticity for the combination group in elbow, wrist, and finger flexors at 6 months post-injection ( <i>P</i> = 0.019, <i>P</i> = 0.019, and <i>P</i> < 0.001, respectively)	positive	Both subscale scores of the MAL increased in the combination group at the 6-month follow-up. The combination group displayed greater improvements on the ARAT scores than the control group, with significant between-group differences at 3 months ( <i>P</i> = 0.012) and 6 months ( <i>P</i> < .001) post-injection. The combination group reported high subjective satisfaction at 3 months and 6 months post-injection.
Kaji [49], RC, DB, PC multicenter	109 pts (74M, 35F), 77 pts (51 BTX-A, 26 placebo), mean age 63.5±9.3 and 63.6±11 for BTX-A and PC in higher dose, respectively; 32 pts (21 BTX-A, 11 placebo), mean age 62.7±9.7 and 62.9±9.6 in lower dose; at least 6 months after stroke	BTX-A (Botox) Lower dose (120-150 MU), higher dose (200-240 MU); wrist and finger flexors	FCR, FCU, FDS, FDP by a nerve stimulator or EMG guidance	MAS ≥ 2 (AUC score primary end-point)	DAS* <sup>2</sup>	Clinical Global Impression § <sup>5</sup>	Significant improvement in wrist and fingers flexors spasticity with higher-dose BTX-A compared to placebo (AUC score) ( <i>p</i> <0.001)	positive	A significant decrease in the DAS score for the principal therapeutic target was noted at every point in the higher and lower dose BTX-A groups compared to placebo groups. No significant differences between groups were noted at any time point in the scores for hygiene and pain. The CGI score by the investigator was significantly higher at every time point in the higher-dose BTX-A group compared to placebo group. No significant differences between lower-dose BTX-A and placebo groups were noted.
Shaw [50], RC, PC, observer-blinded trial; multicenter	332 pts (225 M, 107 F); 170 BTX-A plus standardized physiotherapy, 162 standardized physiotherapy; median age 66 and 67 yrs in BTX-A and control group; mean time from stroke onset 23.3 and 27 months for BTX-A and control group, respectively.	BTX-A (Dysport) 1000 MU; elbow, wrist, hand (finger flexors); standardized upper limb therapy &&	BB, BR, FCR, FCU, PQ, PT, FDS, FDP, thumb flexors using anatomical landmarks	MAS ≥ 2	ARAT* <sup>7</sup> (primary end-point), NHPT, basic upper limb functional activity questions* <sup>4</sup> , BI, Canadian Occupational Performance Measure	MI, grip strength, pain, Stroke Impact Scale, EQ-5 D and the Oxford Handicap Scale,	Significant reduction of elbow spasticity at 1 month. No difference in spasticity was seen at 3 or 12 months. Improvement in upper limb muscle strength (MI) at 3 months	positive	no significant difference in ARAT, BI, dexterity (NHPT), and pain. Significant improvement in some basic activities: dressing a sleeve, to clean the palm and opening the hand to cut fingernails in favor of the intervention group were seen at 1, 3, and 12 months
Wolf [51] RC, DB, PC; single center	25 pts (15 M, 10 F), 12 BTX-A plus physical therapy, 13 PC plus physical therapy; mean age 49.8 yrs; time from stroke 3 to 24 months	BTX-A (Botox) 300 MU; wrist, hand (finger flexors); standardized upper limb therapy &&&	FCR, FCU, FDS, FDP by EMG guidance	MAS (secondary end-point)	WMFT* <sup>8</sup> (primary end-point)	Stroke Impact Scale (SIS), active ROM (secondary end-point)	Significant reduction of spasticity. MAS scores improved for the BTX-A group and worsened for the control group after injection ( <i>P</i> =0.02)	negative	no mean WMFT differences were identified between the BTX-A and PC group. However significant improvements in proximal joint task times and inter-joint total limb coordinated activities were observed in BTX-A group compared to control group

**Legend:** PM = pectoralis major, BB = biceps brachii, B = brachioradialis, T = triceps, FDS = flexor digitorum superficialis, FDP = flexor digitorum profundus, FCU = flexor carpi ulnaris; FCR = flexor carpi radialis; PQ = pronator quadratus, PT = pronator teres; FLP = flexor longus pollicis; AS = Ashworth scale; MAS = modified Ashworth scale; AUC = area under the curve; MRC = Medical Research Council scale; MVG = maximum voluntary grip strength; ROM = range of motion; MI = motricity Index; RMA = Rivermead Motor Assessment Scale; MMAS = Modified Motor Assessment Scale; GAS = Goal Attainment scale; MAL = Motor Activity Log; ARAT = Action Research Arm Test; FMS = Fugl-Meyer Scale; WMFT = Wolf Motor Function Test; NHPT = Nine-Hole Peg Test; DAS = Disability Assessment Scale; PDS = Patient Disability Scale; CBS = Carer Burden Scale; GAB = Global assessment of benefit; CGI = clinical global impression, BI = Barthel Index; ADL = Activity daily living; FIM = functional independence measure; VAS = visual analogue scale; SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey; AQoL = Quality of Life scale; EQ-5D = European Quality of Life-5 Dimensions; EQ VAS = visual analogue scale; MOS-36 Item Short-Form Health Status Survey; Rand 36-Item Health Survey; mCIT = modified constraint induced movement.

#### Upper Limb measurements\*

**Difficulties during three activities of daily living\*\*:** cleaning the palm, cutting fingernails and putting the affected arm through a sleeve, rated between 0 (no difficulties) and 4 (unable) [38,39,11].

**DAS\*\*** (Disability Assessment Scale): 0, no disability; 1, mild disability; 2, moderate disability; and 3, severe disability assessed on four functional domains (hygiene, dressing, pain, and limb position) [41,45,49].

**GAS\*\*** (Goal Attainment Scaling): a 5-point scale, where "0" denotes the expected level of achievement; "+1" and "+2" are respectively "a little" and "a lot" better than expected, whilst "-1" and "-2" are correspondingly a little and a lot less than the expected level. (Mc Crory<sup>13</sup>, in Bakheit<sup>11</sup> was reported as very good, good, unchanged, worse and much worse).

**Upper limb functional activity questions\*\*:** ability to dress a sleeve, open the hand for cleaning the palm, open the hand for cutting the fingernails, ability to use cutlery, scored on a Likert scale from 1 (unable to perform activity) to 5 (no difficulty) [50].

**PDS\*\*** (Patient Disability Scale): (8 items) identifies the patients' ability to care for their affected limb (dressing, maintaining hygiene, etc.) and to use it actively, for example, for standing/walking balance [40,13].

**MAL\*\*** (Motor Activity Log): valid and reliable scale of arm use and movement quality in real-world settings. It includes a 6-point amount of use (AOU) scale and a 6-point quality of movement (QOM) scale to rate how much and how well patients are using their affected arms for common daily tasks [48,46].

**ARAT\*\*** (Action Research Arm Test): functional assessment of upper extremity strength, dexterity, and coordination. It includes 19 items focusing on grasping objects of different shapes and sizes, and gross movement in the vertical and horizontal planes. The performance of each task is rated on a 4-point scale, ranging from 0 (no movement possible) to 3 (movement performed normally). The maximum sum score is 57 [48,43,49].

**WMFT** (Wolf Motor Function Test): It consists of 17 items: 2 strength measures and 15 timed performances on various tasks. The first half of the test involves simple limb movements; the second half involves more complex tasks involving coordinated motion.

#### Investigators, patients and caregivers assessment evaluation scales §

**§<sup>1</sup> Global Assessment of Spasticity Scale:** physician's and patient's independent evaluation of response to treatment, graded from 0 = unchanged, to +4 = complete abolishment of symptom or to -4 = severe worsening [37].

**§<sup>2</sup> Global Assessment Scale** with a score of -4 indicating very marked worsening, 0 no change, and +4 very marked improvement [41,42].

**§<sup>3</sup> The Carer Burden scale:** It identifies care tasks, such as dressing and maintaining hygiene, where these are performed by a carer. Items include cleaning the palm of the affected hand, cutting the fingernails of the affected hand, cleaning the armpit of the affected arm, and putting the affected arm through a sleeve. Each item is scored on a 5-point Likert scale rated from 0 = none to 4 = maximum disability or carer burden [45,13,40].

**§<sup>4</sup> Global Assessment of Benefit:** The patient was asked "How would you rate the overall benefit you have received to your arm in the time since your last injection?", and the response was categorized on a 5-point Likert scale [11,13,45].

**§<sup>5</sup> Clinical Global Impression<sup>8</sup>:** The global impression of functional disability was assessed using the 11-point Numeric Rating Scale, with -5 indicating worst possible and 5 best possible, by the investigator, the patient, and the physical or occupational therapist [49].

**§<sup>6</sup> Patient's global satisfaction** resulting from the treatment on a 7-point categorical scale weighted from completely satisfied to completely dissatisfied [48].

**£ Pain scale:** 0= no pain, 1 = mild pain, 2 = moderate pain, 3=severe pain

**§** The items were weighted according to a scheme. The person received a score based on whether they had received help while doing the task. The scores for each of the items were summed to create a total score. The higher the score the more "independent" the person. Independence meant that the person needed no assistance at any part of the task. If a person did any of the task about 50% independently then the "middle" score would apply to that particular task [44].

A BTX-A global dose ranging from 75 to 360 MU and from 350 to 1500 MU per intramuscular injection was injected for onabotulinumtoxinA (Botox) and abobotulinumtoxinA (Dysport), respectively. IncobotulinumtoxinA (Xeomin) was used in a single study and the mean dose was 307 MU (range 80-435 MU). One study investigated the effect of lower (120-150 MU) and higher dose (200-240 MU) of BTX-A (Botox) [49]. In four trials pre-determined different doses of BTX-A for intramuscular injection were injected. Of these, 2 trials used onabotulinumtoxinA (Botox) at dose of 75, 150 and 300 MU [37]; and 90, 180, 360 MU [42] respectively, and two studies used BTX-A (Dysport) at dose of 500, 1000, 1500 MU [39] and 350, 500 and 1000 MU [43] for intramuscular injection, respectively. Significant reduction of muscular tone in a dose dependent manner for BTX-A treated subjects compared to placebo group was detected in all studies, regardless of BTX-A formulations. Duration effect of BTX-A injections was variable, ranging from 2 to 12 weeks. The trials in which different dosage of BTX-A was used, higher doses produced more reduction of spasticity compared to lower dosage [11,37,39,42,43,49]. Contrasting results emerged about the proper dose of BTX-A avoiding weakness in patients with residual arm motor capacity. Bakheit et al. suggested 1000 MU BTX-A dose when using Dysport, since 1500 MU produced excessive weakness [39]. By contrast, too much weakness was reported by Suputtitada et al. with 1000 MU of BTX-A (Dysport) [43]. No suggestion in this respect emerged in using Botox formulation.

#### Functional outcome

Investigated functional outcome included patient's global ability in activities of daily living and upper limb ability recovery. No study had patient's global ability as primary end-point. The evaluation of functionality in activity daily living was quite homogeneous including Functional Independence Measure (FIM) [37, 42] and Barthel Index (BI) [11,39,43,44,46,50]. The sole patient's global functionality and upper limb ability were investigated in 3 and 8 trials respectively,

whereas both evaluations were reported in 5 studies. Patient's global functionality was evaluated in 8 trials. Of these, 6 and 2 studies used BI and FIM scale, respectively. No significant difference in global functional disability was detected in BTX-A treated patients compared to control group regardless of neurotoxin and functional scale, in all but one study. In this trial, the subjects were injected by BTX-A (Dysport) and they showed BI score improvement during the first 8 weeks that became stable throughout the 6-month study period [43]. Of trials in which BI was used, 3 studies did not report BI scores [11,46,50], whereas in remaining 3 studies different evaluation timing and modality of data reporting did not permit to pool results [39,43,44].

#### UL functional recovery

A huge of measures was used in evaluating patient's upper limb ability: Rivermead Motor Assessment Scale (RMA) [39], Patient Disability Scale (PDS) [40,13], Goal Attainment Scaling (GAS) [11,13], Disability Assessment Scale (DAS) [41,45,49], Motor Activity Log (MAL) [46,48], Action Research Arm Test (ARAT) [48,50], Fugl-Meyer Scale (FMS) [37], Wolf Motor Function test (WMFT) [51], Nine-Hole Peg Test (NHPT) [50]. A further measurement consisted in the evaluation of difficulties encountered by the patients during three activities of daily living [11,38,39]. No UL assessment was more employed compared to each other. Indeed, none of these measures is easily applicable to be widely used in clinical practice. UL functional evaluation was investigated in 13 trials, but only four study focused the UL functional improvement as primary outcome [40,41,50,51]. The measures widely varied across studies as ten tools were employed. Of those, DAS [41,45,49], ARAT [48,50], MAL [46,48] and GAS [11,13], were used in almost 2 studies.

The DAS is a measurement that evaluates arm disability on four functional domains (hygiene, dressing, pain, and limb position); generally each patient, together with the investigator, select one of

the four disability domains as the principal therapeutic target. It was employed in 3 RCT and all reported significant improvement score in BTX-A treated patients compared to placebo group [41,45,49] in the principal therapeutic target. In addition to the significant change in the domain chosen as principle therapeutic target, significant superiority over placebo was also observed in each individual's DAS domain in two studies [41,45]. On the other hand, significant differences in BTX-A group was noted in the scores only for dressing and limb position at any time point by Kaij et al. [49]. Likewise, ARAT was employed in three trials. Of these, only one was RC placebo study [43], whereas the remaining studies did not provide placebo group [48,50]. In RC placebo study, three different dosage (350 MU, 500 MU and 1000 MU) of BTX-A (Dysport) were injected and ARAT score significantly increased at 8 and 24 weeks in patients who were treated with 500 MU of BTX-A (Dysport) [43]. By contrast, the group receiving 1000 MU of BTX-A (Dysport) had a statistically significant ARAT score decrease at same time compared to the placebo group. Of remaining two studies, one was a large sample trial in which UL functional recovery was the primary end-point. In this study BTXA (Dysport) plus standardized physical therapy was compared to only physical therapy [50]. Although no significant improvement to ARAT score was detected in BTX-A group at 1, 3 and 12 months, some domains concerning basic activities including dressing a sleeve, to clean the palm and opening the hand to cut fingernails, in favor of the BTX-A group compared to control group increased significantly at same time evaluation. In the other trial, a BTX-A (Dysport) plus mCIT therapy group were compared to a BTX-A plus conventional rehabilitation group [48]. The BTX-A plus mCIT group displayed greater improvement on the ARAT scores than the control group, with significant between-group differences at 3 and 6 months.

The MAL is a valid and reliable scale of arm use and movement quality in real-world settings. It includes a 6-point amount of use (AOU) subscale and a 6-point quality of movement (QOM) subscale to rate how much and how well patients are using their affected arms for common daily tasks. MAL was used in two studies [46,48] which also varied in method design. One study has been previously described and did not provide placebo group [48]. In this study, significant MAL score improvement was observed in BTX-A plus mCIT group. The other study was a RC cross-over trial [46] and significant improvement were only detected to MAL (QOM) subscale in BTX-A (Botox) combined with physiotherapy group as compared with therapy alone group.

Goal attainment scaling (GAS) is a method of assimilating achievement in a number of individually-set goals into a single goal attainment score. This measurement was employed in two studies [11,13]. In the former, formal statistical analysis was not performed because of the small sample size [11]. In the latter, BTX-A (Dysport) treated patients had significantly higher levels of personal goal attainment than those treated with placebo at 20 weeks [13]. A secondary analysis of data from those patients who completed this trial showed significant treatment effect with respect to goal attainment. Furthermore goal-scaling outcome T-scores were highly correlated with reduction in UL spasticity and global benefit [47].

In five trials, active and/or passive range of motion (ROM) at elbow, wrist and fingers was documented using a goniometer [11,39,40,46,51]. Not significant passive and active ROM increase was detected in BTX-A group compared to placebo group when this measurement was applied, apart the finding of Bakheit et al., who reported significant improvement in the passive ROM at the elbow ( $P=0.036$ ) in BTX-A group compared to placebo at 16 weeks.

Although reduced UL spasticity by BTX-A treatment, no functional improvement was reported in three studies [37, 42,51]. The UL measurements were Fugl-Meyer Scale, motor/function task rating scale [37], FIM (arm section) [42] and Wolf Motor function test [51], respectively. Nevertheless, in the study by Wolf et al., the BTX-A group completed more tasks governing proximal joint motions compared to placebo. Furthermore, significant improvement on physicians and patients global assessment in the high (300 MU) and low-dose (75 MU) groups at 4 and 6 weeks were reported by Simpson. Likewise, significant improvement on global assessment scale for high dose (360 MU) at weeks 1, 2, 3 and 5 respectively, compared to placebo was observed by Childers et al. [42].

### Patient and carer satisfaction

Several measurements concerning satisfaction of investigators, patients and carer were used to ascertain UL functional outcome after BTX-A treatment including Care Burden Score (CBS) Caregiver Dependency Scale (CDS) [13,37,40,45], physician and patient global assessment [41,42], Global Assessment of Benefit [11,13,45], Patient Global satisfaction [48], Clinical global impression [48,49]. Almost all employed assessment registered by subjects, family members, or clinicians showed score increase in BTX-A treated patients regardless of BTX-A formulations compared to placebo group. Reduction in carer burden was particularly evident for the item "cleaning the palm" and significant benefit in BTX-A treated subjects compared to placebo group was widely observed [11,13,37,40,41, 45,48,49].

### Discussion

Focused person-centered activities involving the arm significantly benefit from reduced spasticity by BTX-A treatment, but demonstration evidence that this intervention unequivocally improves the upper limb functionality in adult post-stroke patients is not compelling. By contrast, global functionality improvement in activity of daily living does not result with BTX-A injection in post-stroke patients.

Thus far, relevant studies are not sufficiently uniform due to different method design, sample size, variety of UL functional measurements, neurotoxin dosage and end points. These limitations obstacle to pool comparable set of data about this challenging issue. Nevertheless, enhanced performance of specific basic upper limb functional activities in BTX-A treated post-stroke patients compared to control group were observed in all but three studies [37,42,51]. Furthermore, six trials showed significant increase of used measurements score in global arm functional evaluation [13,41,43,45,47,48]. To overcome the difficulty in evaluating the complex and wide UL functionality, it has been suggested that pre-specified goal attainment have to be individuated and provide more targeted measurement. The selection of outcome measures that are able to track specific functional improvements may be critical in evaluating of BTX treatment and to identify patients who are likely to respond best to this therapy. Indeed, McRory et al. reported significant improvement in goal attainment score at week 20 for BTX-A treated subjects compared to placebo group. Similar finding were observed in studies in which pre-specified activities or disability domains as the principal therapeutic target were identified and discussed with patients and caregivers [11,13,41,45, 47,49]. A recent RCT by Lam et al. showed significant GAS and CBS score increase at 6 weeks in chronic UL spastic patients treated with 1000 MU of BTX-A (Dysport) compared to placebo group [54]. Likewise, a previous meta-analysis concerning the efficacy and safety of BTX-A toxin (Botox or Dysport) showed significant improvement of GAS score at 4–6 weeks after injecting BTX-A (odds ratio= 5.85, 95% CI=3.12–10.95) [10].



Among the 17 selected studies, 14 and 3 showed positive and negative effects, respectively. The distribution was very asymmetric with 9, 3 and one studies demonstrating positive effect when Disport, Botox and Xeomin formulation, respectively were injected. Several reasons could explain this finding such as BTX-A dosage, injected muscles, method design, time of evaluation, functional scales employed and number of studies using specific BTX-A formulation. Although no UL functional improvement was reported in three studies, more arm tasks governing proximal joint motions compared to placebo and significant improvement on physicians and patients global assessment were observed in BTX-A treated subjects [37,42,51]. Furthermore, only the study by Wolf et al. had the arm functional gain as primary outcome [51].

Several challenging issues remain unsolved in evaluating the effect of spasticity reduction on the functional UL recovery after BTX-A treatment including the lack of suitable and simple measures to assess functional upper limb recovery; the role of spasticity on the motor activity; the effect of associated rehabilitative interventions; and the time evaluation of functional outcome after BTX-A injections.

One of major concern in rehabilitation is the difficulty to evaluate and quantify UL functional recovery by proper instruments and measurements and this is underscored by the huge of scales employed. In this respect, it is critical to distinguish “motor recovery” from “functional recovery”. Motor recovery refers to a reduction in impairment such as the strength, speed, or accuracy of an affected extremity, whereas functional recovery refers to improvement in activity limitation or task performance, such as dressing, bathing, or eating [55,56]. So far, no assessment can efficaciously differentiate and quantify these closely interacting components of recovery. Indeed, functional recovery of an arm that enables grasping, holding and manipulating objects requires the recruitment and complex integration of muscle activity from the shoulder to the fingers. Furthermore, it is needed to consider how spasticity interact with motor performance and functional recovery. Spasticity is only one among several clinical signs of well-known upper motor neuron (UMN) syndrome following cerebral lesion and characterized by positive and negative symptoms. Someone hypothesizes that spasticity does not contribute to the limitation of function and that the underlying weakness is the only significant cause of activity limitation [5,23,57,58]. Thereby, a key role could be represented by residual active movement in affected arm. The thread is to understand how much the spasticity affects the motor performance and how much the strength impairment influences the functional recovery. Spasticity in people with severe paralysis can foster persistent postural disorder or hamper arm motor onset or minimal movement capacity. In this condition, the primary aim treating spastic muscles is to allow normal positioning of the limbs to prevent secondary soft tissue shortening and to facilitate care and nursing. Consequently, it would be difficult to obtain quantifiable functional improvement and only increase of passive joint ROM would be expected with BTX-A treatment. Therefore, the benefit should be individuated on specific target such as limb posture facilitation and reduction of care burden. Indeed, significant global benefit and carer burden score improvement have been reported in post-stroke patients after UL spasticity reduction by BTX-A compared to placebo [11,36,37, 41,45,49]. Apart muscles co-contraction condition, in which BTX-A injection is expected to fully or partially recover lost function [59], when UL residual motor capacity is present, spasticity could hamper motor performance and increase functional limitation. In this case, its reduction may improve active ROM and upper limb ability. Not significant active ROM was detected in studies of the present review, but Wolf et al. showed that

participants with some retained active upper limb activity (ARAT 4 to 56) were more likely to experience a “successful outcome” than participants with no retained upper limb function (ARAT 0 to 3); (OR, 2.41; 95% CI, 1.40 to 4.14). Sun et al. enrolled only post-stroke patients with residual upper limb strength. Although the study method design did not provide placebo comparing BTX-A plus mCIT to BTX-A plus conventional physiotherapy, ARAT and MAL score increased in both groups of patients, even if BTX-A plus mCIT displayed significant greater improvements on ARAT scale compared to control group. Considered the huge of functional scales employed to assess the UL functional recovery, ARAT, MAL and WMFT can represent suitable measures to evaluate UL functionality after BTX-A injection, though not easy administration and time consuming in clinical practice.

No significant BTX-A effect on global functional disability was observed by reduced UL spasticity in BTX-A treated patients. This is not surprising because of the poor sensitivity of global functional outcome assessment scales in this situation. For example, the BI evaluates functions such as urinary continence and bowel control, which are unlikely to be affected by treatment of localized muscle spasticity [11]. Some functional improvements may be seen after BTX injections, but global functional assessment tools do not consistently reflect these changes.

In evaluating the BTX-A effect on UL functional recovery is need consider the role of additional treatments and in particular the rehabilitation strategies employed in these patients. Generally, BTX-A injection is carried out as an adjunct to rehabilitative interventions that are based on an individualized, multidisciplinary programmes and targeted to achieve patient goals. Some rehabilitative techniques such as mCIT and task-oriented strategies resulted more efficacy, regardless BTX-A treatment than conventional physical therapy [48,51], thereby raising questions as to the extent to which BTX-A contributed to the outcomes more than the exercise program. On the other hand, BTX-A as adjunct to rehabilitation has been demonstrated to improve performance of specific basic upper limb functionality [24,46,50]. Anyway, recent consensus statements for adult spasticity recommend BTX as an adjunctive therapy to an integrated treatment programme or multi-modal approach [60].

Other challenging issues have to be considered other than those previously discussed including time from stroke onset, time evaluation of functional outcome after BTX injection and proper BTX-A dosage. In the present review, studies in which botulinum toxin was given early after the stroke before clinical evidence of severe spasticity were excluded, because confounding results. In all included studies BTX-A was injected almost three months from stroke onset. In particular, in 3 and 3 studies BTX-A treatment was performed after 3 and 6 months after stroke, respectively [39,11,51,41,46,49]. In remaining studies, time elapsed from stroke was from 9 months to 10 years [13,37,38,40,42-45,48,50]. Furthermore, the functional benefit may potentially lag behind the reduction in spasticity itself. This may possibly reflect the time needed to adapt and learn how to use the new reduction in hypertonicity. Meta-analysis demonstrates that there is often a time lag between maximum reduction in spasticity and functional gain, so that the latter may be missed if primary outcomes are measured only at a single early time-point [61].

Other key point is the effect of the neurotoxin on the muscle tone and muscle strength. BTX-A has dose dependent effect [62], therefore it is important to titrate the dose in patients with an ‘incomplete’ UMN lesion to reduce muscle tone sufficiently without inducing excessive weakness [63]. Treatment plans must consider a trade-off between

reduction of spastic hypertonia and preservation of residual motor function [64]. Although there is no clear evidence from the literature to guide optimal timing of interventions (e.g. early versus late), frequency of interventions, dilutions, injection sites or doses, algorithms have been formulated to highlight the optimal candidate, where and when to inject/re-inject, which assessment tools to use, which goals should be targeted and which techniques should be applied in BTX-A injections for UL spasticity [65]. However, a low dose can result unsuccessful and by contrast an high dose can result in excessive muscular weakness that in turn, limit active movements and hamper functional outcome. Formulation potency, inappropriate injection site of target muscle, neurotoxin diffusion from site of inoculation could be responsible for reported conflicting finding.

### Final Considerations

Many challenging questions about relationship between reduced UL spasticity and functional recovery remain unsolved and well designed, future researches should consider and address following issues:

- Upper limb functional recovery by reduced spasticity as primary end-point.
- The development of validated scales applicable across the spectrum of upper limb tasks eliciting the abnormal movements and sensitive to changes with focal treatment such as BTX-A. The measures have to be easy administration, feasibility, not time consuming and able to track specific functional improvements after BTX-A treatment to identify patients who are likely to respond best to this therapy.
- Presenting spasticity pattern and clearly identified functional goals before BTX-A treatment.
- Evaluating the role of rehabilitation intervention and how much specific strategy can effect functional recovery of post-stroke reduced UL spasticity after BTX-A injection.
- Proper evaluation time between maximum reduction in spasticity and functional gain.

### Clinical Application

Despite the previous mentioned questions, some suggestions and recommendations can be carry out to accomplish more evident functional improvement of post-stroke spastic UL after BTX-A treatment, in clinical practice: identification of functional attainable goals before BTX-A injection of spastic UL according to patient's and caregiver preference; choice of proper muscles and BTX-A dosage avoiding excessive weakness; appropriate measures of success or failure such as ARAT, MAL and WMFT in assessing functional outcome; association of specific rehabilitative techniques including mCIT and task-oriented strategies that resulted more efficacy regardless of BTX-A treatment.

### Conclusion

UL spasticity is a common challenging disorder in adult post-stroke patients. The present review of relevant studies show that some oriented-focused movements of UL unequivocally improve after reduced spasticity by BTX-A treatment, but evidence that arm functionality in adult post-stroke patients significantly benefit from this intervention is still doubt. By contrast, no improvement has been observed in global functionality of activity daily living. Further proper designed researches have to be planned to clarify unsolved questions

focusing UL functional recovery after BTX-A treatment, and by using rehabilitative strategies and selected outcome measures that are able to track specific functional improvements.

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