

Spotlight on botulinum toxin and its potential in the treatment of stroke-related spasticity

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Abstract: Poststroke spasticity affects up to one-half of stroke patients and has debilitating effects, contributing to diminished activities of daily living, quality of life, pain, and functional impairments. Botulinum toxin (BoNT) is proven to be safe and effective in the treatment of focal poststroke spasticity. The aim of this review is to highlight BoNT and its potential in the treatment of upper and lower limb poststroke spasticity. We review evidence for the efficacy of BoNT type A and B formulations and address considerations of optimal injection technique, patient and caregiver satisfaction, and potential adverse effects of BoNT.

Keywords: poststroke spasticity, botulinum toxin, onabotulinumtoxinA, incobotulinumtoxinA, rimabotulinumtoxinB

Introduction

Spasticity is a velocity-dependent increase in muscle tone as a part of the upper motor neuron syndrome and is seen in a wide variety of neurologic diseases including stroke.¹ Poststroke spasticity can develop as early as 1 week after stroke,² and it is estimated to occur in up to one-half of stroke survivors.³ The most frequent predictors of spasticity include weakness and reduced motor control.² Long-term spasticity may lead to tendon contractures and limb deformities that can cause significant pain and functional impairment. Depending on the location of the spasticity, this can impact mobility, activities of daily living such as toileting, dressing, and transferring, and quality of life (QoL) and increase the dependence on caregivers.⁴

The aim of the treatment in poststroke spasticity is focused on muscle limb overactivity reduction. Treatment modalities are used to alleviate spasticity including physical therapy, systemic and intrathecal medications, and surgery. Systemic medications can be helpful if spasticity is generalized. Agents such as baclofen (gamma-aminobutyric acid [GABA]-B receptor agonist) diazepam (GABA-A receptor agonist), dantrolene (decreases calcium release from skeletal muscle sarcoplasmic reticulum), or tizanidine (TZD; alpha-2 adrenergic receptor agonist) often have systemic side effects such as dry mouth, dizziness, sedation, or generalized weakness.⁵ After several months of treatment, tolerance may develop to systemic medications.

Chemodenervation and neurolytic procedures with alcohol or phenol may be utilized as second-line management. These techniques are more localized and are injected perineurally to destroy the nerve causing spasticity. The effect may be limited by partial nerve regeneration and adverse effects such as bladder, bowel, and sexual dysfunction.⁶ Intrathecal baclofen acts on GABA receptors in the lumbar spinal cord and may improve walking speed and functional mobility in poststroke spasticity. However, this therapy is

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invasive and limited by side effects including nausea, vomiting, and urinary retention. Overdosing may lead to death.^{7,8}

The aim of this review is to highlight botulinum toxin (BoNT) and its potential in the treatment of upper and lower limb poststroke spasticity. Optimal treatment may include BoNT injections into focal muscles in conjunction with an integrated multidisciplinary team approach and intensive rehabilitation programs or to help utilize affected muscles.⁹ Higher-intensity rehabilitation programs (≥ 3 1-hour weekly session for ~ 10 weeks) may help patients achieve more upper limb goals following BoNT injections for spasticity when compared with usual care programs (≤ 2 1-hour weekly sessions).¹⁰ A recent consensus panel of 44 neurologists and physiatrists with experience in BoNT therapy recommended starting a rehabilitation program during the first week after BoNT injection therapy.¹¹

Pharmacology

There have been major advances in synthesizing BoNT for therapeutic use since the German physician Justinus Kerner first proposed using it clinically in the early 19th century and coined the term “sausage poison.”¹² BoNT is synthesized by the anaerobic bacteria *Clostridium botulinum*, *Clostridium baratii*, and *Clostridium butyricum*.¹³ Serotypes A through G are produced by *C. botulinum*, serotypes F and C are produced by *C. baratii*, and serotype E is produced by *C. butyricum*. Each serotype has a different neurotoxin complex protein structure and is synthesized as polypeptides. All serotypes exert their mechanism of action by inhibiting the release of acetylcholine from nerve endings at the neuromuscular junction.^{14,15} However, each exerts its effects via different protein structures and intracellular targets and, therefore, has different potencies and length of effect.¹⁶ There are currently two serotypes of BoNT, serotypes A and B, that are widely available on the market. The US Food and Drug Administration (FDA) has approved four preparations in the USA. The serotype A (BoNT-A): abobotulinumtoxinA (Dysport; Ipsen, Paris, France), onabotulinumtoxinA (Botox; Allergan, Inc., Irvine, CA, USA), and incobotulinumtoxinA (Xeomin, Merz Pharmaceuticals GmbH, Frankfurt, Germany) and serotype B (BoNT-B): rimabotulinumtoxinB (Myobloc/Neurobloc; Solstice Neurosciences, Inc., San Francisco, CA, USA). OnabotulinumtoxinA and more recently abobotulinumtoxinA are currently the only approved treatments for upper limb spasticity in adults approved by the FDA.

Each toxin serotype consists of a light chain (50 kDa) and a heavy chain (100 kDa) that is linked by a disulfide bond. This forms a protein with a total molecular weight of 150 kDa.

Of the BoNT-A formulations, abobotulinumtoxinA and onabotulinumtoxinA contain the 150 kDa neurotoxin as part of a larger complexing protein, whereas incobotulinumtoxinA contains only the 150 kDa neurotoxin.¹⁷ In order to become active, the neurotoxin must be nicked by proteases into two fragments.¹⁸ Under normal circumstances, a nerve action potential causes acetylcholine to be released by vesicles from the presynaptic membrane. This requires a complex set of proteins called soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins to help to mediate fusion of synaptic vesicles. The light chains of BoNT cleave SNARE proteins, thereby preventing vesicle fusion of acetylcholine and inhibiting its release into the neuromuscular junction. BoNT-A and BoNT-E work by removing amino acids from a SNARE protein called synaptosomal-associated protein 25. BoNT B, D, F, and G work by cleaving vesicle-associated membrane protein/synaptobrevin, and BoNT-C cleaves syntaxin and synaptosomal-associated protein 25.^{19,20} Proposed mechanisms of axonal sprouting play a role in nerve regeneration and eventual repair of paralyzed endplates²¹ and may play a role in the wearing-off effect after ~ 3 months.

The potency of each preparation of BoNT is measured by mouse units, which is the dose that is lethal in 50% of mice tested.¹⁷ Although studies comparing dosage equivalencies between different toxin types have been published, the conversion ratios are not clear, and the FDA specifies that dose conversions should not be performed.

BoNT for upper limb spasticity

The goals of the current review are to highlight the use of BoNT in the treatment of upper and lower limb spasticity. The current review combines class I and II studies addressing the efficacy and safety of BoNT for the treatment of poststroke spasticity (Tables 1 and 2) by assigning levels of evidence according to the American Academy of Neurology guidelines. A broader search was used for the rest of the article. Studies were reviewed from the 2008 Report of Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology,²² and additional literature search was conducted using the PubMed, OvidSP, and Medline databases from January 2008 to October 2015 with the search items “post stroke spasticity,” “upper-limb post stroke spasticity,” “lower limb post stroke spasticity,” “botulinum toxin,” “botulinum neurotoxin,” “abobotulinumtoxinA,” “onabotulinumtoxinA,” “incobotulinumtoxinA,” and “rimabotulinumtoxinB.” Most studies utilized the Modified Ashworth Scale (MAS) as the primary outcome measure for spasticity reduction.

Table 1 Botulinum toxin for poststroke upper limb spasticity

References	Class	Methods	Cohort size	Treatment (serotype/dose)	Targeting technique	Follow-up	Outcome measures/results (1, primary; 2, secondary)	Efficacy	Adverse events
Hesse et al ²³	I	R, DB, PC	24	A/Abo; 1,000 U	EMG	12 wk	1) MAS 2) Limb position at rest, difficulties during ADLs	No significant difference for MAS and limb position. Minor benefit for hygiene	No significant difference between study groups in frequency and nature of adverse events
Bakheit et al ³²	I	R, DB, PC	82	A/Abo; 500 U/1,000 U/1,500 U	Anatomic landmarks	16 wk	1) MAS best change from baseline at wk 4 in either elbow, wrist, or fingers by at least one point 2) Barthel Index, hygiene or dressing, Rivermead motor score	1) Significant reduction in the MAS score in any joint at 4 wk compared with placebo 2) No significant differences between study groups in scores of pain, the Rivermead Motor Assessment Scale, or the Barthel Index	No significant difference between study groups in frequency and nature of adverse events
Bhakta et al ³³	I	R, DB, PC	40	A/Abo; 1,000 U/100 U	Anatomical landmarks	12 wk	1) Subject disability scale and caregiver disability scale at 6 wk 2) MAS, passive ROM, grip strength, pain	1) Improved disability, caregiver burden, finger but not elbow spasticity 2) Improved finger flexor spasticity but not arm pain	Self-limiting arm pain in two patients at 1 wk
Smith et al ²⁶	I	R, DB, PC	21	A/Abo; 500 U/1,000 U/1,500 U	Not specified	12 wk	1) MAS and passive/active ROM 2) Frenchay Arm Test, dressing time, global assessment	1) Passive ROM increased significantly in wrist but not at fingers 2) No significant difference	Flu-like symptoms for 2 days in one patient
Bakheit et al ³¹	I	R, DB, PC	59	A/Abo; 1,000 U/500 U	Anatomic landmarks	16 wk	1) MAS at elbow, wrist, or fingers at 4 wk 2) Joint ROM, muscle pain, functional ability, goal attainment scale, global assessment of benefit	1) Significantly reduced MAS at 4 wk 2) Passive ROM at the elbow significantly increased at 16 wk, but no significant functional improvement	Fatigue and pain in arm following injection in the BoNT group
Suputtitada and Suwanwela ²⁹	I	R, DB, PC	50	A/Abo; 350 U/500 U/1,000 U	EMG	24 wk	1) MAS score 2) ARAT, Barthel Index, VAS	1) MAS improved in all dose groups at 8 wk 2) ARAT improved at 8 wk and 24 wk; Barthel Index improved at 8 wk and 24 wk in the 500 U group; VAS improved at 8 wk and 24 wk compared with placebo in the 500 U and 1,000 U groups	Muscle weakness in 5/5 patients in the 1,000 U group

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Table 1 (Continued)

References	Class	Methods	Cohort size	Treatment (serotype/dose)	Targeting technique	Follow-up	Outcome measures/results (1, primary; 2, secondary)	Efficacy	Adverse events
McCrory et al ²⁴	I	RCT, blinded outcome assessment	96	A/Abo: 750–1,000 U, repeat 500–1,000 U at 12 wk	EMG or E-stim	20 wk	1) Patient well-being and the quality of life as measured by AQoL 2) Pain, depression, goal attainment scale, MAS, modified motor assessment scale, patient disability and carer burden, patient functional outcome measure, global assessment of benefit	1) AqoL scores were not significantly different between treatment and controls 2) Greater reduction in MAS, higher GAS, and greater global benefit in the BoNT group	Mild adverse events reported in both treatment and placebo group
Turner-Stokes et al ³⁰	I	Secondary analysis; McCrory et al ²⁴ study	90	A/Abo: 750–1,000 U at wk 0 and 500–1,000 U at wk 12	EMG or E-stim	20 wk	GAS outcome T-scores compared with change from baseline in MAS, disability and carer burden, pain, mood, AQoL	Significant change in GAS score between baseline and wk 8 and 20 for the BoNT group only	No significant difference between the study groups in frequency and nature of adverse events
Shaw et al ²⁵	I	RCT, blinded evaluators	333	A/Abo: 200–300 U; repeat injection at 3 mo, 6 mo, and 9 mo if needed	Not specified	4 wk, 12 wk and 48 wk	1) ARAT 2) MAS, Motricity Index, grip strength, Barthel Index, nine-hole peg test, pain	1) No significant difference in ARAT 2) Improvement in MAS at 4 wk and in pain at 48 wk	No significant difference between the study groups in frequency and nature of adverse events. Only one serious adverse event (dysphagia of unknown cause) was believed to be potentially related to BoNT
Rosales et al ²⁷	I	R, DB, PC; parallel group	163	A/Abo: 500 U	Not specified	24 wk	1) MAS score at 4 wk from baseline for the most affected joint (wrist or elbow flexors) 2) Changes from baseline in MAS, Barthel Index, Modified Rankin Scale scores and Functional Motor Assessment Scale scores for upper arm function, hand movements, and advanced hand activities at 2 wk, 4 wk, 8 wk, 12 wk, and 24 wk	1) BoNT was significantly more effective in improving MAS scores than placebo at 4 wk 2) No significant change in functional motor assessment scale scores	No significant difference between study groups in frequency and nature of adverse events

Lam et al ³⁵	I	R, DB, PC	55	A/Abo; max 100 U	Individual judgment	24 wk	<p>1) CBS</p> <p>2) GAS, Tardieu scale and MAS, resting angular position, passive ROM, finger position at rest and at maximal passive extension, pain assessment using PAINAD, incidence of fracture, pressure sores and skin infections</p>	<p>1) Significant four-point reduction in the CBS in the treatment group</p> <p>2) Improvements in GAS, Tardieu, and MAS, passive ROM, resting position, resting PAINAD score but no significant difference overall in the change in PAINAD scores between groups</p>	<p>Three patients died in the treatment group that was believed to be unrelated to BoNT. No significant difference between the study groups in frequency and nature of adverse events</p>
Simpson et al ³⁸	I	R, DB, PC	39	A/Ona; 75 U/100 U/300 U, 25 U/ml/50 U/ml/100 U/ml	EMG	16 wk	<p>1) Change in muscle tone per AS</p> <p>2) Physician and patient global assessment, FIM, caregiver dependency, Fugl-Meyer</p>	<p>1) Significant improvement in AS in the treatment group compared with placebo</p> <p>2) Significantly higher global assessment of response and grip strength in the treatment group compared with placebo. No significant differences between groups on the FIM, Fugl-Meyer, caregiver dependency, function and pain assessment, motor/function task-rating scale, or Rand 36-item healthy survey</p>	<p>No significant difference between the study groups in frequency and nature of adverse events</p>
Richardson et al ³⁹	I	R, DB, PC	32	A/Ona; 50 U/ml	EMG	12 wk	<p>1) Passive ROM by MAS, subjective rating of problem severity</p> <p>2) Focal disability, Rivermead Motor Assessment Scale, Modified Goal Attainment, nine-hole peg test</p>	<p>1) Significant improvement on MAS and ROM</p> <p>2) No significant treatment effects on Rivermead Motor Assessment Scale, Modified Goal Attainment, or nine-hole peg test</p>	<p>Pain at injection in four patients</p>
Brashear et al ²⁸	I	R, DB, PC	126	A/Ona; 200–240 U	Not specified	16 wk	<p>1) Functional disability by DAS at 6 wk</p> <p>2) Ashworth, GAS</p>	<p>1) At least one-point improvement in DAS in the treatment group at 6 wk and all follow-up visits</p> <p>2) Scores for physician's, patient's, or caregiver's global assessment were significantly higher in the treatment group</p>	<p>Muscle weakness in 6% of the BoNT patients</p>
Childers et al ⁴⁰	I	R, DB, PC	91	A/Ona; 90 U/180 U/320 U	EMG guidance	6 wk and 24 wk	<p>1) MAS wrist flexor tone</p> <p>2) MAS elbow and finger flexor tone, physician/Pt global assessment, pain, SF-36, FIM</p>	<p>1) Significant dose-dependent reduction in muscle tone in wrist flexors, elbow flexors, and finger flexors</p> <p>2) No significant change in pain, SF-36, FIM</p>	<p>Pain and hematoma at BoNT-injected patients</p>

(Continued)

Table 1 (Continued)

References	Class	Methods	Cohort size	Treatment (serotype/dose)	Targeting technique	Follow-up	Outcome measures/results (1, primary; 2, secondary)	Efficacy	Adverse events
Jahangir et al ³⁷	II	RCT with masked outcome assessment	50	A/Ona; 80 U wrist and finger flexors	Not specified		1) Change in wrist and finger flexor tone using MAS 2) Barthel Index, EQ-5D, and VAS	1) Significant improvement in MAS of wrist flexor and finger flexor muscles compared with placebo 2) Significant improvement in median scores of the Barthel Index, EQ-5D, and VAS between the BoNT group and placebo	No significant difference between the study groups in frequency and nature of adverse events
Simpson et al ³⁶	I	R, DB, PC; parallel group trial	60	A/Ona; fixed dose at the wrist, flexible dosing for other muscles	E-stim	22 wk	1) Change in wrist flexor using MAS at 6 wk 2) Change in elbow and finger joint MAS, DAS, Modified Frenchay Scale, walking speed, contralateral grip strength, finger tap test, Epworth Sleepiness Scale, cognitive evaluations	1) Significantly greater reduction in wrist flexor tone in the BoNT group vs TZD or placebo at 6 wk 2) Trend toward improvement in DAS at 6 wk	Greater incidence of AEs in tizanidine vs placebo or BoNT treatment groups
Kaji et al ^{62,50}	I	R, DB, PC	109	A/Ona; 200–240 U/120–150 U	EMG/E-stim	12 wk	1) AUC of change in wrist flexor tone using MAS in the high-dose group 2) AUC of change in MAS wrist score in low-dose group, wrist, fingers, and thumb MAS, DAS, CGI	1) Significant improvements in the high-dose group 2) No significant difference in MAS wrist in the low-dose group. Finger differences significant at 6 wk, significant decrease in DAS scores, significantly higher CGI scores by investigator	No significant difference between the study groups in frequency and nature of adverse events
Marciniak et al ⁴¹	I	R, DB trial	21	A/Ona; 140–200 U		12 wk	1) MAS for shoulder adductors/internal rotators, flexors, extensors, and shoulder pain at 4 wk 2) Passive ROM, McGill Pain Questionnaire-Short Form, Beck Depression Inventory, Fugl-Meyer Scale, Daily Diaries, Functional Independence Measure, FIM, DAS	1) Significant main effects for shoulder adductors/internal rotators, flexors, and extensors 2) No significance for pain, depressive symptoms, ROM, disability	Ten AEs in both groups, not likely related to BoNT

Ward et al ⁴³	I	R, DB, PC	273	A/O _{na}	Not specified	24 wk, open-label extension to 52 wk	1) Number of patients achieving their principal active functional goal at 24 wk 2) Number of patients achieving their active functional goal at 12 wk and 52 wk; secondary active or passive goal attainment at 12 wk, 24 wk, and 52 wk; median level of functional goal attainment (principal and secondary); REPAS-26 score at baseline and each study visit	1) No significant differences in the number of patients achieving principal functional goal 2) No significant difference in patients achieving their secondary active functional goal. Significantly more patients achieved their secondary passive goal as well as GAS levels of upper limb and ankle flexor subgroups	Local muscle weakness, falls, and musculoskeletal pain in the treatment group
Kaňovský et al ⁴⁴	I	R, DB, PC	148	A/Inco; ≤400 U	EMG or E-stim	12 wk	1) Muscle tone as measured by AS 2) DAS, global assessment of efficacy	1) Significant change in AS in the treatment group 2) Changes in DAS for principal therapeutic target were statistically significant for all injection intervals	No significant difference between the study groups in frequency and nature of adverse events
Brashear et al ⁴⁷	I	R, DB, PC	15	B/Rima; 10,000 U	E-stim	16 wk	1) AS at 4 wk 2) Global assessment, pain	1) No significant differences in AS scores between groups 2) No significant differences between groups	Dry mouth in 8/9 BoNT-treated subjects vs 1/5 in the placebo group
Gracies et al ⁴⁸	I	R, DB, PC	24	B/Rima; 10,000 U/15,000 U		12 wk	1) MAS at 4 wk 2) PGA at 4 wk and change from baseline to 4 wk in DAS	1) Significant mean changes in MAS at wk 4 in both BoNT groups vs placebo 2) Significant changes in mean PGA scores in the 500 U and 1,000 U groups compared with placebo; no significant changes in DAS scores compared with placebo	Ten AEs in both groups, not likely related to BoNT

Abbreviations: A/QoL, Assessment of Quality of Life scale; ARAT, Action Research Arm Test; AUC, area under curve; BoNT, botulinum toxin; CBS, Carer Burden Scale; CGI, clinical global impression; DAS, Disability Assessment Scale; DB, double blind; EMG, electromyography; EQ-5D, EuroQoL-5 dimensions; E-stim, electrical stimulation; FIM, Functional Independence Measure; GAS, Global Assessment Scale; MAS, Modified Ashworth Scale; PAINAD, Pain Assessment in Advanced Dementia Scale; PC, placebo controlled; PGA, Physician Global Assessment; R, randomized; REPAS, Resistance to Passive Movement Scale; ROM, range of movement; SF-36, Study 36-Item Short-Form Health Survey; TZD, tizanidine; wk, weeks; A/Abo, abobotulinumtoxinA; A/O_{na}, onabotulinumtoxinA; A/Inco, incobotulinumtoxinA; A/Inco, onabotulinumtoxinB; ADL, activities of daily living; VAS, visual analogue scale; RCT, randomized controlled trial; AS, ashworth scale; AE, adverse events.

Table 2 Botulinum toxin for poststroke lower limb spasticity

References	Class	Methods	Cohort size	Treatment (serotype/dose)	Targeting technique	Follow-up	Outcome measures/results (1, primary; 2, secondary)	Efficacy	Adverse events
Pitcock et al ⁵¹	I	R, DB, PC	234	A/Abo; 500 U/1,000 U/1,500 U	Anatomic landmarks	12 wk	1) Two-minute walking distance and stepping rate 2) Step length, stepping rate, leg and trunk section of the Rivermead Motor Assessment and active and passive ROM, MAS, pain, use of walking aids, global assessment of benefit	1) Distance walking increased significantly compared with baseline, but no group-to-group differences 2) Significant improvements in spasticity as measured by MAS limb pain and reduction in the use of walking aids. No significant benefit with respect to walking speed, stepping rate, or step length	No significant difference between the study groups in frequency and nature of adverse events
Richardson et al ³⁹	I	R, DB, PC	20	A/Ona; variable dose; flexible protocol	EMG guidance	12 wk	1) Passive ROM by MAS, subjective rating of problem severity 2) Focal disability, Rivermead Motor Assessment Scale, Modified Goal Attainment	1) Significant improvement on MAS and ROM 2) Rivermead scores significantly better for treated patients. No effect on gross motor function or goal attainment	Pain at injection in four patients
Kaji et al ^{10,20}	I	R, DB, PC	120	A/Ona; 300 U	EMG/E-stim	16 wk	1) AUC of change in MAS ankle 2) Gait pattern, gait speed, CGI	1) Change in MAS AUC significantly higher with treatment vs placebo 2) MAS and physician-assessed CGI superior in the treatment group at 4 wk, 6 wk, and 8 wk. Gait speed and patient-assessed CGI, not significant	No significant difference between the study groups in frequency and nature of adverse events
Dunne et al ⁴⁹	I	R, DB, PC	85	A/Ona; 200 U/300 U		12 wk	1) Plantar flexor ashworth scale 2) Self-reported spasm frequency and pain, physician rating of hypertononia severity, gait quality, and active dorsiflexion	1) Significant reduction in ashworth scale in patients with a baseline ashworth scale >3 2) Improvement in gait quality	No significant difference between the study groups in frequency and nature of adverse events

Abbreviations: AUC, area under curve; CGI, clinical global impression; DB, double blind; EMG, electromyography; E-stim, electrical stimulation; MAS, modified Ashworth Scale; PC, placebo controlled; R, randomized; ROM, range of movement; wk, weeks; A/Abo, abobotulinumtoxinA; A/Ona, onabotulinumtoxinA.

AbobotulinumtoxinA

AbobotulinumtoxinA was approved by the FDA in 2015 for the treatment of upper limb poststroke spasticity. Eleven class I trials have found that abobotulinumtoxinA is effective and safe for the reduction in upper limb poststroke spasticity.^{23–33} Studies assessing both active and passive functional outcomes have demonstrated a significant improvement in passive function (improved range of motion, etc), while failing to show substantial improvement in active muscle function.^{24,25,27}

A trial conducted at 34 neurology and rehabilitation clinics in the USA and in Europe randomized 243 patients to placebo, abobotulinumtoxinA (500 U), or abobotulinumtoxinA (1,000 U). The primary endpoint of mean change in muscle tone of hypertonic muscle groups of the upper limb was significant in both abobotulinumtoxinA groups vs placebo. The secondary endpoint of mean change in the Physician Global Assessment, clinician-rated clinical benefit independent of the MAS, was significantly different after 4 weeks, although the perceived function Disability Assessment Scale (DAS) was not significantly different.³⁴

A study in Australia which assessed 96 patients comparing abobotulinumtoxinA (500–1,000 U) with placebo reported no significant difference in their primary outcome of QoL. However, there was a significant improvement in secondary outcomes including greater reduction in spasticity ($P<0.001$) and Goal Attainment Scale, pain, mood, global benefit, disability, and carer burden.²⁴ Further analysis of these data suggested significantly higher levels of goal attainment in the treatment group and a cumulative effect over two cycles of treatment.³⁰

Another study randomized 333 patients from 12 stroke services in the UK and found no significant difference in the primary outcome of improved arm function at 1 month, 3 months, or 12 months. Muscle tone and spasticity at the elbow were decreased at 1 month as a secondary outcome measure.²⁵ A final study enrolled 163 patients and randomized them to abobotulinumtoxinA (500 U) vs placebo and found improved scores in the treatment group but failed to find a clinically significant difference in the Functional Motor Assessment Scale.²⁷

Further studies that found improvement in spasticity and passive range of movement in spastic upper limbs have noted improvement in disability with caregiver assistance such as helping dressing and cleaning of the affected limb and decreased caregiver burden.^{26,31,33,35}

OnabotulinumtoxinA

OnabotulinumtoxinA has been studied extensively and found to be safe, and to significantly reduce upper limb spasticity

after stroke.^{28,36–40} Studies also used the MAS and found dose-dependent improvements with sustained benefits at 3 months; however, the reduction in pain measurements was not demonstrated.^{28,37,39–42} Although some studies have found improvements in functional disability on the DAS²⁸ and the Global Assessment of Response to Treatment,³⁸ others failed to demonstrate gains in functional activity.^{37,40,43} For example, a class II trial in Malaysia found improvement in flexor tone of the wrist and finger muscles at 1 month and 3 months. Although there were improvements in measures of global function and QoL in the onabotulinumtoxinA group, there were no significant differences between the onabotulinumtoxinA group and placebo.³⁷ The Botox Economic Spasticity Trial randomized onabotulinumtoxinA plus standard of care to placebo plus standard of care and was assessed for passive and active functional goals (as defined by both the patient and the investigator) at 12 weeks followed by an open-label period of 52 weeks. Although more patients in the treatment group achieved their secondary passive goal, there was no difference between groups in the principal and secondary active functional goals.⁴³

Three class I studies assessing the effects of onabotulinumtoxinA vs placebo have found improvements in spasticity but not in pain. The first study randomized 109 patients to receive a lower- (120–150 U) or higher-dose (200–240 U) onabotulinumtoxinA or placebo in spastic upper limbs after stroke and found significant improvements in spasticity with the higher-dose onabotulinumtoxinA. No significant differences were found with the lower-dose onabotulinumtoxinA and placebo. Secondary outcome measures of functional disability showed a significant decrease in the DAS score for limb position and dressing in the higher-dose onabotulinumtoxinA group, but not for hygiene and pain.⁴² The second study randomized 91 stroke patients to two treatments of placebo and 90 U, 180 U, or 360 U of onabotulinumtoxinA for upper limb spasticity. A dose-dependent response was observed in tone reduction but not in functional disability, pain, or QoL.⁴⁰ The third study (only 21 patients) assessed the efficacy of onabotulinumtoxinA in reducing pain, impairment, and disability in patients with shoulder pain and spasticity. They found no significant differences in pain scores on the McGill Pain Questionnaire between those injected with BoNT and those injected with placebo ($P>0.05$), although they did find improvements in hygiene on the DAS ($P<0.05$) with a similar trend toward significance for improvement on the DAS dressing scale ($P=0.061$).⁴¹

There are few trials comparing BoNT serotypes. Our group reported differences between onabotulinumtoxinA

and TZD. This class I study compared injections of onabotulinumtoxinA with TZD vs placebo in 60 patients with upper limb spasticity from either stroke or traumatic brain injury. Patients were randomized to intramuscular onabotulinumtoxinA plus oral placebo, oral TZD plus intramuscular placebo, and intramuscular placebo plus oral placebo. OnabotulinumtoxinA elicited greater reduction in tone than TZD or placebo in finger and wrist flexors at 3 weeks ($P < 0.001$ vs TZD; $P < 0.02$ vs placebo) and 6 weeks ($P = 0.001$ vs TZD; $P = 0.08$ vs placebo). Dressing, hygiene, cosmesis, and pain demonstrated a nonsignificant trend to a greater reduction in the primary therapeutic target 6 weeks after injection in the onabotulinumtoxinA group.³⁶

IncobotulinumtoxinA

Two class I trials have demonstrated reduction in tone with incobotulinumtoxinA. The first study assessed incobotulinumtoxinA by randomizing 148 upper limb poststroke spasticity patients to 400 U of incobotulinumtoxinA vs placebo who were then followed for 20 weeks. At 4 weeks, there was a >1 -point improvement in the Ashworth scale score in the finger flexor muscles compared with patients who received placebo (odds ratio 3.91, 95% confidence interval: 1.9–9.3).⁴⁴ Subsequent open-label extension of the study continued to show benefit, with most investigators, patients, and caregivers rating positive benefit and efficacy throughout the open-label period of 69 weeks.⁴⁵ The second study randomized 349 patients to incobotulinumtoxinA (400 U) or placebo at 46 international sites. There was a reduction in the Ashworth scale score in the primary target clinical pattern (-0.9 incobotulinumtoxinA vs -0.5 placebo; $P < 0.001$) with >1 -point improvement (69.6% incobotulinumtoxinA vs 37.5% placebo) when compared with placebo.⁴⁶ Both studies demonstrated significant improvements in DAS scores from baseline across domains of dressing, limb position, hygiene, and pain.^{45,46}

RimabotulinumtoxinB

Two smaller class I trials on rimabotulinumtoxinB (BoNT-B) have been completed. The first study randomized 15 patients to 10,000 U of rimabotulinumtoxinB or placebo in elbow, wrist, and fingers and found a significant decrease in wrist tone 2 weeks after injection, but it did not find a decrease in tone at the finger flexors or elbow at 10,000 U of rimabotulinumtoxinB over a 16-week period.⁴⁷ The second trial randomized 24 patients with elbow flexor spasticity after stroke or traumatic brain injury to 10,000 U or 15,000 U of rimabotulinumtoxinB or placebo and followed for 3 months. Patients

who had received either dose of rimabotulinumtoxinB had significantly improved active elbow extension compared with placebo.⁴⁸

BoNT for lower limb spasticity

There are fewer studies assessing the effects of BoNT in the treatment of lower limb poststroke spasticity compared with upper limb poststroke spasticity (Table 2). Most class I studies have assessed the efficacy and safety of abobotulinumtoxinA and onabotulinumtoxinA.

There are three class I studies of onabotulinumtoxinA which have established significant reduction in muscle tone in poststroke lower limb spasticity. In the first study, 85 subjects received 200 U or 300 U of onabotulinumtoxinA or saline injections with the primary measure being plantar flexor Ashworth scores at 12 weeks. Subjects noted significantly greater decrease in spasm frequency ($P = 0.01$), pain reduction ($P = 0.02$), active dorsiflexion ($P = 0.03$), and gait quality ($P = 0.02$).⁴⁹ In the second study, Kaji et al randomized 120 patients with lower limb spasticity to BoNT-A (300 U) or placebo. Although a significant improvement in spasticity was seen, no change in the speed of gait was found between groups.⁵⁰ In the third study, Richardson et al assessed onabotulinumtoxinA vs placebo with assessments at 3-week intervals after injection until 12 weeks in patients with either upper or lower limb spasticity from a variety of injuries including stroke. Among 52 people, 20 of which had lower limb spasticity; onabotulinumtoxinA had an effect on focal disability and impairment in lower limbs.³⁹

There is one class I study of abobotulinumtoxinA. In this study, the effects of three doses of abobotulinumtoxinA at 500 U, 1,000 U or 1,500 U in 234 stroke patients were assessed. The primary outcome measure of 2-minute walking distance and stepping rate increased significantly in both groups, but no significant difference was found between groups including placebo. Significant improvements in calf spasticity, limb pain, and reduction in the reuse of walking aids were found with abobotulinumtoxinA compared with placebo, with the greatest benefits found in patients receiving 1,500 U.⁵¹

Technical considerations

Optimal dosing and time of administration

Minor differences exist between storing and preparing the various BoNT serotypes, and care should be taken to read the package insert to ensure optimal preparation. For example, onabotulinumtoxinA and abobotulinumtoxinA

are both available as powders for reconstitution which must be refrigerated at 2°C–8°C, whereas incobotulinumtoxinA does not need to be refrigerated. RimabotulinumtoxinB does not require reconstitution and is stable for 21 months in refrigerator storage.

Better outcomes may be obtained if BoNT is injected after a shorter duration of onset to spasticity.^{52,53} This may be attributed to the fact that contractures begin to develop as early as 2 weeks after stroke.² There are currently no well-defined guidelines regarding optimal BoNT dosing, although several strategies have been implemented. The European Consensus data on BoNT-A for adult spasticity recommend 600 U of onabotulinumtoxinA and incobotulinumtoxinA and up to 1,500 U of abobotulinumtoxinA per injection session.⁵⁴ More recent literature suggests using higher doses for poststroke spasticity. Baricich et al recently recommended dosing of up to 600–800 U of onabotulinumtoxinA in upper and lower poststroke spasticity.⁵⁵ A recent review article of eight selected studies suggests that higher doses of BoNT-A are efficacious in reducing upper and lower limb poststroke spasticity, with mild adverse effects.⁵⁶

Another study aimed at characterizing the dose–response relationships between muscle tone and onabotulinumtoxinA tone pooled data from seven trials. A total of 544 patients were randomized to receive onabotulinumtoxinA or placebo. Dose–response relationships demonstrated greater improvements in muscle tone with increasing doses of onabotulinumtoxinA. Doses estimated to cause a decreased muscle tone were 22.5 U, 18.4 U, 66.3 U, and 42.5 U in the flexor carpi radialis, flexor carpi ulnaris, flexor digitorum superficialis, and flexor digitorum profundus, respectively, and not determinable in the biceps brachii.⁵⁷

Injection patterns and optimal targeting

The most frequently injected upper and lower limb muscles were reported in a meta-analysis of 70 randomized, nonrandomized, and single-arm studies evaluating onabotulinumtoxinA muscle injection patterns in 2,163 adult spasticity patients. The upper limbs included the flexor carpi radialis (64.0%), flexor carpi ulnaris (59.1%), flexor digitorum superficialis (57.2%), flexor digitorum profundus (52.5%), and biceps brachii (38.8%). The most commonly injected lower limb muscles included the gastrocnemius (66.1%), soleus (54.7%), and tibialis posterior (50.5%).⁵⁸ A modified Delphi panel of ten clinical experts identified a treatment paradigm for muscle selection, dose for each muscle and for each posture, and use of localization techniques for injecting onabotulinumtoxinA in poststroke upper limb spasticity.

The authors identified three common aggregating upper limb postures in poststroke spasticity including 1) adducted shoulder, flexed elbow, pronated forearm, flexed wrist, and clenched fist; 2) flexed elbow, pronated forearm, flexed wrist, and clenched fist; and 3) flexed wrist and clenched fist. They recommended a dilution of onabotulinumtoxinA of 50 U/mL (2:1 dilution ratio) and starting doses for each aggregate were 300 U, 300 U, and 200 U with total maximum doses of 400 U, 400 U, and 300 U, respectively. They also concluded that localization techniques were needed to identify muscles.⁵⁹

Practitioners commonly used landmark localization, electrical stimulation, electromyography guidance, and ultrasound to identify targeted muscles for injection. The knowledge of high-density endplate areas can maximize yield when using anatomic landmarks for injection. Although some muscles have well-defined motor endplates, other muscles may require a more even spread of injection across the muscle⁵⁴ or higher dilutions.⁶⁰ Optimal targeting based on anatomic knowledge of highest endplate density may yield the highest results. Amirali et al histologically mapped endplate bands in relation to external landmarks in human biceps brachii muscles. The study found that the area of highest endplate density is an inverted V-shaped band 1 cm in width between the lower third and upper two-thirds of the muscle belly.⁶¹ In an attempt to determine the effects of onabotulinumtoxinA dilution and endplate targeting in elbow flexors, Gracies et al randomized 21 patients in four groups, 4 months after a 160 U injection of BoNT-A into spastic biceps brachii muscles. These four groups included 1) 100 U/mL dilution, 0.4 cc/site, four-quadrant injection; 2) 100 U/mL dilution, 0.4 cc/site, four sites along endplate band; and 3) 20 U/mL dilution, 2 cc/site, four-quadrant injection. They found that a high-volume dilution (20 U/mL) and an endplate-targeted injection are superior to a low-volume, endplate nontargeted injection, when injecting biceps brachii.⁶⁰

Although anatomic knowledge of surface landmarks and endplate densities may be important while injecting, electrical stimulation and ultrasound have been shown to be important tools for ensuring accurate injection into the targeted muscles. One study found that only 37% of needle placement attempts reached target muscle fascicles, suggesting that further guidance tools may be needed for correct localization, particularly for small or deep muscles.⁶² Picelli et al randomized 60 poststroke spasticity patients to manual needle placement, electrical stimulation, and ultrasound techniques using abobotulinumtoxinA. They found that patients injected using electrical stimulation and ultrasound guidance

had improved MAS scores, Tardieu angle, and passive range of motion when compared with the manual needle placement group. They found no differences between the ultrasound and electrical stimulation groups.⁶³

Two additional studies have found the benefit of ultrasound over surface landmark techniques and manual needle placement. One study compared surface landmark technique with ultrasound guidance when injecting spastic muscles of the upper extremity with abobotulinumtoxinA and found significant differences between methods, concluding that ultrasound guidance can help avoid injection into nerve and vascular structures and ensure the injection remains within the fascicle borders.⁶⁴ Another randomized study compared ultrasound guidance with surface landmark techniques by measuring MAS and finger position in poststroke patients with upper limb spasticity treated with incobotulinumtoxinA. After 1 month of follow-up, MAS and finger position at rest were significantly improved in both groups, although they were significantly better in patients treated with ultrasound guidance than those with manual needle placement.⁶⁵

Adverse events associated with BoNT

Adverse short-term issues related to BoNT include local pain at the site of injection and spread, or the diffusion of toxin from the injected muscle into neighboring muscles causing undesirable weakness. Depending on the location, spread can be dangerous and adverse events that have been reported include dysphagia, dysarthria, dysphonia, respiratory compromise, and rarely death.⁶⁶ A solid knowledge of the muscle anatomy can help decrease this risk. The long-term effects include anatomic denervation and muscle atrophy, as well as immunoresistance. However, more recent studies demonstrate that a relatively small group of patients actually develop immunoresistance. One study measured 207 patients' posttreatment serum samples for neutralizing antibodies who received onabotulinumtoxinA with poststroke spasticity and found that one patient who had received four treatments tested positive to neutralizing antibodies after the first injection and did not respond to treatment.⁶⁷ A meta-analysis assessing rates of neutralizing antibody conversion with onabotulinumtoxinA found that only one subject out of 317 (0.32%) of poststroke spasticity subjects converted from a baseline status of antibody negative to antibody positive after treatment.⁶⁸ Given the relatively low rate of antibody formation, authors suggest considering other factors when faced with a patient with nonresponsiveness such as technical issues. Several ways of minimizing these effects include increasing doses of BoNT⁶⁹ and switching serotypes of

BoNT.⁷⁰ IncobotulinumtoxinA theoretically may have less immunoresistance given that it is free of complexing proteins, although no study has confirmed this.

Satisfaction

No significant differences were found in caregiver dependency in a small study of 39 patients randomized to onabotulinumtoxinA vs placebo. Two recent cross-sectional surveys conducted in the USA, Canada, France, and Germany of 79 patients found that 40.5% of patients were very satisfied, 48.1% were somewhat satisfied, and 11.4% were not satisfied with at least two treatment sessions of any of the BoNT-A formulations. Interestingly, patient satisfaction was the lowest right before injection and the highest at the time-of-peak effect. Most of the participating physicians were moderately (57.7%) or very (36.5%) satisfied with the BoNT-A treatment.⁷¹ AbobotulinumtoxinA decreases caregiver burden in the long-term care patients who are treated for upper limb spasticity. In this study, 55 patients randomized to abobotulinumtoxinA vs placebo noted a four-point reduction in carer burden ($P < 0.001$) when treated with abobotulinumtoxinA.³⁵ Another study randomized 40 patients with poststroke spasticity to receive abobotulinumtoxinA vs placebo and found a reduction in carer burden at week 6 after injection with abobotulinumtoxinA. This benefit was extended for at least 12 weeks.³³

Cost analysis

The cost of BoNT may be prohibitive to patients without insurance coverage, and even for those with insurance coverage that cannot get approval for treatments such as booster injections within 3 months. The BoNT for Upper Limb after Stroke trial assessed the cost-effectiveness of BoNT-A plus an upper limb therapy program in the treatment of poststroke upper limb spasticity in England and Wales. They found that the addition of BoNT-A was not estimated to be cost-effective and in fact two-and-a-half times the cost-effectiveness threshold as set by the National Institute for Health and Clinical Excellence.⁷² Another study evaluated the cost per patient per injection of two types of BoNT-A, onabotulinumtoxinA (100 U) and abobotulinumtoxinA (500 U), using the recommended dosing of 300 U and 1,000 U for upper limb spasticity, respectively. The cost per patient per injection for upper limb spasticity was less for abobotulinumtoxinA than for onabotulinumtoxinA in 18 of the 19 countries assessed, while allowing for different prices per vial in each country. Ultimately, the authors suggested that substantial savings could be made by using abobotulinumtoxinA in the treatment of upper limb spasticity.⁷³

Conclusion

Poststroke spasticity can be a major source of morbidity and has an impact on activities of daily living, hygiene, caregiver burden, and QoL. The mainstays of conventional treatment include a multifaceted approach that may include incorporating a structured rehabilitation program and/or multidisciplinary team approach, although more data are needed in this area. Based on current class I and II studies, we suggest that BoNT is used as part of a dynamic approach to treating poststroke spasticity. The current data on BoNT demonstrate that it effectively decreases muscle tone in poststroke spasticity of the upper and lower limbs. However, studies assessing both improvements in active function as well as pain reduction have not had as robust a response.

The lack of strong active functional outcomes when compared with passive functional outcomes may reflect the need for more sensitive assessment scales that assess more than just muscle tone. Most studies currently utilize the MAS, while more flexible and patient-centered approaches may be considered, including the Goal Attainment Scale that allows for the use of individualized functional treatment goals.⁷⁴ Investigators from the BoNT for Upper Limb after Stroke trial who demonstrated reduction in spasticity but not in active function of the upper limb suggest that weakness is more important than spasticity in reduced upper limb function.²⁵ The cumulative data on pain reduction are mixed in poststroke spasticity, but interestingly there have been some data suggesting a role for BoNT in the reduction of pain including diabetic neuropathic pain,^{75,76} occipital neuralgia,⁷⁷ trigeminal neuralgia,⁷⁸ and complex region pain syndrome.⁷⁹

Strategies to reduce adverse effects on BoNT injections include having a solid knowledge of anatomy of muscles to be injected before injection, using additional methods such as electromyography, electrical stimulation, or ultrasound guidance. It is important to identify and exclude populations who may have hypersensitivity to BoNT including neuromuscular junction disorders and anterior horn cell disorders prior to injection. In addition, as botulinum serotypes can differ, reading the packaging label before use and being familiar with proper storage techniques, planning out dosing, and knowing reconstitution techniques may be prudent.⁶⁶

Thus far, there have been only few comparator trials comparing different BoNT formulations, and one study comparing BoNT with an oral therapy, TZD.³⁶ Future head-to-head trials are needed to determine the efficacy of one BoNT serotype and formulation when compared with another in addition to BoNT in comparison with other treatments. Determining which muscles to inject should be tailored

to each patient individually. Further research is needed to identify standard muscles in the upper and lower extremity, and further recommendations are needed to identify the number and location of injection sites. As the usage of the other formulations continues to grow, we expect to acquire more information on safety, dosing, efficacy, and potential uses for particular muscles in upper and lower limb spasticity. Given the differences in formulation, mechanism of action, dosing and potential adverse effect profile, we recommend that future studies address formulations individually.

Disclosure

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