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# The Effectiveness of Botulinum Toxin Injections to Treat Post-Stroke Arm Dysfunction

Audrey Tsai[1] and Jane Sullivan[2#]

[1]Los Altos High School
[2]Northwestern University
[#]Advisor

## ABSTRACT

This review was written to determine the effectiveness of Botulinum Toxin (BoNT) as a treatment for upper extremity dysfunction in post-stroke patients. As most patients survive a stroke, many are burdened with disability and impaired limb function. Seventy percent of stroke patients experience motor dysfunction in the arm, with thirty percent of patients suffering from upper extremity spasticity. Spasticity is a speed-dependent condition where certain muscles are abnormally stiff, resulting in involuntary contraction when the spastic muscle is used. BoNT treatment includes injections in localized muscles and is primarily used to treat spasticity by temporarily paralyzing the injected muscle. Seven systematic reviews/meta-analyses and ten randomized-controlled trials were used to determine the effectiveness of BoNT in post-stroke patients. Overall, BoNT is effective in reducing spasticity and may be effective in reducing pain. However, its ability to improve motor function is still unclear. In addition, there is mixed evidence on the most effective way to administer BoNT treatment, such as the proper dosage or combining BoNT with another therapy. The treatment's effectiveness is well documented in the chronic stage of stroke but less so in the acute and subacute stages. More research is needed to determine the potential adverse effects of long-term exposure to BoNT and the most appropriate dose to administer.

## Introduction

Stroke is the fifth leading cause of death and the primary cause of long-term disability in the US. Ischemic strokes caused by blood clots make up 87% of strokes; hemorrhagic strokes caused by ruptured blood vessels make up the rest.[1] Because most patients survive a stroke, many are left with long-term handicaps or disabilities. A common post-stroke impairment is motor dysfunction which affects approximately 80% of patients and is characterized by limited muscle control, movement, and mobility.[2] Seventy percent of patients experience some form of motor impairment in the arm, and 62% do not recover hand dexterity within six months of the stroke.[3] Arm dysfunction is also of particular significance because 50% of reduced health-related quality of life is related to a lack of arm function, and only 5% of stroke patients regain full arm function.[4]

Spasticity is a motor disorder that involves speed-dependent muscle hypertonia — increased muscle tone and overactivity — resulting from impaired reflex function. It is characterized by involuntary and abnormal muscle contraction and can be found in around 30% of post-stroke patients. While it presents itself equally in the upper and lower extremities, it is often more severe in the upper limbs.[5] Spasticity is associated with a decreased health-related quality of life for the patient and increased caregiver burden.[6] It often leads to limited mobility, weakness, and pain from muscle stiffness and spasms.[7] Various interventions have been developed and studied to alleviate spasticity, including chemodenervation.[5]

Chemodenervation is a treatment that involves an injection in a targeted muscle area to decrease muscle overactivity. The drugs used for chemodenervation include phenol, alcohol, and botulinum toxins (BoNT).[8] Botulinum toxin is now considered the "golden standard" of spasticity treatments[9] but is a much more recent development. Historically, alcohol and phenol were used as neurolytic agents, a form of nerve block injection that deliberately destroys nerve tissue to prevent nerve conduction.[10] This temporarily or permanently weakens and destroys nerve fibers to prevent the transmission of nerve signals and reduce pain.[10] However, neurolysis may produce side effects such as dysesthesia and muscle fibrosis, and causes pain during injection.[8]

Botulinum toxin (BoNT) is one of the most poisonous biological substances and has been called a" miracle poison" for its use in cosmetic and clinical settings.[11] It is a neurotoxin produced by the bacterium *Clostridium botulinum* and has eight distinct types (A, B, C1, C2, D, E, F and G).[12] Recently, Botulinum toxins type-A and type-B (BoNT-A and BoNT-B) have been used as an alternative form of chemodenervation to control spasticity instead of neurolysis.[8] BoNT selectively prevents the release of acetylcholine, the main neurotransmitter at the neuromuscular junction, to decrease muscle contraction and temporarily paralyze the injected muscle.[12] Depending on the dose, BoNT can have effects that last from two to four months before requiring reinjection for sustained effects.[12] While all three forms of chemodenervation can be effectively used to treat spasticity, BoNT has shown itself to be the safest and most commonly used treatment.

However, research also indicates that BoNT injection may result in adverse effects. These effects may be due to improper dosage or injection techniques. However, recent evidence suggests that the nature of the toxin may lead to muscle shortening and a restricted range of motion if repeatedly injected.[13] This paper will provide a scoping review on the effectiveness of Botulinum Toxin for post-stroke arm dysfunction and its overall effect on the patient.

## Methodology

This scoping review evaluates seven systematic reviews and meta-analyses and ten randomized controlled trials (RCTs) to determine the effectiveness of Botulinum Toxin for the treatment of arm dysfunction post-stroke. PubMed, EBSCO, Cochrane Library, and the Oberlin Library were searched for Randomized Controlled Trials (RCTs). In addition, four systematic reviews and three RCTs on constraint-induced movement therapy (CIMT) were used as a comparison treatment.

Papers were not reviewed if they were not published in English, had sample sizes below 20, or lacked objective outcome measures to determine the effectiveness of BoNT. In addition, only papers published after 2010 were included in the literature review.

## Literature Review

This section reviews the current literature on Botulinum Toxin for post-stroke arm dysfunction. Seven meta-analyses/systematic reviews and ten randomized controlled trials were evaluated. The effectiveness of BoNT treatments was evaluated on pain, spasticity, and motor function. In addition, other factors such as the type of BoNT, combined use of BoNT + other therapies, the dosage of BoNT, the time post-stroke of the treatment, and potential adverse effects were also examined. Table 1 lists the outcome measures cited in the literature review.

**Table 1.** Outcome measures cited in this review

| Outcome Measure | Test |
|---|---|
| Action Research Arm Test (ARAT) | Evaluates arm function using objects of different sizes, weights, and shapes (grasp, grip, pinch, and gross movement) |
| Active range of motion (AROM) | Evaluates voluntary range of motion |
| Barthel index | Evaluates patient's ability to independently perform activities of daily living |
| Carer Burden Scale (CBS) | Evaluates the caretaker's perception of their quality of life by isolation, disappointment, emotional involvement, and environment |
| Disability Assessment Scale (DAS) | Evaluates the degree of disability in the upper extremities in patients with spasticity (hand hygiene, dressing, limb position abnormality, and pain) |
| EMG activity | Recording of the electrical activity of muscle |
| Fatigue Severity Scale (FSS) | Evaluates patient perception of how fatigue interferes with daily function |
| Fugl Meyer Assessment (FMA) | Evaluates motor control, sensorimotor impairment, joint pain, and joint range of motion |
| Functional Motor Assessment Scale (FMAS) | Evaluates motor function through a series of functional tasks |
| Global Self-Assessment (GSA) | Evaluates patient perception on levels of pain, stiffness, and function |
| Medical Research Council Scale (MRCS) | Evaluates muscle strength |
| Modified Frenchay Scale (MFS) | Evaluates active upper limb function |
| Modified Rankin Scale (MRS) | Evaluates the degree of disability in stroke patients |
| Motor Activity Log (MAL) | Evaluates patient-reported upper limb amount of use and quality of movement |
| Modified Ashworth Scale (MAS or AS) | Evaluates muscles spasticity, the degree of muscle resistance to passive movement |
| Numeric Rating Scale (NRS) | Evaluates patient-perceived pain |
| Passive range of motion (PROM) | Evaluates range of motion during passive movement |

| Outcome Measure | Test |
|---|---|
| Physician Global Assessment | Evaluates physician perception of overall patient response to treatment |
| Tardieu Scale (TS or MTS) | Measures muscles spasticity |
| Visual Analog Scale (VAS) - pain | Evaluates patient-reported pain intensity |
| Wolf Motor Function Test (WMFT) | Evaluates upper extremity tasks by speed and quality |

## Effect of Botulinum Toxin by Construct

The use of BoNT as a treatment for arm dysfunction post-stroke has been studied in numerous randomized control trials (RCTs), systematic reviews, and meta-analyses. The ten RCTs reviewed used a total of 21 outcome measures to evaluate the effects of BoNT on spasticity, pain, motor function, health-related quality of life, caretaker burden, range of motion, fatigue, disability, and muscle strength. The primary constructs evaluated in the reviews and RCTs were spasticity, pain, and motor function.

Spasticity was the most commonly measured outcome in the selected reviews and RCTs — all seven reviews and ten RCTs examined spasticity. Most studies used the Modified Ashworth Score or Ashworth Score to measure spasticity, but the Tardieu Scale, muscle tone, and EMG readings were also used. Malhotra and colleagues suggest that spasticity is difficult to measure as it is not clearly defined, and there is no direct measurement of spasticity.[14] For example, the Modified Ashworth Score measures muscle tone and resistance to passive movement[15] while other outcome measures focus on stiffness or rely on tools such as EMG readings to capture muscle activity.[14] This inconsistency makes it difficult to compare studies with different outcome measures for spasticity and may lead to mixed results.[14] Future research should aim to produce a universal definition for spasticity and agree upon the use of a consistent outcome measure that is aligned with the definition.

All but two reviews[16,17] reported a significant decrease in spasticity after BoNT treatment. One review attributed the lack of significant improvement in elbow spasticity to the highly heterogeneous data from 10 RCTs that examined the effects of Botox, Dysport, and Xeomin and subdivided results by joint.[17] The inconsistency in the other review[16] may be because the review focused on pain instead of spasticity and only examined two studies from 2007 that used the Modified Ashworth Scale. All RCTs included reported a significant improvement in spasticity. The Disability Assessment Scale (DAS), which evaluates the degree of functional disability in patients with spasticity,[18] was used in one RCT[19] and one meta-analysis.[20] Both studies found a significant decrease in disability following BoNT treatment. The included literature indicates that BoNT is effective in reducing spasticity and may also be effective in managing related disabilities. Overall, the vast majority of evidence examined indicates that BoNT is effective in treating spasticity.

Multiple reviews and RCTs evaluated BoNT as a treatment for pain, especially in the hemiplegic shoulder. Of the four reviews that examined the effects of BoNT on pain, three determined that BoNT significantly decreased pain[16,21,22] while one review found no significant difference in pain.[17] However, this review noted that the data was highly heterogeneous and included trials using various types of BoNT, which may have contributed to inconsistent results.[16] In addition, out of the three RCTs that used the pain Visual Analogue Scale (VAS),[23–25] two found that BoNT had a significant effect on pain[24,25] while one did not.[23] A potential cause for this disparity is the various outcome measures used to evaluate pain, including the VAS, Numerical Rating Scale, and semi-quantitative rating scale, in addition to the various doses and injection techniques. Not all of the studies used the same BoNT guidance techniques,

dilution, or dose, which affects the efficacy of the injection. This evidence suggests BoNT likely reduces pain, but more research is still required for definitive conclusions. Specific suggestions for evaluating BoNT as a pain treatment can be found in section 5.1.1.

Evidence of the effects of BoNT on motor function is highly mixed. Some of the outcome measures used to assess motor function include the Fugl-Meyer Assessment (FMA), Functional Motor Assessment Scale (FMAS), and the Modified Frenchay Scale (MFS). Of the six RCTs that evaluated motor function,[23,25–29] one found a significant improvement in motor function in the BoNT group before and after injection,[26] and two found between-group differences favoring BoNT groups.[25,27] Similarly, most reviews concluded that the effect of BoNT on motor function is unclear,[16,18] with one review reporting significant improvement[30] and another finding no significant difference between BoNT and controls.[20] The mixed results indicate that more research is necessary to draw conclusions on the effectiveness of BoNT on motor function. Specifically, research should use the same outcome measures to assess motor function.

Table 2 provides information about randomized controlled studies used in the literature review with details on subjects, intervention, outcome measures, and results.

**Table 2.** Randomized controlled trials cited in this review

| Author (year) Sample Size | Injection location(s) | Stroke Acuity and length of treatment: | Experimental (E) and Control (C) groups | Outcome Measures and Results |
|---|---|---|---|---|
| Hung et al (2022)[26] RCT n=37 | - elbow flexors<br>- forearm pronators<br>- wrist flexors<br>- fingers flexors | Chronic<br>- 8 wks, 75 min training 3 days per wk after injection<br>- Assessed: pre-treatment, post-treatment, and 3 months follow up | E1: 50 U/mL onobotulinumtoxinA + robot assisted therapy<br><br>E2: 50 U/mL onobotulinumtoxinA + mirror therapy<br><br>C: Active Control 50 U/mL onobotulinumtoxinA | <u>E1/E2/C</u><br>- FMA (+exp, +exp2, C)<br>- MAS (+exp, +exp2, C)<br>- MAL (+exp, +exp2, C)<br><br><u>E1 vs E2 vs C</u><br>- FMA (-)<br>- MAS (-)<br>- MAL (-) |
| Maulet et al (2021)[24] RCT n=33 | - brachialis anticus<br>- biceps brachii<br>- flexor carpi radialis<br>- flexor carpi ulnaris<br>- flexor digitorum profundus<br>- flexor digitorum superficialis<br>- interossei | Chronic<br>- 30 min daily 4 wk self-rehabilitation treatment<br>- Assessed: wk before and after treatment, 4 wks post injection | E: average of 22-81 U per muscle onobotulinumtoxinA + Self-rehabilitation<br><br>C: average of 25-79 U per muscle onobotulinumtoxinA | <u>E vs C</u><br>- WMFT (-)<br>- MAS (-)<br>- MRCS (-)<br>- ARAT (-)<br>- PROM (-)<br>- MAL (-)<br>- VAS (-)<br>- FSS (-)<br><br><u>E group</u><br>- WMFT (+exp) |

| Author (year) Sample Size | Injection location(s) | Stroke Acuity and length of treatment: | Experimental (E) and Control (C) groups | Outcome Measures and Results |
|---|---|---|---|---|
| | | | | - MAL (+exp)<br>- PROM (+exp)<br>- VAS (+exp) |
| Tan et al (2021)[25] RCT n=36 | subscapularis | Chronic<br>- Assessed: baseline, 1, 4, 12, and 24 wks post-injection | E: 100 U of lanbotulinumtoxinA (Hengli)<br><br>C: placebo | - VAS (+exp)<br>- MAS (+exp)<br>- PROM (+exp)<br>- FMA (+exp)<br>- EQ-5D (+exp) |
| Lindsay et al (2020)[31] RCT n=93 | - biceps brachialis<br>- Flexor digitorum superficialis<br>- Flexor digitorum profundus<br>- Flexor carpi ulnaris<br>- Flexor carpi radialis | Acute (stroke within the past 42 days)<br>- Assessed: baseline, 12 wks post-injection, 6 months post-stroke<br>- Spasticity and contractures assessed: 2, 4, 6 wks post-injection | E: 15-40 U per muscle onabotulinumtoxinA (Botox)<br><br>C: placebo | - ARAT (-)<br>- EMG elbow and wrist (+exp)<br>- PROM (+exp)<br>- Stiffness – elbow (+exp)<br>- Stiffness – wrist (-) |
| Masakado et al (2020)[19] RCT n=100 | - wrist flexor<br>- upper-limb muscle groups (finger, elbow, thumb, forearm) | Chronic<br>- Assessed: baseline, wk 4, wk 12 | E1: 400 U incobotulinumtoxinA (Xeomin)<br><br>E2: 250 U incobotulinumtoxinA (Xeomin)<br><br>C1: High dose placebo<br><br>C2: Low dose placebo | <u>E1 vs C1</u><br>- MAS wrist (+exp)<br>- DAS (+exp)<br><br><u>E2 vs C2</u><br>- MAS wrist (+exp2)<br>- DAS (-)<br><br><u>E1 vs E2</u><br>- MAS wrist (-)<br>- DAS (+exp) |
| Nasb et al (2019)[27] RCT n=54 | - biceps brachii<br>- flexor carpi radialis<br>- flexor carpi ulnaris<br>- flexor digitorum profundus<br>- flexor digitorum superficialis | Chronic<br>- Assessed: baseline, 4 wks | E: 150-200 U of onabotulinumtoxinA (Botox) per muscle + mCIMT<br><br>C: 150-200 U of onabotulinumtoxinA (Botox) per muscle + intense conventional therapy | <u>E vs C:</u><br>- MAS (-)<br>- FMA (+exp)<br>- Barthel (+exp)<br><br><u>E group</u><br>- MAS (+exp)<br>- FMA (+exp) |

| Author (year) Sample Size | Injection location(s) | Stroke Acuity and length of treatment: | Experimental (E) and Control (C) groups | Outcome Measures and Results |
|---|---|---|---|---|
| | | | | - Barthel (+exp) |
| Rosales et al (2018)[28] RCT n=42 | - Individualized for the patient (UE) | Acute/Subacute (2-12 wks)<br>- Assessed: | E: 500 U abobotulinumtoxinA (Dysport)<br><br>C: Placebo | - MAS (+exp)<br>- FMA (-) |
| Marvulli et al (2016)[32] RCT n=36 | - Flexor Digitorum Superficialis | Chronic<br>- Assessed: baseline, 20 days, 3 months post 1st injection<br>- Reinjected at 4 months<br>- Assessed: 20 days, 3 months post 2nd injection<br>- Reinjected at 8 months | E: (118±34 U) incobotulinumtoxinA (Xeomin) + physical therapy + functional electrical stimulation<br><br>C: (116±36 U) incobotulinumtoxinA (Xeomin) + physical therapy | - MAS (+exp)<br>- PROM (+exp)<br>- ARAT (+exp) |
| Gracies et al (2014)[29] RCT n=24 (19 due to stroke) | - elbow flexors<br>- biceps brachii,<br>- brachialis anterior<br>- brachioradialis<br>- additional upper limb muscles | Subacute/Chronic (at least four weeks)<br>- Assessed: baseline, 1, 2, 3 months post-injection (Data in table collected at one month) | E1: Two doses of 10,000 U (fixed 2,500 U into elbow flexors) rimabotulinumtoxinB, BoNT/B (Mybloc)<br><br>E2: Two doses of 15,000 U (fixed 5,000 U into elbow flexors) rimabotulinumtoxinB, BoNT/B (Mybloc)<br><br>C: Placebo | <u>E1 vs C:</u><br>- AROM (+exp)<br>- MFS (-)<br>- AS (-)<br>- Tardieu (-)<br>- GSA stiffness (-)<br>- PROM (-)<br><br><u>E2 vs C:</u><br>- AROM (+exp2)<br>- MFS (-)<br>- AS (+exp2)<br>- Tardieu (-)<br>- GSA stiffness (+exp2)<br>- PROM (-)<br><br><u>E1 vs E2:</u><br>- AROM (-)<br>- MFS (-)<br>- AS (-)<br>- Tardieu (-)<br>- GSA stiffness |

| Author (year) Sample Size | Injection location(s) | Stroke Acuity and length of treatment: | Experimental (E) and Control (C) groups | Outcome Measures and Results |
|---|---|---|---|---|
| | | | | (+exp2)<br>- PROM (-) |
| Rosales et al (2012)[23]<br>RCT<br>n=163 | - biceps brachii<br>- brachioradialis<br>- flexor carpi ulnaris<br>- flexor carpi Radialis<br>- Optional: flexor digitorum superficialis, flexor digitorum profundus, flexor pollicis longus | Acute/subacute (Within 2-12 weeks of stroke)<br>- Assessed: baseline, 2, 4, 8, 12, 24 wks after injection | E: AbobtulinumtoxinA (Dysport) 500 U<br><br>C: Placebo | - MAS (+exp)<br>- FMAS (-)<br>- Barthel index (-)<br>- MRS (-)<br>- Active ROM (-)<br>- Passive ROM<br>  - Elbow (+exp)<br>  - Wrist (+exp)<br>  - Finger (-)<br>- VAS pain (-) |

Table legend: U – units; wk(s) – week(s); E – experimental group; C – control group; RCT – randomized controlled trial
(+exp) – statistical significance in favor of the experimental group
(+exp2) – statistical significance in favor of the second experimental group
(+con) – statistical significance in favor of the control group
(-) – no statistical significance

## Effect of Botulinum Toxin by Type

There are four main BoNT preparations currently used to treat post-stroke arm dysfunction. Three forms, onabotulinumtoxinA (Botox), abobotulinumtoxinA (Dysport), and incobotulinumtoxinA (Xeomin), are BoNT type-A while rimabotulinumtoxinB (Mybloc) is BoNT type B. While all four forms have been FDA approved for treatment, there have been fewer studies on BoNT-B compared to BoNT-A.[18] There is level A evidence indicating that the three BoNT-A types should be offered as a treatment for spasticity, while there is only level B evidence indicating that BoNT-B should be considered for treatment.[33,34] Only one RCT[29] examined the use of BoNT-B. It concluded that high dosage significantly improved active range of motion, spasticity (Ashworth Scale), and stiffness, but not motor function, passive range of motion, or spasticity (Tardieu scale). While both BoNT types A and B effectively reduce spasticity, the examined evidence indicates BoNT-A is more well-studied.

Each type also requires varying doses to produce the same effect as different types have different potencies. Through trials, it has been estimated that there is a potency ratio of 1 U Botox to 1 U Dysport to 2-4 U Xeomin to 50-100 U Mybloc.[34] This further indicates that fewer units of BoNT-A are needed to be effective, while a much higher dose is required if BoNT-B is used. Lower doses are generally preferred as increased dosage increases the risk of adverse effects. However, these ratios have only been calculated through trials and conversions between types are not recommended.[34]

Other types of BoNT have been recently developed but have not been FDA approved. These include letibotulinumtoxinA (Botulax),[35] NeubotulinumtoxinA (Neuronox),[36] and Prabotulinumtoxin A (Daewoong),[37]. However, there is limited research investigating these forms of BoNT for treating post-stroke arm dysfunction compared to the four approved forms. Some studies have also investigated whether other types of BoNT, such as BoNT-D, might be an effective alternative to BoNT-A or B.[38] Preliminary research in rodents found that these alternatives may be effective but have shorter-lasting effects than their approved counterparts.[38] The use of unapproved forms of BoNT has not been thoroughly investigated, and future research should examine the efficacy of alternative BoNT types to determine the best form of BoNT for patients.

Table 3 provides information about meta-analyses and systematic reviews discussed in the literature review with details on subjects, intervention, outcome measures, and results.

**Table 3**. Meta-analyses and systematic reviews cited in this review

| Author (year)<br>Study Design | Constructs examined/Outcome Measures | Main Conclusions |
|---|---|---|
| Saikaley et al (2018)[18]<br>SR: 48 RCTs | Motor Function<br>Activities of Daily Living<br>Dexterity<br>Range of Motion<br>Stroke Severity<br>Muscle Strength<br>Spasticity | - BoNT-A decreases spasticity in the UE<br>- BoNT-A does not improve range of motion or activities of daily living.<br>- BoNT-A effect on motor function is unclear<br>- BoNT-A with other treatments may be more effective than BoNT alone<br>- BoNT-A is more studied than BoNT-B |
| Andringa et al (2019)[21]<br>SR/MA: 40 RCTs in synthesis; 28 RCTs in MA | Pain<br>Involuntary movements<br>Passive joint motion<br>Care ability<br>Arm and Hand Use<br>Spasticity | - BoNT reduces spasticity in the wrist and fingers (no further trials necessary)<br>- BoNT improves self-care in the arm and hand (no further trials necessary)<br>- BoNT does not improve arm-hand capacity (no further trials necessary)<br>- BoNT significantly reduces spasticity-related pain, involuntary movements, and caregiver burden<br>- BoNT improves passive range of motion<br>- More studies are needed on the other outcome measures |
| Singh et al (2010)[16]<br>SR: 6 RCTs (5 RCTs post-stroke shoulder pain) | Pain (VAS, NRS, semi-quantitative rating scale)<br>Adverse effects<br>Function/Disability<br>Range of Motion<br>Quality of Life (SF-36)<br>Spasticity<br>Barthel Index<br>Functional Independence Measure (M-FIM)<br>Modified Ranking Scale (MRS) | - Significant improvement in shoulder pain 3-6 months post-injection<br>- Effect on motor function and disability unknown<br>- Significant improvement in external shoulder rotation one-month post-injection (not 3-6 months)<br>- No significant difference in spasticity between groups<br>- No significant difference in adverse effects between groups |

| Author (year)<br>Study Design | Constructs examined/Outcome Measures | Main Conclusions |
|---|---|---|
| Nasb et al (2021)[30]<br>SR/MA: 2 RCTs | Spasticity (MAS)<br>Motor functional activities<br>Activities of Daily Living | - No significant difference in spasticity between BoNT-A + Constraint-induced movement training (CIMT) and BoNT-A + conventional therapy<br>- Promising improvement in wrist and finger spasticity at 4 weeks from BoNT-A + CIMT combination<br>- All participants saw decreased spasticity<br>- Significant improvement in ADLs and motor function |
| Xie et al (2021)[22]<br>SR/MA: 9 RCTs | Pain (VAS)<br>Range of Motion<br>Limb function<br>Spasticity (MAS)<br>Adverse effects | - Significant decrease in pain between BoNT-A groups and control groups (placebo or steroid)<br>- Significant increase in ROM between groups<br>- No significant difference in spasticity<br>- Increased upper limb mobility |
| Jia et al (2020)[17]<br>MA: 10 RCTs | Spasticity (MAS at elbow, wrist, finger)<br>Activities of Daily Living (Barthel Index)<br>Pain | - No significant difference between BoNT-A and placebo for spasticity<br>- No significant difference between BoNT-A and placebo for pain or ADLs<br>- Significant improvement in elbow spasticity comparing Dysport and placebo |
| Sun et al (2019)[20]<br>SR/MA: 27 RCTs (18 upper limb focus) | Spasticity – Muscle tone<br>Physician Global Assessment<br>Disability Assessment Scale<br>Active limb function | - BoNT-A significantly decreases muscle tone and spasticity<br>- BoNT-A significantly decreases disability (DAS)<br>- No significant difference in active upper limb function<br>- Significant increase in PGA<br>- No significant adverse effects |

Table legend: MA – Meta-Analysis; SR – Systematic Review; RCT – randomized-controlled trial; UE – upper extremities

## Effect of Botulinum Toxin Alone or with Other Treatments

BoNT treatments are frequently administered with conventional therapy. The injection allows the patient to train the antagonist muscles with reduced interference from the spastic muscles. However, evidence suggests that BoNT may be more effective when used in conjunction with other treatments instead of or in addition to conventional therapy. This review will address BoNT combined with constraint-induced movement therapy, robotics, mirror therapy, and functional electrical stimulation.

One RCT examined the use of BoNT with mirror therapy (MT) and robot-assisted therapy (RT). Two experimental groups of MT + BoNT and RT + BoNT were compared to BoNT with conventional therapy. While each experimental group had significant improvement pre-and post-injection, when compared to BoNT + conventional therapy, there were no significant between-group differences in spasticity, activities of daily living, or motor function.[26] More research is needed to assess the efficacy of robotic or mirror therapy in combination with BoNT, but this study indicates that MT or RT with BoNT may not be more effective than BoNT with conventional therapy.

Studies have shown BoNT combined with constraint-induced movement therapy (CIMT) or modified constraint-induced movement therapy (mCIMT) may be more beneficial than BoNT alone. One RCT[27] that compared BoNT + conventional therapy and BoNT + mCIMT found a significant improvement in motor function and activities of daily living (ADLs) when mCIMT was used, but no difference in spasticity. Similarly, a meta-analysis found no significant improvement in spasticity when BoNT was combined with CIMT compared to BoNT with conventional therapy, but did find improved ADLs and motor function.[30] Overall, the use of CIMT or mCIMT with BoNT has displayed promising results and warrants further investigation.

Electrical stimulation is another potentially effective therapy when used in combination with BoNT. An RCT that examined the combined use of BoNT with functional electrical stimulation found improved spasticity, passive range of motion, and motor function compared to BoNT with conventional therapy.[32] This may indicate that electrical stimulation is another effective combination of treatments when used with BoNT. However, more research is needed to validate these findings.

## Effect of Botulinum Toxin by Dosage

Current clinical guidelines suggest a maximum dose of 600 units of onabotulinumtoxinA or incobotulinumtoxinA, or 1,500 units of abobotulinumtoxinA to balance efficacy and adverse effects.[39] Exceeding the recommended dosage raises the risk of the toxin spreading to surrounding tissue or the bloodstream, especially if the targeted muscle is not precisely injected.[39]

Despite the risk, other research has demonstrated that higher doses may be more effective in severe spastic patients.[9,39,40] An RCT comparing 250 U to 400 U of incobotulinumtoxinA found that while both doses improved spasticity, only the higher dose led to a significant reduction in disability.[19] Another trial reported that while 10,000 U of rimabotulinumtoxinB increased the patient's active range of motion, only doses of 15,000 U were effective for decreasing spasticity and stiffness.[29] A systematic review examining BoNT treatments above recommended doses found a general lack of severe adverse effects and improved functional outcomes.[9] These studies may indicate a need to reevaluate dosage guidelines. Future research should investigate the potential increase in the effectiveness of BoNT treatment from higher doses, but also the adverse effects associated with those doses.

## Effect of Botulinum Toxin by Time Course Post-Stroke

Post-stroke patients can be broadly categorized by the time elapsed since the stroke. Patients within a month of a stroke are acute, within one to six months are subacute, and beyond six months are described as chronic stroke patients.[41] Most studies investigating BoNT examine chronic stroke patients because spontaneous improvement in the acute or subacute stages of stroke makes it difficult to attribute changes to the experimental. To gather accurate data, a trial would need a sufficient sample size to meet its power analysis as well as a control group, both of which may be challenging to obtain in acute stroke patients. Medical professionals may also be wary of using BoNT early on due to the lasting effects of the treatment — up to several months — and its potential interference with spontaneous recovery.

However, there is some evidence indicating that BoNT can be used safely and effectively in the early stages of stroke. Six RCTs examined the effect of BoNT in chronic stroke,[19,24–27,32] while four enrolled patients in the acute or subacute stages.[23,28,29,31] All four RCTs that examined acute and subacute patients found a significant decrease in spasticity but no improvement in motor function.[23,28,29,31] The effectiveness of BoNT in chronic stroke is much more well-researched and understood, but more research is needed to explore the effect of BoNT in acute and subacute stroke. Research should examine potential adverse effects and ensure that the benefits of injection outweigh the potential harms of paralyzing a muscle that may still be in the healing process.

### Effect of Botulinum Toxin by Adverse Effects

As a toxin, using BoNT comes with potential risks to the patient. In the clinical setting, adverse effects have been reported to be minimal and temporary.[11] These effects include slight pain, swelling, numbness, rash at the injection site, headache, and nausea.[11] A more serious adverse effect is the spread of BoNT to other muscles near the injection site. The resulting paralysis of surrounding muscles is a temporary effect and is typically resolved in weeks or months.[11] In rare cases, a localized injection of BoNT can lead to generalized muscle weakness that mimics botulism[42] and may be caused by the accidental injection of BoNT into the bloodstream.[11,42] The most commonly reported adverse effects are mild, and more severe effects can generally be avoided with proper technique and materials.

However, one concern with the use of BoNT is that its long-term effects have not been well studied, and the potential adverse effects from repeated exposure are not well investigated. With prolonged exposure to the toxin comes the risk of immunogenicity.[11,43] Patients may develop neutralizing antibodies (NAbs) and resistance to BoNT, decreasing the effectiveness of the treatment. While this effect is not common, large doses, brief breaks between injections, and booster injections may trigger immunity against the toxin.[11] Some particular BoNT types also present an elevated risk of immunogenicity. RimabotulinumtoxinB has the most significant presence of NAbs (up to 42.4%), while BoNT-A Nabs range from 0-17%.[44] This immune response can generally be avoided by choosing types with lower protein load, controlling the time between injections, and calculating the lowest dose possible that will maintain effectiveness.[44]

More recently, research has shown that repeated use of BoNT may also lead to decreased passive muscle capacity.[13] Studies done in rodents indicated that BoNT injection led to a decrease in function, range of motion, and an increase in passive resistance.[45–48] A systematic review examining BoNT injections in humans and animals found similar results, such as lingering muscle atrophy and changes in muscle elasticity.[49] Another trial studied the effects of repeated and long-term exposure to BoNT in patients with a clinical history of BoNT treatments. The trial's results indicate that BoNT may lead to increased stiffness and impaired passive range of motion, counteracting the benefits of BoNT for spasticity.[13] More research is needed before it is clear whether these adverse effects are severe or pervasive enough to warrant serious reconsideration of BoNT as the optimal treatment for spasticity. However, clinicians should be wary of this potential effect and be conservative with repeated dosage. More specific details regarding potential research in this area can be found in section 5.1.2.

## Discussion

### Appropriate Patients for Botulinum Toxin

While the use of BoNT to treat post-stroke arm dysfunction has been well-established, BoNT remains a deadly toxin that should not be administered to all patients. In general, suitable patients should have enough discomfort or muscle overactivity to warrant the treatment of chemodenervation. If the patient's arm dysfunction is not severe enough to interfere in their health-related quality of life or interrupt their activities of daily living, BoNT is not recommended. Some of the critical exclusionary criteria include pregnancy, allergies, muscle location, and other pre-existing medical conditions.

Botox is classified by the FDA as a category C drug, meaning that there is inadequate information about its effects during pregnancy. It should only be administered if "the potential benefit justifies the potential risk to the fetus." [50] While limited reports of BoNT-A treatments during pregnancy may indicate that its localized effects cause little to no complications,[51,52] other studies in pregnant rodents have led to severe consequences, including death.[53] Overall, it is inappropriate to administer a dose of any size to pregnant or nursing patients as the potential effects are largely unexplored and potentially dangerous. There is also inadequate research around the use of BoNT to treat

spasticity in patients below the age of 18. Physicians should proceed with extreme caution if administering a dose to young patients.

Allergies, autoimmune disorders, and the use of drugs or the presence that affect the neuromuscular junction may also render a patient inappropriate for BoNT treatments. Patients allergic to BoNT should also be excluded as allergic reactions, while rare, can have severe and unpleasant side effects such as angioedema, urticaria, and more.[54,55] Patients with confirmed problems with their immune system, such as an autoimmune disorder, may have an adverse reaction from the injection of a foreign substance and should proceed with caution.[56] BoNT should not be administered in conjunction with drugs that could potentially interfere with neuromuscular transmissions, such as certain muscle relaxants, neuromuscular blockers, acetylcholinesterase inhibitors, magnesium sulfate, aminoquinolines, cyclosporine, D-penicillamine, some classes of antibiotics such as aminoglycosides, polymyxins and lincosamides, and more. The medication could potentially induce a botulism-like clinical state, muscle weakness, and respiratory failure.[19,21,29] Patients with neuromuscular disorders such as Lambert-Eaton Syndrome and myasthenia gravis should not receive BoNT treatment as it may exacerbate the condition.[53,57]

It is also important to note that while spasticity can occur in muscles all over the body, BoNT is only suitable for treating localized spastic muscles. Regional spastic muscle groups such as spasticity affecting an entire arm or systemic spastic muscle groups affecting the entire body are not candidates for BoNT treatment as the high dosage required to reduce spasticity in many muscles would have severe, potentially fatal consequences.

## Comparison Treatment: Constraint-Induced Movement Therapy

This section will compare BoNT treatment to constraint-induced movement therapy (CIMT). The two treatments will be evaluated by cost, time and dosage, appropriate patients, and construct. Four systematic reviews and three randomized controlled trials were used to examine the effects of CIMT.

### *Overview of Constraint-Induced Movement Therapy*

Constraint-induced movement therapy (CIMT) is a post-stroke upper extremity treatment that involves the restriction of the healthy limb to improve the function of the affected limb. A mitt or sling constrains the healthy arm for approximately 90% of the patient's waking hours, during which the patient is given repetitive functional tasks to perform with their affected limb and encouraged to use their affected limb in activities of daily living (ADLs).[58] This process is known as shaping, a training method that provides a functional task with progressively difficult iterations.[59] The treatment works to increase the frequency of use in the affected limb and associated neural pathways to decrease learned non-use, where the patient has the capacity for higher motor function but does not have high performance.[60] After training, there is also a transfer package to integrate these practices into the patient's daily life. Through this process, CIMT is intended to improve the quantity and quality of movement in the impaired arm.[61]

Standard CIMT is highly intense, including six to eight hours of training per day for two weeks.[62] However, the nature of this training makes compliance to a strict training regimen difficult. As a result, modified constraint-induced movement therapy or mCIMT was also created. The modified regimen reduces the daily training burden, distributes the training across an extended period, and reduces the time the patient spends in the constraint.[61]

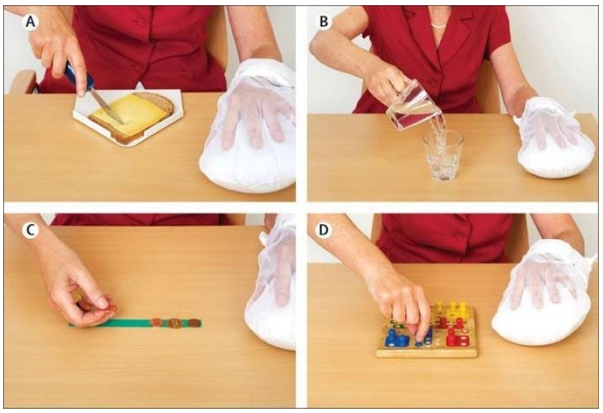


**Figure 1.** Four examples of CIMT tasks while the unaffected hand is constrained by a mitt [43]

## *Comparison by Construct*

More literature is available on CIMT compared to BoNT treatments, as CIMT treatments are more established and have been used in clinics for longer. BoNT treatments for clinical use were only FDA approved in 1989 and were specifically approved for adult upper limb spasticity in 2010 in the form of onabotulinumtoxinA (Botox) only.[63] While there is strong evidence indicating that both CIMT and mCIMT are effective in upper limb rehabilitation during the chronic stage of stroke recovery, there is a lack of clarity about the long-term effects of CIMT.[62]

Current research indicates that CIMT may improve motor function compared to conventional therapy or bilateral arm training,[18,62] but the evidence is mixed as to the appropriate frequency and its application during the acute and subacute stages of stroke.[18] Research also indicates that mCIMT can restore more normal motor function,[18,64] but there is no clear consensus as to whether the improvement in motor function leads to a decrease in disability.[62] In comparison, the effect of BoNT on motor function is still unclear as indicated in section 3.1. The studies examined suggest that CIMT may be more effective in improving motor function than BoNT, given the mixed evidence for BoNT. However, the limited studies examined for CIMT may hinder the accuracy of this assessment.

Regarding spasticity, BoNT treatments are generally recognized to reduce spasticity, while CIMT lacks comprehensive literature examining spasticity as an outcome measure.[18] Reduction in spasticity is not a specific intent of CIMT, but there is some research surrounding its application. One RCT examined the effects of CIMT on spasticity using the Modified Ashworth Scale and found a significant improvement.[65] However, the general lack of evidence for CIMT as a treatment of spasticity shows that BoNT is likely more effective in reducing spasticity.

Because of the two treatments' effectiveness in targeting different stroke impairments, there have been studies examining the use of the two treatments in combination. A systematic review of the two treatments found that while the decrease in spasticity was insignificant, the combination of BoNT and CIMT was more effective for reducing spasticity than BoNT and conventional therapy combined. The authors of this review also concluded that a combination of BoNT and CIMT may be effective in improving motor function and ADLs.[30] Overall, more research is needed to assess whether combining BoNT and CIMT benefits the patient.

## *Comparison by Time*

CIMT is much more time intensive than BoNT treatments, making compliance with a training program difficult. In addition, a significant portion of that time must be spent with a therapist. In contrast, BoNT treatments are much more

time-efficient as the patient only needs to go to a clinic for the injections. The conventional care used between injections is typically not as intense as CIMT. Even mCIMT, which reduces the active training period from 6 to 3 hours a day for two weeks, remains a much more intense treatment than BoNT.

### *Comparison of Appropriate Patients*

CIMT and BoNT treatments have very different inclusion and exclusion criteria for appropriate patients. Before a patient starts CIMT, they must have at least 10 degrees of active thumb and finger extension and 20 degrees of active wrist extension.[66] This active range of motion test is used to ascertain whether the patient has an imbalance between capacity and performance. If the patient cannot demonstrate this movement, they likely lack the capacity for effective CIMT treatment. The patient must also demonstrate that they are cognitively sound and motivated for the treatment. Because of the time-intensive nature of CIMT, patients unable to independently practice each movement every day are not suitable for the treatment. Patients unable to stand and walk without their constrained arm, such as those who use a cane, should not start CIMT treatment as this may increase their risk of falling.[67] Only approximately 15% of stroke patients qualify for CIMT due to these criteria.[58] In contrast, the same exclusion criteria do not apply to BoNT treatments. The patient does not need to be cognitively sound or demonstrate a high capacity to start treatment. However, the patient needs to be checked for other medical conditions such as allergies, autoimmune diseases, or neuromuscular disorders that may interfere with the treatment. Section 4.1 describes appropriate patients for BoNT treatment in more detail. Compared to the exclusion criteria for CIMT, more stroke patients are likely to qualify for BoNT treatments as around 83% of post-stroke patients exhibited cognitive impairment in at least one domain.[68] Based on exclusion criteria alone, BoNT treatments are more accessible for patients than CIMT treatments.

### *Comparison by Cost and Equipment*

CIMT equipment cost is relatively inexpensive compared to BoNT treatments as the only required material is either a sling, splint, or mitt to constrain the unaffected limb. Additional equipment may be required for specific task-based exercises, but most are everyday objects such as pages, pens, and balls. In contrast, the cost of BoNT treatment is much higher though they differ depending on BoNT type and dosage. However, the cost of a therapist for around six hours a day for CIMT is expensive, while BoNT treatment only requires a medical professional's presence during the injection. Overall, BoNT is more expensive in terms of equipment cost but cheaper when compared to the cost of employing a medical professional.

## Conclusion

Botulinum toxin injections are most likely effective for treating upper limb spasticity post stroke. Injections may also reduce pain. However, the effect of BoNT on motor function is still uncertain. More research is needed to determine BoNT effectiveness by dosage, time post-stroke, BoNT type, and the use of BoNT combined with other therapies. Future studies should prioritize determining the long-term effects of BoNT, including potential adverse effects.

### Unanswered Questions from the Botulinum Toxin Research

#### *How does BoNT treatment improve health-related quality of life and the ability to perform activities of daily living in patients with pain in the upper extremity?*

Most reviews and RCTs chose to evaluate the effectiveness of BoNT by outcome measures in spastic muscles, resulting in limited research investigating the toxin's analgesic effects in patients with upper extremity pain. While most of

the studies examined concluded that BoNT significantly reduces pain, heterogenous data indicates the need for additional research.

It would be relevant to measure not just the decrease in pain but also the patient's quality of life, arm function, and ability to perform activities of daily living (ADLs). Patients should be randomly split into placebo and experimental groups and assessed at baseline, then every month or so for complete results. This research would aim to determine to what degree BoNT treatments reduce pain and improve quality of life in post-stroke patients with upper extremity pain.

Future studies should evaluate patients by the same outcome measures so that collected data is easily synthesized. These measures may include the Modified Ashworth Score, Visual Analog Scale, and Disabilities of the Arm Shoulder and Hand. The Modified Ashworth Score (MAS) is the most commonly used outcome measure to assess spasticity.[15] The Visual Analog Scale (VAS) is a simple method to measure the patient's perceived pain on a 10 cm scale with "no pain" and "worst pain" on each side.[69] Disabilities of the Arm, Shoulder and Hand (DASH) is a self-reported assessment that measures patient perception of disability and physical function.[70] Other assessments may also provide accurate measurements for spasticity, pain, and disability, as well as tests that assess the quality of life and activities of daily living and can be used effectively in future research. Regardless of the outcome measures selected, having uniform measurements across studies will significantly improve the validity of the results.

In addition, only adult patients with good cognition, are in the chronic stage of stroke, and fit the other inclusion criteria described in section 4.1 should be enrolled. Because many of the outcome measures proposed are based on patient perception, uninhibited cognitive abilities are necessary for accurate results. Patients in the chronic stage of stroke are also preferred because there is less research on BoNT for acute and subacute stroke, making it difficult to attribute change or lack of change to the trial. A baseline must also be established for tests such as MAS and VAS to ensure that the patient's spasticity and pain are severe enough to warrant treatment, and to show improvement if the treatment is effective. Ideally, each trial would have a sample size above the power analysis to ensure they receive statistically relevant results.

### *What is the association between the number of BoNT injections and muscle tissue length?*

Recent research[13] has revealed that repeated BoNT injections may cause muscle shortening and stiffness. While it may be effective in the short-term, long-term exposure could lead to adverse effects. Given that this potential danger is relatively unexplored, it is vital to understand the adverse effects of BoNT to ensure patients are not unnecessarily harmed from prolonged treatment.

Future research should further investigate the potential long-term adverse effects of BoNT injections. In particular, muscle tissue length and passive range of motion should be re-examined as studies in rodents[45–48] and human patients[13,49] have shown harm from BoNT treatment. Various other outcome measures, such as motor function, active range of motion, and disability, could be assessed.

Evidence should be collected in a trial involving patients with post-stroke upper extremity spasticity. There should be a control group of patients who have not received BoNT injections and an experimental group of patients who have received one or more injections. A patient's affected and unaffected arms can be tested and compared to evaluate muscle tissue length and other outcome measures. Data can be collected and evaluated by the number of injections each patient received, and the difference between the two arms should be recorded. The results can then be compared between the control and experimental group to assess if there is a significant difference in outcome measures. This trial would examine if the arm that received BoNT injections experienced any sustained effects such as muscle shortening compared to the healthy arm. Patients should be in the chronic stage of stroke, and information should be collected about the number of BoNT injections, dosage size, and time elapsed since the last injection. These results would clarify the long-term impacts of BoNT injections and whether repeated doses harm the patient.

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