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Original Research

OnabotulinumtoxinA Injection for Poststroke Upper-Limb Spasticity: Guidance for Early Injectors From a Delphi Panel Process

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Abstract

Background: OnabotulinumtoxinA reduces muscle hypertonia associated with poststroke spasticity (PSS). PSS manifests as several common postures.
Objective: To define treatment paradigms for PSS upper-limb common postures.
Design: Modified Delphi method.
Setting: Expert panel.
Participants: Ten injectors experienced in the treatment and clinical research of PSS (physiatrists and neurologists) were invited to participate in the Delphi panel.
Methods: The Delphi panel reviewed an electronic worksheet with PSS upper-limb postures to define onabotulinumtoxinA treatment paradigms (Round 1). During Round 2, panel members discussed in person Round 1 results and voted until consensus (≥66% agreement). Recommendations were geared toward those with new or early injection experience.
Main Outcome Measurements: Expert consensus on onabotulinumtoxinA treatment parameters for PSS including muscles to inject, dose per muscle and posture, and treatment adjustments for suboptimal response.
Results: For each posture, consensus was reached on targeted subsets of muscles. Doses ranged for individual muscles (10-100 U) and total doses per posture (50-200 U). An onabotulinumtoxinA dilution 50 U/mL (2:1 dilution ratio) was considered most appropriate; dilution ratios of 1:1 to 4:1 may be appropriate in some circumstances. The majority (89%) of panel members would increase the dose and/or the number of muscles treated for a suboptimal response to onabotulinumtoxinA. The panel identified 3 common aggregate upper-limb postures: (1) adducted shoulder + flexed elbow + pronated forearm + flexed wrist + clenched fist; (2) flexed elbow + pronated forearm + flexed wrist + clenched fist; and (3) flexed wrist + clenched fist. The recommended starting dose per aggregate was 300 U, 300 U, and 200 U, with a total maximum dose of 400 U, 400 U, and 300 U, respectively. Localization guidance techniques were considered essential for all postures.
Conclusions: Consensus on common muscles and onabotulinumtoxinA treatment paradigms for postures associated with upper-limb PSS was achieved via a modified Delphi method. The purpose of this analysis is to educate early onabotulinumtoxinA injectors rather than provide an evidence-based review.
Level of Evidence: V

Introduction

Upper-limb spasticity is characterized by overactivity in muscles after injury to the central nervous system. When left untreated, poststroke spasticity (PSS) can lead to contractures [1], pain and deformity [2], involuntary movement, and greater functional impairments (eg, reduced mobility, self-care, dressing) and medical complications (eg, skin maceration and pressure sores) [1]. In patients with PSS, muscle hypertonia typically manifests in several common postural patterns [3-5], likely because of the location of the lesion in relation to the descending pathways controlling spinal reflex excitability [6-9]. These patterns were described in an international, cross-sectional survey of clinicians in 31 countries [10] and

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subsequently used to develop a classification system for upper-limb postures [6].

Effective management of spasticity is multifaceted and should involve the coordinated efforts of an interdisciplinary team [1]. Treatment of exacerbating factors such as skin breakdown, infection, and pain is paramount. Rehabilitation therapy and limb positioning to maintain muscle length and reduce deformity is important for the effective management of spasticity. Adjunctive systemic antispasmodics may be required, and surgical release of contracture may be indicated if spasticity is uncontrolled or left untreated. Botulinum toxins, including onabotulinumtoxinA, have become an integral part of the treatment paradigm for spasticity and have proven clinical efficacy in reducing focal muscle hypertonia [11-22] and improving passive function (eg, muscle tone and limb position) [23]. Improvements in active function have been observed in case studies and qualitative retrospective analyses [23,24].

There is still a gap between the existing Class 1 evidence for the clinical efficacy of onabotulinumtoxinA in reducing upper- and lower-limb PSS and providing clinicians with comprehensive information to effectively manage their patients with PSS. There is no clear guideline for an optimal botulinum toxin intervention regimen, including the frequency of injections (early versus late), muscle localization technique, injection sites, dilutions, and doses [25]. This finding is supported by published studies of botulinum toxin A for PSS that reported inconsistently the localization of the injection into each muscle [11-14,26,27] or the number of sites injected per muscle [11,16,27]. In addition, some studies did not provide sufficient information on concomitant therapy (including oral medications, rehabilitation, or implantable devices) [11,12,15].

This study was designed for people with new or early injection experience to bridge portions of this information gap via a modified Delphi methodology [28]. This approach is helpful when the literature contains insufficient evidence for treatment protocols and when the evidence requires further review and deliberation by experts [28]. The Delphi method [29] has been used to obtain consensus on the use of onabotulinumtoxinA to treat patients with stroke [30] and overactive bladder [31] and also on the use of intravenous thrombolytics for ischemic stroke [32]. We used a modified Delphi method to obtain insights relevant to the management of patients with focal upper-limb PSS who were receiving onabotulinumtoxinA therapy. Other botulinum toxins were not considered because the potency units are specific to each botulinum toxin product, and doses or units of biological activity cannot be compared or converted from one product to any other botulinum toxin product [33]. The Delphi panel members' judgments were collected and applied systematically to define treatment algorithms for the use of onabotulinumtoxinA by early injectors for the common postures associated with upper-limb spasticity. The emphasis, therefore, has been focused on treatment individualization rather than evidence-based clinical trial findings with regard to the degree and location of the spasticity, the condition of the patient, and dose limitations.

Methods

Delphi Panel Process

Overview

Ten injectors (physiatrists and neurologists) experienced in the treatment and clinical research of PSS were invited to participate in the Delphi panel [34]. The panelists had a mean of 22.0 years of experience in the treatment and clinical research of PSS. The focus of the panel was to provide guidance from the perspective of a new or early injector. A modified panel approach was used, consisting of 2 formal rounds of feedback with an allowance for a third round of voting if consensus was not achieved. The first round was conducted by the use of a survey, with responses kept anonymous; the second round was conducted as an in-person Delphi panel.

Initial Development of Upper-Limb Common Postures of Spasticity Picture Guide

Before the Delphi panel, the most common spasticity postures observed among adult individuals with spasticity were identified by 5 specialists in spasticity, including 2 of the Delphi panel members (I.O. and K.D.). Patients with spasticity resulting from stroke or brain or spinal cord injury were photographed at a rehabilitation clinic. Although the focus of the Delphi panel was treatment of PSS, the characteristic postures of spasticity were observed in this population with diverse etiologies. Initially, clinicians separately ranked the most representative photo for each posture based on how well they apply to PSS and the potential need for treatment. In the final round, a summary of the first-round results was presented and again ranked. A medical illustrator converted the most highly ranked photos into representative sketches to create the draft Common Postures of Spasticity [35].

Delphi Panel: Round 1

For Round 1, an e-mail containing 2 worksheets was sent to the 10 Delphi panel members. The worksheet contained the Common Postures of Spasticity (Figure 1) and asked the following questions:

1. Which muscles would you inject with onabotulinumtoxinA for a naive patient?
2. What is the total dosage of onabotulinumtoxinA you would use to treat this posture?

Clenched Fist

Questions	Answers	
	Muscles	**Initial dose/muscle**
1. Which muscles would you inject with onabotA for a naive patient? *(Please indicate with an X)* 2. How would you distribute the dose within the muscles you selected?	A. Flexor digitorum superficialis (per fascicle)	A.
	B. Flexor digitorum profundus (per fascicle)	B.
	C. Opponens pollicis	C.
	D. Flexor pollicis brevis	D.
	E. Flexor pollicis longus	E.
	F. Adductor pollicis	F.
	G. Lumbricales	G.
	H. Other (specify):	H. Other (specify):
3. What is the total dosage of onabotA you would use to treat this posture?	Total dose: ____________	
4. If you don't see optimal efficacy (no safety concern) at the next treatment, how would you adjust? *(Please indicate with an X)*	A. Increase dose B. Increase number of muscles treated C. A and B	D. Repeat previous treatment paradigm E. Redistribute the same dose F. Discontinue patient

Figure 1. Delphi panel Round 1: example from Common Postures of Spasticity Worksheet. OnabotA, onabotulinumtoxinA.

3. How would you distribute the dose among the muscles you selected?
4. If you don't see optimal efficacy (no safety concern) after the first treatment, how would you adjust at the next treatment?

The panel then answered the questions based on the following patient scenario: an upper-limb PSS patient in need of onabotulinumtoxinA treatment. The patient had never received botulinum toxin and had no major safety concerns. The focus of the panel was from the perspective of a new or early injector. The worksheet contained a comment area in which the Delphi panel members could provide additional feedback (Figure 1).

The second worksheet, Aggregate Postures, contained a listing of the same 7 common postures, and the panel was asked to rank the 3 most common posture combinations typically treated together for a patient with moderate PSS. The panel members could choose any combination on the basis of their clinical experience (Figure 2).

Frequency distributions were calculated for muscle-related questions. For questions related to total onabotulinumtoxinA doses and dose per muscle, means, medians, and ranges were calculated. Data were presented to the panel during Round 2 as descriptive summary statistics, with individual responses kept anonymous. Recommendations for aggregate postures were rank-ordered, and the top 3 were presented and discussed during Round 2.

Delphi Panel: Round 2

Round 2 was an 8-hour, in-person session. Facilitated by an experienced independent moderator, the panel focused on the 4 key aspects of the treatment paradigm for onabotulinumtoxinA and PSS postures: (1) muscles to be injected, (2) total dose, (3) dose and number of injection sites per muscle, and (4) use of muscle injection localization techniques. Other treatment elements, including but not limited to, injection site and onabotulinumtoxinA dilution also were captured, and at a later date, the injection site voting occurred.

The panel members were asked to consider how they would treat 80% of their patients when they selected answers for each posture. The panel also was asked to consider the onabotulinumtoxinA treatment paradigm for patients who were treatment-naive and for physicians who were less experienced. Individual treatment goals [36] and physician's comfort with injection can vary considerably, depending on the clinical experience and the patient's degree of spasticity. Therefore, specific treatment paradigms may have considerable variability among patients on the basis of the specifics of their spasticity and preclinical evaluation.

Aggregate postures		
Question	**Answers**	
	Postures	**Top 3 Combinations**
1. Which upper-limb postures commonly aggregate?	A. Adducted shoulder	1.
Please indicate letters of postures	B. Flexed elbow	2.
(Example 1: D, E – flexed wrist, flexed fingers)	C. Pronated forearm	3.
	D. Flexed wrist	
(Example 2: B, E, F – flexed elbow, flexed fingers, thumb-in-palm)	E. Flexed fingers	
	F. Thumb-in-palm	
(Example 3: A, C – adducted shoulder, pronated forearm)	G. Clenched fist	
	H. Intrinsic plus hand*	

Figure 2. Delphi panel Round 1: example from Aggregate Postures Worksheet. *The panel agreed that the prevalence of intrinsic plus hand in their practices is low (5%-10% of patients). Therefore, the panel agreed to remove the posture from further consideration in Round 2.

The panel was able to review and discuss the Round 1 results and then vote again for each common posture treatment paradigm (ie, total dose, muscles injected, dose per muscle). This session was audio-recorded and transcribed.

During the first round of voting for each posture, consensus was defined as ≥75% agreement. If consensus was <75%, the item was voted on again. If ≥66% of panel members agreed during the second round, the item was included. If <66% of the panel agreed, the item was excluded. For total onabotulinumtoxinA dose recommendation, consensus was achieved if ≥66% of the panel agreed on the same total dose. If <66% of the panel agreed on a total dose, further discussion would ensue, and another round of voting would take place until ≥66% agreement was reached. The panel members were asked to distribute the agreed-on total dose among the muscles for that posture. The dose that received the most votes was confirmed as the consensus dose for that muscle, unless there were strong objections from panelists. The panel was asked to discuss and vote on how they would adjust their treatment approach if they did not observe optimal effectiveness after the first treatment (barring any safety concerns). Finally, the panel was asked to discuss and vote on those muscles requiring a muscle localization technique (eg, electromyography [EMG], electrical stimulation, and ultrasonography).

Results

For Round 1, the Common Postures of Spasticity and Aggregate Postures worksheets were completed by 8 of 10 panelists. Nine of the 10 panelists attended the Delphi meeting (April 12, 2014, Newport Beach, CA). The findings from Round 2 for each of the postures are presented separately below, and the final Common Postures Picture Guide is shown in Figure 3.

Adducted Shoulder With Internal Rotation

An initial list of 7 muscles was reduced to 2 during second round voting. Overall, ≥75% of the panel agreed the pectoralis complex and latissimus dorsi should be targeted for injection (Table 1). The most frequently recommended total dose of onabotulinumtoxinA was 150 U (range, 100-200 U). During postvoting discussions, it was mentioned that EMG should be performed to determine potential involvement of the teres major, and others cautioned that this is a difficult target for the less-experienced injector. It was also recommended that an early injector should not inject the subscapularis, because injecting the other muscles addresses the spasticity. Overall, the panel felt that for this posture it was best to limit the number of muscles injected by the less-experienced injector; however, a more-experienced injector may feel that targeting more muscles would likely improve outcomes.

Flexed Elbow

Of the initial 5 muscles, the list was reduced to 3 after second round voting. Complete consensus was reached for injection into the brachioradialis, and ≥75% agreement was reached for the biceps brachii and brachialis (Table 1). The most frequently recommended total dose for all 3 muscles was 150 U (range, 100-150 U). During postvoting discussions, the panel noted that elbow flexion is a critical movement for arm function and revised the original figure in the assessment tool to illustrate this (the revised figure is used in this article).

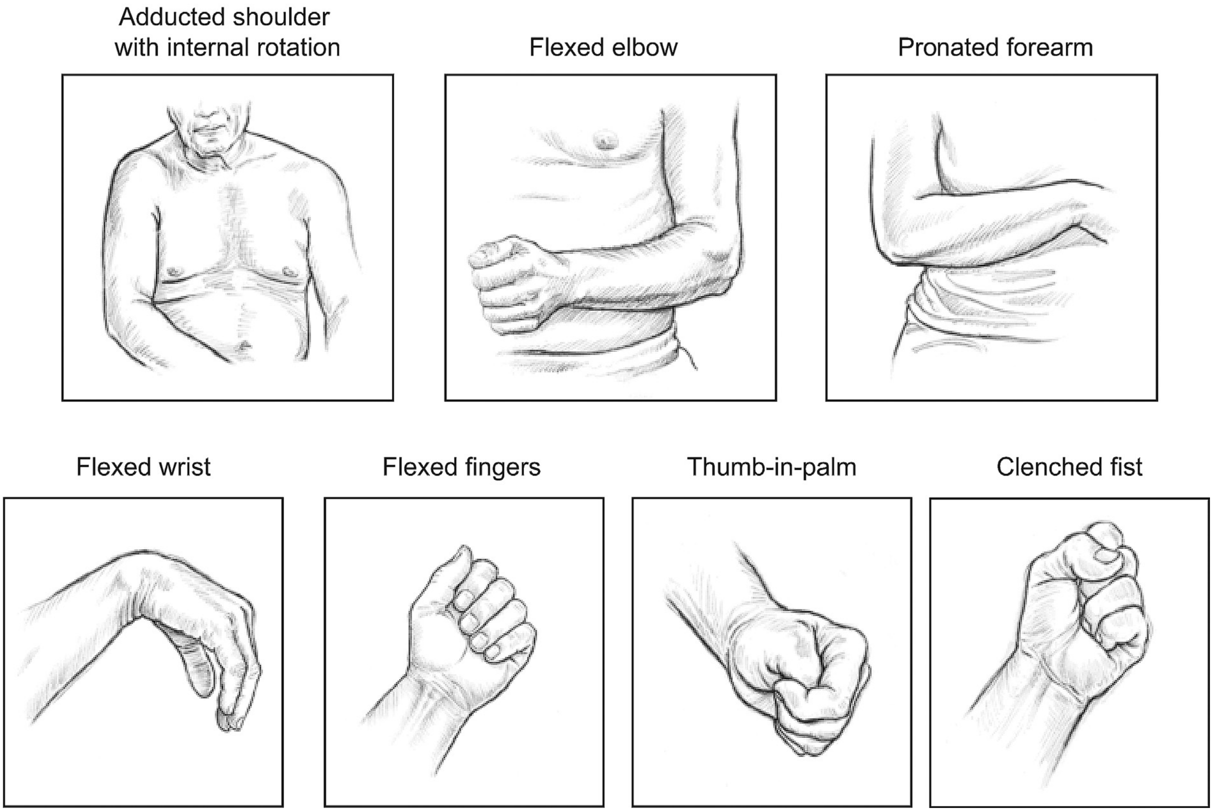

Figure 3. Post-Delphi revisions: final redrawn images for Common Postures of Spasticity Picture Guide: Upper Limb.

Moreover, the position of the forearm is critical in terms of the amount of onabotulinumtoxinA injected into the biceps brachii, as the biceps is both a flexor and a supinator muscle. Two panel members indicated that they do not inject the biceps, or inject low doses, in an effort to not overweaken supination.

Pronated Forearm

An initial list of 5 muscles was reduced to 2; complete consensus was reached on the pronator quadratus and pronator teres during second round voting (Table 1). The most frequently recommended total dose of onabotulinumtoxinA was 75 U (range, 50-100 U). In postvoting discussions, it was noted by some Delphi panel members that physical exam can help determine if the pronator quadratus is involved: the elbow can be flexed to see whether the patient has tightness with supination.

Flexed Wrist

An initial list of 6 muscles was reduced to 2 during second round voting. Complete consensus was reached for injection into the flexor carpi radialis and the flexor carpi ulnaris (Table 1). The most frequently recommended total dose of onabotulinumtoxinA was 100 U (range, 60-100 U). During postvoting discussions, it was noted that the dosing for this posture should be based on the desired function and presentation. The 100-U dose is appropriate when attempting to improve passive function; however, a more conservative approach with lower doses might be appropriate when gains in active function (voluntary movement) are the goal. Thus, one might start with a lower dose (eg, 75 U). In cases where finger flexors contribute to the flexed wrist posture, these muscles should also be injected.

Flexed Fingers

An initial list of 4 muscles was reduced to 2 during second round voting; complete consensus was reached for injection into the flexor digitorum superficialis and flexor digitorum profundus (Table 1). The most frequently recommended total dose of onabotulinumtoxinA was 100 U (range, 50-100 U). During postvoting discussions, it was noted that involvement of the flexor digitorum superficialis and the flexor digitorum profundus almost always occurs together. When making dosing decisions, the panel felt that consideration for dose adjustment must be given to whether patients are using their grip for active function (eg, a patient who uses a walker for ambulation).

Thumb-in-Palm

An initial list of 4 muscles was reduced to 3 after the second round of voting. Complete consensus was

Table 1
Summary of panel recommendations (round 2)

Adducted Shoulder*	Muscles: Pectoralis Complex	Latissimus Dorsi	Technique and Total Dose
Panelists (%) recommending injection of this muscle	87.5	75	LT: yes†
OnabotulinumtoxinA dose, U (mode)	75	75	150
OnabotulinumtoxinA dose, U (range)	75-100	75	100-200
Number of injection sites per muscle	4	4	

Flexed Elbow	Muscles: Brachioradialis	Biceps Brachii	Brachialis	Technique and Total Dose
Panelists (%) recommending injection of this muscle	100	87.5	75	LT: yes†
OnabotulinumtoxinA dose, U (mode)	25	50	75	150
OnabotulinumtoxinA dose, U (range)	25-50	0-50	50-100	100-150
Number of injection sites per muscle	2	4	2	

Pronated Forearm	Muscles: Pronator Quadratus	Pronator Teres	Technique and Total Dose
Panelists (%) recommending injection of this muscle	100	100	LT: yes†
OnabotulinumtoxinA dose, U (mode)	25	50	75
OnabotulinumtoxinA dose, U (range)	0-25	45-60	50-100
Number of injection sites per muscle	1	2	

Flexed Wrist	Muscles: Flexor Carpi Radialis	Flexor Carpi Ulnaris	Technique and Total Dose
Panelists (%) recommending injection of this muscle	100	100	LT: yes†
OnabotulinumtoxinA dose, U (mode)	50	50	100
OnabotulinumtoxinA dose, U (range)	50-75	25-50	60-100
Number of injection sites per muscle	2	2	

Flexed Fingers	Muscles: Flexor Digitorum Superficialis	Flexor Digitorum Profundus	Technique and Total Dose
Panelists (%) recommending injection of this muscle	100	100	LT: yes†
OnabotulinumtoxinA dose, U (mode)	50	50	100
OnabotulinumtoxinA dose, U (range)	20-60	25-75	50-100
Number of injection sites per muscle	2	2	

Thumb-in-palm	Muscles: Flexor Pollicis Longus	Adductor Pollicis	Flexor Pollicis Brevis	Technique and Total Dose
Panelists (%) recommending injection of this muscle	100	87.5	87.5	LT: yes†
OnabotulinumtoxinA dose, U (mode)	40	15	20	75
OnabotulinumtoxinA dose, U (range)	40-50	10-20	12.5-20	50-75
Number of injection sites per muscle	2	1	1	

Clenched Fist	Muscles: Flexor Digitorum Superficialis	Flexor Digitorum Profundus	Flexor Pollicis Brevis	Flexor Pollicis Longus	Adductor Pollicis Longus	Technique and Total Dose
Panelists (%) recommending injection of this muscle	100	100	75	100	75	LT: yes†
OnabotulinumtoxinA dose, U (mode)	50	50	15	25	10	150
OnabotulinumtoxinA dose, U (range)	40-50	25-60	10-15	25-30	10-12.5	125-175
Number of injection sites per muscle	2	2	1	2	1	

LT = Localization technique.
* The Delphi panel only reached consensus on these 2 muscles (pectoralis complex and latissimus dorsi) for the adducted shoulder with internal rotation as the goal was to provide common postures for inexperienced injectors, and the panel felt that the other muscles might be too difficult for someone without more substantial injection experience. They do agree that an experienced injector would most likely inject more muscles.
† All of the Delphi panel members voted that using a localization technique (electromyography, electrical stimulation, or ultrasound) was critical for all postures.

reached for injection into one muscle (flexor pollicis longus); 87.5% agreed on the adductor pollicis and flexor pollicis brevis (Table 1). The most frequently recommended total dose of onabotulinumtoxinA was 75 U (range, 50-75 U). During postvoting discussions, a panel member noted the importance of aggressive treatment, as patients with this posture often have little to no hand function.

Clenched Fist

An initial list of 8 muscles was reduced to 5 after a second round of voting. Complete consensus (100% agreement) was reached for 3 of the 5 muscles involved (flexor digitorum superficialis, flexor digitorum profundus, flexor pollicis longus); 75% agreement was attained for the other 2 muscles (Table 1). The most frequently recommended total dose of onabotulinumtoxinA was 150 U (range, 125-175 U). During the postvoting discussion of the clenched fist, it was noted that the opponens pollicis and flexor pollicis brevis were major contributors to the thumb-in-palm posture, but that the opponens pollicis was not a major contributor to the clenched fist deformity.

Aggregate Postures

During Round 1, the 3 most commonly selected upper-limb aggregate postures were discussed. The panel agreed that it would be of value to gain consensus on the recommended starting dose and the maximum total dose of onabotulinumtoxinA for each aggregate posture combination. The final results of these discussions are summarized in Table 2. Some panel members noted that for less-experienced injectors treating naive patients, 400 U is the maximum dose that should be used for aggregate upper-limb postures. The dose should be reduced if there is excessive weakness. Less-experienced injectors should talk to their patients about which postures, in complex combinations, might benefit from treatment, and then use the minimum recommended dose based on those postures. Preservation of active function is an important consideration when making dosing decisions for aggregate postures.

Table 2
Three most common aggregate postures

	Aggregate Postures	Starting Dose (Typical)	Total Dose (Maximum)
1	Adducted shoulder Flexed elbow Pronated forearm Flexed wrist Clenched fist	300 U	400 U
2	Flexed elbow Pronated forearm Flexed wrist Clenched fist	300 U	400 U
3	Flexed wrist Clenched fist	200 U	300 U

During Round 2, all panel members agreed that localization technique for onabotulinumtoxinA injection is critical. When asked how they would adjust a second treatment if they did not observe optimal effectiveness after the first injection with onabotulinumtoxinA, 8 of the 9 panelists responded that they would increase the dose and/or the number of muscles they would inject for that posture.

Other Treatment Considerations

Safety issues described in the U.S. Food and Drug Administration (FDA)-approved prescribing information for onabotulinumtoxinA were acknowledged, but specific management of potential adverse events was beyond the scope of this panel. Clinical experience should guide treating physicians on appropriate adverse event management. In addition, clinicians should consider local approved prescribing information for dosing guidelines (ie, the U.S. FDA-approved labeling for onabotulinumtoxinA states a maximum dose of 400 U per 3-month interval). The panel agreed that the recommendations on optimal technique for each group of target muscles should mitigate risks related to inappropriate dosing and inadvertent injection of the incorrect muscle(s) or adjacent structures (eg, blood vessels, nerves, pleural cavity).

Although the worksheets were developed to target less-experienced injectors, and the Delphi panel members were instructed to complete the worksheets with these health care professionals in mind, the panel noted that it would be of value to expand the targeted audience to include experienced injectors. During panel voting discussions, panelists strongly agreed that treatment insights, treatment techniques, and expertise were enhanced by experienced clinicians.

The panel also noted that treatment algorithms should include consideration of active function. Defining expected treatment outcomes for a patient with PSS is an essential component of injector training. Dosing decisions are made, at least in part, on an assessment of functional needs: those that already exist or that need to be achieved. Understanding passive and active function is important in goal-setting [37].

An onabotulinumtoxinA dilution of 50 U/mL (2:1 dilution ratio) was considered most appropriate (dilution ratios of 1:1 to 1:4 were appropriate in some cases) and recommended for patients with PSS in the scenario presented for the exercise. However, although 2:1 was appropriate for this exercise, in practice an injector might vary the dilution based on the muscles involved. In clinical practice, several factors are involved in determining the dilution ratio, including the posture, muscle size, location of motor endplates, to the limited extent that they are known, intended injection location relative to neighboring structures, EMG activity, previous interventions, and level of experience of the treating clinician [38,39].

Some panelists noted that the common postures treatment algorithms may be more informative if they provided dosing ranges rather than discrete amounts for each posture's total dose and dose per muscle, as the presentation of PSS may vary during the treatment period. The panelists also summarized the number of injection sites needed per upper-limb muscle, regardless of the posture that was being presented (Table 1). Almost all panelists (88.9%) agreed to increase the dose, increase the number of muscles treated, and/or modify the dilution at the next visit if suboptimal efficacy (with no safety concerns) was observed.

Discussion

In this study, we used a modified Delphi method to obtain consensus-based recommendations on onabotulinumtoxinA treatment paradigms for upper-limb common postures in patients with PSS and to develop guidance for clinicians, especially those with limited injection experience, toward the application of individualized onabotulinumtoxinA treatment paradigms for PSS. The goal was to fill an educational gap and provide practicing clinicians with no or very little injection experience with guidance on how to effectively manage their patients with PSS. The panel agreed that injection localization techniques are essential for each muscle involved, concurred on the 3 most common aggregate posture combinations, and agreed on the typical starting dose and maximum total dose for each combination. Because these recommendations were intended to guide injectors with limited or no injection experience, certain muscles that require a high level of skill, such as the subscapularis and hand intrinsics, were excluded.

Beyond the original worksheet content, panel members expressed interest reaching consensus on an onabotulinumtoxinA dilution ratio. The discussion focused on a number of contributing factors, including muscle size, the etiology of the spasticity, total dose, injection technique, chronicity, and the presence of contractures, as well as the level of experience of the treating physician. Ultimately, it was decided that a 2:1 dilution ratio was appropriate in the context of the exercise and the patient scenario provided, although that dilution ratio might vary based on the clinical presentation and experience of the injector.

Notably, the FDA has included in the labeling of all formulations of botulinum toxins that they are not interchangeable, and units cannot be converted using a dose ratio. Therefore, the recommendations are specific to onabotulinumtoxinA, and the conclusions reported here should not be extrapolated to other botulinum toxin formulations.

The panel emphasized that the effects of PSS, and the treatment thereof, should be considered with regard to the level of impairment (eg, hypertonicity, limb deformity) and the impact on function—active and passive [36]. One advantage of onabotulinumtoxinA is that it can reduce local muscle overactivity, without an impact on cognition or alertness, and usually without creating generalized weakness, or other significant adverse effects. Nevertheless, to date, limited data support a benefit of botulinum toxin on active function in patients with upper-limb spasticity, with inconsistent results in both controlled and open-label studies [23-25]. The authors and clinical experts agree that future study designs may fill these data gaps [40].

Recommendations generated during the Delphi process are not designed to supersede evidence-based treatment guidelines, peer-to-peer training, clinical judgment, particularly that of experienced physicians, or clinical research. Randomized controlled trials are the gold standard, but their strict protocols may not allow an individualized patient approach or treatment interventions applicable to many clinical scenarios. Thus, many research findings generated from placebo-controlled trials do not adequately guide treatment for the entire PSS patient population.

The Delphi approach helps bridge some of these gaps. Not surprisingly, the panel's recommendations are in concordance with previously published treatment algorithms [3,5] and clinical guidelines [1,2,4,25,41-43]. This study specifies the particular muscles involved in common postures associated with upper-limb spasticity, details the importance of localization, and suggests onabotulinumtoxinA dosing and dilution ratios.

As summarized in Table 3, there is large overlap between published guidelines and the panel's final recommendations with regard to the muscles for onabotulinumtoxinA injection associated with each posture. This is particularly noteworthy for the clenched fist, flexed elbow, and pronated forearm postures. By contrast, for the adducted shoulder with internal rotation, the Delphi panel agreed to inject the pectoralis complex and latissimus dorsi, as they were concerned that less-experienced injectors may have difficulty injecting some of the other affected muscles initially identified. Previous published reports also included the teres major and subscapularis [3-5,25]. The variability in the recommendations is partially based on the directives of the Delphi panel to consider early injectors. Indeed, more-experienced injectors may be also comfortable injecting the teres major and subscapularis when presented with a patient with adducted shoulder and internal rotation.

Table 3
Summary of Delphi panel recommendations from Round 1 (italics)* and Round 2 (bolded)* and comparison with other published recommendations

Posture	Muscles								
Adducted Shoulder With Internal Rotation†	**Pectoralis Complex**	**Latissimus Dorsi**	*Teres Major*	*Subscapularis*	*Deltoid Media*	*Brachialis*	*Levator Scapulae*		Total Dose, U
Muscle frequency	87.5%	75%	75%	50%	12.5%	12.5%	12.5%		
OnabotulinumtoxinA dose, U (mode)	75	75							150
OnabotulinumtoxinA dose, U (range)	75-100	75	50-75	75	20	75	38		100-200
Muscles Included for Injection in Published Algorithms/Recommendations									
Citation									
Brin 1997 [3]	X	X	X	X					
Mayer et al 1997 [5]	X	X	X	X					
Royal College of Physicians 2009 [4]	X	X	X	X			X	Rhomboids	
Sheean et al 2010 [25]	X	X	X	X	X				
Flexed Elbow	**Brachioradialis**	**Biceps Brachii**	**Brachialis**	*Pronator Teres*	*Pronator Quadratus*				
Muscle frequency	100%	87.5%	75%	50%	12.5%				
OnabotulinumtoxinA dose, U (mode)	25	50	75						150
OnabotulinumtoxinA dose, U (range)	25-50	0-50	50-100	38-100	N/A				100-150
Muscles Included for Injection in Published Algorithms/Recommendations									
Citation									
Brin 1997 [3]	X	X	X						
Mayer et al 1997 [5]	X	X	X						
Royal College of Physicians 2009 [4]	X	X	X						
Sheean et al 2010 [25]	X	X	X	X		*FCR*			
Pronated Forearm	**Pronator Quadratus**	**Pronator Teres**	*FCU*	*Brachialis*	*Brachioradialis*				
Muscle frequency	100%	100%	12.5%	12.5%	12.5%				
OnabotulinumtoxinA dose, U (mode)	25	50							75
OnabotulinumtoxinA dose, U (range)	0-25	45-60	20	100	25				50-100

Muscles Included for Injection in Published Algorithms/Recommendations								
Citation								
Brin 1997 [3]	X	X						
Mayer et al 1997 [5]	X	X						
Royal College of Physicians 2009 [4]	X	X						
Sheean et al 2010 [25]	X	X	X					
Flexed Wrist	**FCR**	**FCU**	*Palmaris Longus*	*Flexor Pollicis Longus*	*Flexor Digitorum Superficialis*	*Flexor Digitorum Profundus*		
Muscle frequency	100%	100%	50%	25%	50%	37.5%		
OnabotulinumtoxinA dose, U (mode)	50	50						100
OnabotulinumtoxinA dose, U (range)	50-75	25-50	13-50	20-75	25-75	25-75		60-100
Muscles Included for Injection in Published Algorithms/Recommendations								
Citation								
Brin 1997 [3]	X	X						
Mayer et al 1997 [5]	X				X	X	Flexor carpus radialis *and brevis*	
Royal College of Physicians 2009 [4]	X	X		X	X	X		
Sheean et al 2010 [25]	X	X						
Flexed fingers[‡]	**Flexor Digitorum Superficialis**	**Flexor Digitorum Profundus**	*FCR/FCU*	*Lumbricales*				
Muscle frequency	100%	100%	12.5%	12.5%				
OnabotulinumtoxinA dose, U (mode)	50	50						100
OnabotulinumtoxinA dose, U (range)	20-60	25-75	30	30				50-100
Posture	Muscles							
Thumb-in-palm	**Flexor Pollicis Longus**	**Adductor Pollicis**	**Flexor Pollicis Brevis**	*Flexor Digitorum Profundus*				
Muscle frequency	100%	87.5%	87.5%	12.5%				
OnabotulinumtoxinA dose, U (mode)	40	15	20					75
OnabotulinumtoxinA dose, U (range)	40-50	10-20	12.5-20	35				50-75
Muscles Included for Injection in Published Algorithms/Recommendations								
Citation								
Brin 1997 [3]	X	X					Opponens pollicis	

(*continued on next page*)

Table 3 (*continued*)

Posture	Muscles				
Thumb-in-palm	**Flexor Pollicis Longus**	**Adductor Pollicis**	**Flexor Pollicis Brevis**	*Flexor Digitorum Profundus*	
Mayer et al 1997 [5]	X	X	X		Abductor pollicis brevis, Opponens pollicis
Royal College of Physicians 2009 [4]		X	X		Opponens pollicis, Lumbricals, Interossei
Sheean et al 2010 [25]	X	X	X		

FCR = flexor carpus radialis; FCU = flexor carpus ulnaris.

* Note: for each posture, muscles in bold face were included in onabotulinumtoxinA treatment algorithm after Delphi panel consensus (≥75% agreement) in Round 2. Muscles shown in italics were voted on in Round 1 but did not move into Round 2 because of lack of consensus—they are shown for reference to other published studies.

† The Delphi panel only reached consensus on these 2 muscles (pectoralis complex and latissimus dorsi) for the adducted shoulder with internal rotation as the goal was to provide common postures for inexperienced injectors, and the panel felt that the other muscles might be too difficult for someone without more substantial injection experience. They do agree that an experienced injector would most likely inject more muscles.

‡ None of the cited articles included onabotulinumtoxinA treatment algorithms/recommendations for the flexed fingers common posture.

Conclusions

This study used a modified Delphi method with a 10-member panel of physiatrists and neurologists with expertise in botulinum toxin injection and research methodology to determine clinical recommendations for treating upper-limb spasticity in patients with PSS with onabotulinumtoxinA. Treatment algorithms for 7 common postures were developed, as were 3 common aggregate postures and included the specific muscles to be injected, the total dose per muscle and posture, dilution ratio, and the use of localization techniques to identify target muscles for injection. Posture pictures were developed to delineate limb position and muscle involvement.

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