


Pain, disability, and quality of life in participants after concurrent onabotulinumtoxinA treatment of upper and lower limb spasticity: Observational results from the ASPIRE study

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Abstract

Introduction: Upper and lower limb spasticity is commonly associated with central nervous system disorders including stroke, traumatic brain injury, multiple sclerosis, cerebral palsy, and spinal cord injury, but little is known about the concurrent treatment of upper and lower limb spasticity with botulinum toxins.

Objective: To evaluate onabotulinumtoxinA (onabotA) utilization and to determine if concurrent onabotA treatment of the upper and lower limbs has supported improvements in participants with spasticity.

Design: Sub-analysis of a 2-year, international, prospective, observational registry (ASPIRE, NCT01930786).

Setting: International clinic sites (54).

Participants: Adult spasticity participants across etiologies, who received ≥ 1 concurrent onabotA treatment of the upper and lower limbs during the study.

Intervention: Participants were treated with onabotA at the clinician's discretion.

Outcomes: Baseline characteristics and outcomes of disability (Disability Assessment Scale [DAS]), pain (Numeric Pain Rating Scale [NPRS]), participant satisfaction, physician satisfaction, and quality of life (QoL; Spasticity Impact Assessment [SIA]) were evaluated. Adverse events were monitored throughout the study.

Results: Of 744 participants enrolled, 730 received ≥ 1 dose of onabotA; 275 participants received treatment with onabotA in both upper and lower limbs during ≥ 1 session; 39.3% of participants were naïve to onabotA for spasticity. The mean (SD) total dose per treatment session ranged from 421.2 (195.3) to 499.6 (188.6) U. The most common baseline upper limb presentation was clenched fist ($n = 194$, 70.5%); lower limb was equinovarus foot ($n = 219$, 66.9%). High physician and participant satisfaction and improvements in pain, disability and QoL were reported after most treatments. Nine participants (3.3%) reported nine treatment-related adverse events; two participants (0.7%) reported three serious treatment-related severe adverse events. No new safety signals were identified.

Conclusion: More than a third of enrolled participants received at least one concurrent onabotA treatment of the upper and lower limbs, with reduced pain, disability, and improved QoL after treatment, consistent with the established safety profile of onabotA for the treatment of spasticity.

INTRODUCTION

Spastic hemiparesis is a progressive, secondary complication of central nervous system damage that encompasses muscle shortening, spastic dystonia, and disabling muscle overactivity.¹ Hemiparesis or hemiplegia associated with spasticity may involve both the upper and lower limbs, often as a result of stroke.^{2,3} Other etiologies associated with spasticity include multiple sclerosis, cerebral palsy, traumatic brain injury, and spinal cord injury.^{4–7} Upper limb (UL) spasticity and muscle overactivity, two positive phenomena of upper motor neuron syndrome,⁸ can result in an abnormal posture of the arm, wrist, elbow, or hand. In the lower limb (LL), deformities such as stiff extended knee, equinovarus foot, striatal toe, and hip adduction or flexion may occur.

People with UL or LL spasticity are at increased risk of secondary limb deformities that may reduce mobility and increase difficulty with self-care and hygiene,⁹ thereby reducing quality of life (QoL) and increasing the physical, psychosocial, and economic burden for patients and their caregivers.¹⁰ Gait impairments, often seen in patients with LL spasticity,¹¹ negatively affect QoL.¹² Patients with hemiparesis or hemiplegia in the UL or LL after stroke report significantly lower life satisfaction than non-stroke patients in life in general, as well as in areas such as independence, leisure, family life, contact with friends, physical health, and psychological health.¹³ One study comparing health-related-quality QoL (HRQoL) reported lower HRQoL for patients with spasticity 1 and 2 years post-stroke as compared to patients without spasticity.¹⁴

OnabotulinumtoxinA (onabotA) is a focally administered native botulinum toxin type A (BoNT/A). When therapeutic doses are injected intramuscularly, it prompts temporary partial chemodenervation of the muscle, thereby decreasing muscle hypertonicity and excessive muscle contractions.¹⁵ Studies have demonstrated the benefits of onabotA treatment in UL and LL spasticity.^{16–18} For example, gross motor movements related to grasp improved in patients with UL spasticity after onabotA treatment.¹⁹ Injection of the LL with onabotA has been shown to improve gait characteristics in patients with LL spasticity.^{12,20} When combined with physical therapy, treatment with onabotA results in improvement in spasticity during post-stroke recovery.²¹

Despite studies demonstrating the effectiveness of treatment of either UL or LL spasticity with BoNT/As,^{22,23} there is limited real-world information related to concurrent BoNT/A treatment of UL and LL

spasticity,^{12,24} highlighting the need for additional studies to address this issue. The Adult SPasticity International Registry (ASPIRE) was a 2-year international observational registry designed to identify the clinical characteristics of patients with spasticity across a variety of etiologies before and after treatment with onabotA.^{22,25–28} Using data from ASPIRE, we examined patient- and physician-reported outcomes after onabotA treatment in a subgroup of patients with spasticity who were treated for both UL and LL spasticity. The aim of this study was to evaluate onabotA utilization and to determine if treatment with onabotA supported improvements in patients receiving concurrent treatment for UL and LL spasticity.

METHODS

Study design and setting

ASPIRE ([Clinicaltrials.gov](https://clinicaltrials.gov), NCT01930786) was an international, multicenter, prospective, observational registry that enrolled patients from 54 North American, European, and Asian sites.²⁵ The study spanned 108 weeks, encompassing a 96-week study period and an additional 12-week follow-up period. Physicians and health care providers (HCPs) treated participants according to their usual clinical practices and in accordance with regional regulations in each country. Participants were re-treated ~12 weeks after the last treatment. Exact intervals between treatments varied, depending on the clinical practice and perceived duration of treatment benefit. Participant-reported outcomes were collected at baseline and ~5 weeks after each treatment; a follow-up interview was conducted 12 weeks after the final treatment. Clinician-reported outcomes for treatments 1 through 7 were collected at each office visit subsequent to treatment. Study requirements did not stipulate a final follow-up visit; thus clinician-reported outcomes for treatment 8 were not evaluated.

Before participation in this study, informed written consent was obtained, including consent related to review of medical records that would allow the enrolling HCP to obtain information about any administration of BoNT/As outside the ASPIRE study, if applicable. Institutional review board approval was required and granted by each site participating in this study, which was conducted in accordance with the Declaration of Helsinki and Guidelines for Good Pharmacoeconomics Practices, as outlined by the International Society for Pharmacoeconomics.^{29,30}

Control for bias

The ASPIRE study was designed to enable generalizability to clinical practice. Broad eligibility criteria were used to minimize selection bias and identify onabotA utilization for spasticity across multiple etiologies and geographic regions, including participants both naïve and non-naïve to BoNTs for the treatment of spasticity. To minimize any selection bias from inclusion of non-naïve participants for which onabotA was tolerable and effective, ASPIRE aimed to enroll at least one-third of participants naïve to BoNTs for the treatment of spasticity. Information bias was minimized with carefully designed case report forms and site staff training; to ensure data quality, assessments were performed by contracting research organization personnel.

Study population/participants

Participants eligible for inclusion in this study were 18 years of age or older and treated with onabotA in the course of routine clinical practice at participating sites for either newly diagnosed or established focal spasticity. Participants treated with BoNT/As (other than onabotA) were excluded. Eligible participants needed the requisite cognitive and linguistic skills to complete study questionnaires (as determined by the enrolling HCP), the ability to answer questions via computer or phone (with or without help from a caregiver), and the provision of informed written consent from the participant or legal guardian prior to participation in any study activity. Any participants who were active in other clinical trials for the treatment of spasticity were excluded, as were participants with any condition or circumstance that the enrolling HCP deemed would markedly interfere with the ability of the person to participate in the study. Participants included in this sub-analysis were treated concurrently for UL and LL spasticity with onabotA at least once throughout the 2-year study.

Outcomes and data sources

Clinical characteristics and participant demographics in patients receiving at least one concurrent treatment for both UL and LL spasticity were collected at baseline; onabotA utilization was collected at each treatment session, and adverse events (AEs) were evaluated throughout the 108-week study. The most common clinical presentations were assessed at baseline; baseline values for participant- and clinician-reported outcomes were collected at the first visit.

Clinician satisfaction data for each treatment were collected at the start of the next office visit and prior to any re-treatment, along with participant-reported

outcomes using the Disability Assessment Scale (DAS) for UL³¹ and LL.³² Other participant-reported outcomes were collected ~4 to 6 weeks after each treatment online or by phone, including the effect of UL and LL spasticity on daily activities using a sponsor-developed questionnaire (Spasticity Impact Assessment [SIA])²⁵; pain, measured by the Numeric Pain Rating Scale (NPRS)^{33,34}; and overall treatment satisfaction. The Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 was used to summarize AEs by preferred term and organ class, with any possible relationship to treatment adjudicated by a panel of safety clinicians, who also evaluated any potential distant spread of toxin. Detailed information on methods and assessments are available.²⁵

Statistical analysis

Analyses were explorative and descriptive in nature and did not test any prespecified hypotheses; missing data were not imputed. NPRS and DAS mean values

TABLE 1 Summary of limbs treated across one or more treatments—all eligible participants.

Number of treatments per patient—summary	
N	730
Mean ± SD	4.3 ± 2.2
Min, Max	1.0, 8.0
Median [IQR]	4.0 [2.0, 6.0]
Number of treatments per participant—tabulated	
N	730
1	103 (14.1%)
2	104 (14.2%)
3	81 (11.1%)
4	109 (14.9%)
5	91 (12.5%)
6	81 (11.1%)
7	116 (15.9%)
8	45 (6.2%)
Limbs treated	
N	730
Lower limb only	246 (33.7%)
Upper and lower limbs – at separate treatments	9 (1.2%)
Upper and lower limbs – both at all treatments	161 (22.1%)
Upper and lower limbs – both at some treatments	114 (15.6%)
Upper limb only	200 (27.4%)
Upper and lower limbs—both at ≥1 treatment	
N	730
No	455 (62.3%)
Yes	275 (37.7%)

Abbreviations: SD, standard deviation; IQR, interquartile range.

and respective 95% confidence intervals (CIs) are estimated using a mixed-effects linear regression model to account for the repeated measurements for each participant up to eight treatment cycles. Sample sizes at each time point are from the observed values, and *p* values are adjusted for all possible pairwise comparisons between treatment cycles using the Tukey method to control the family-wise error rate. Note that although all possible pairwise comparisons were performed, only a subset is presented for each treatment cycle and compared to baseline. All analyses were performed with R version 4.1 or later (The R Foundation for Statistical Computing, <http://www.rproject.org/>).

RESULTS

Participant disposition, demographics, and clinical characteristics

Of the 744 participants enrolled in the 2-year study, 730 received at least one dose of onabotA (Table 1). Within this group, 275 participants received at least one concurrent treatment of UL and LL at the same treatment visit at least once during the study. Although most participants were from the United States, participants were drawn from seven countries (Table 2), including Taiwan, Italy, the United Kingdom (UK), Germany, France, and Spain. The mean number of treatments per participant ranged from (mean, SD) 1.8 (1.2) treatments for participants from Taiwan to 6.2 (2.2) for participants from Germany.

Participants (*N* = 275) had a mean age of 53.2 years and were predominantly White, with 50.2% (138/275) reporting their employment status as disabled (Table 3). Less than half of participants (39.3%, 108/275) were naïve to onabotA for spasticity; the most common etiology was stroke (72.7%, 200/275). Most participants had been treated with physical therapy or occupational therapy (84.2%, 223/275), orthotics (61.5%, 163/275), or assistive devices (72.1%, 191/275). Information on medication history in this cohort of participants is available in Table S1.

Clinical presentations and treatment utilization

The most common clinical presentations among the 275 participants concurrently treated for UL and LL spasticity are highlighted in Figure 1 for treatments (Tx) 1 to 4 and include clenched fist, flexed elbow, equinovarus foot, flexed wrist, pronated forearm, and adducted shoulder (described in^{16,17,35}). Presentations for all treatments (Tx 1 to Tx 8) are detailed in Table S2.

Of the participants receiving concurrent treatment for UL and LL spasticity at least once over the 2-year study, 72.4% or more of participants who were treated at any given treatment session received treatment to both UL and LL (Table 4). The average number of weeks between sessions decreased over the course of the study from 18.8 weeks between the first and second sessions to 13.1 weeks between the seventh and eighth sessions. Treatment providers used guided, anatomic, or a combination of both methods in treating participants (Table 5). When guidance methods were aggregated across all treatments, anatomic location was used to treat 45.5% of participants in at least one treatment and 8.4% of participants at all treatments; guided location was used to treat 91.6% of participants at least once and 54.5% of participants at all treatments; and the combination of anatomic and guided location methods was used to treat 37.1% of participants at all treatments.

The mean dose of onabotA across eight treatment sessions ranged from 421 to 500 U (Table 6), with individual dosing at the treating physician's discretion according to clinical need and product labeling.³⁶ Data presented in Table 6 demonstrate the variation in onabotA utilization in clinical practice.

Treatment outcomes

Baseline values for participant-reported SIA and NPRS were collected at the first office visit; values post-treatment for these participant-reported outcomes (as well as participant satisfaction) were collected via

TABLE 2 Participants by country.

		Country						
Value	Total	USA	Taiwan	Italy	UK	Germany	France	Spain
Number of treatments per participant								
<i>N</i>	275	187	27	27	14	8	6	6
Mean (SD)	4.6 (2.2)	5.0 (2.2)	1.8 (1.2)	4.4 (1.4)	4.4 (1.4)	6.2 (2.2)	4.8 (1.9)	4.7 (1.2)
Min, Max	1.0, 8.0	1.0, 8.0	1.0, 5.0	1.0, 7.0	1.0, 7.0	2.0, 8.0	2.0, 8.0	3.0, 6.0
Median [IQR]	5.0 [3.0, 7.0]	5.0 [3.0, 7.0]	1.0 [1.0, 2.5]	5.0 [3.5, 5.0]	4.5 [4.0, 5.0]	7.0 [5.5, 8.0]	5.0 [4.2, 5.0]	4.5 [4.0, 5.8]

Abbreviations: SD, standard deviation; IQR, interquartile range.

TABLE 3 Baseline participant demographics and clinical characteristics.

Characteristic	N = 275
Mean age (SD), years	53.2 (15.4)
Male, <i>n</i> (%)	141 (51.3)
Race, <i>n</i> (%)	
White	187 (68.0)
Black	39 (14.2)
Asian	31 (11.3)
Other	18 (6.5)
Employment status, <i>n</i> (%)	
Full time	19 (6.9)
Part time	17 (6.2)
Unemployed	30 (10.9)
Retired	64 (23.3)
Disability	138 (50.2)
Other	7 (2.5)
OnabotA treatment naïve, <i>n</i> (%)	108 (39.3)
OnabotA treatment within the past 12 weeks, <i>n</i> (%)	2 (0.7)
Practice type, <i>n</i> (%)	
Public	137 (49.8)
Private	128 (46.5)
Both	10 (3.6)
Spasticity etiology, <i>n</i> (%)	
Cerebral palsy	22 (8.0)
Multiple sclerosis	21 (7.6)
Spinal cord injury	9 (3.3)
Stroke (ischemic, hemorrhagic, or embolic)	200 (72.7)
Traumatic brain injury	24 (8.7)
Other etiology	12 (4.4)
Caregiver employment status, <i>n</i> (%)	
Full time	19 (35.8)
Part time	6 (11.3)
Unemployed	5 (9.4)
Retired	18 (34.0)
Other	5 (9.4)
Treatment type, <i>n</i> (%)	
Acupuncture	29 (10.9)
Assistive device	191 (72.1)
Casting	28 (10.6)
Chemodenervation	16 (6.0)
Intrathecal therapy	26 (9.8)
Orthotics	163 (61.5)
Physical therapy/occupational therapy	223 (84.2)
Surgeries or procedures	34 (12.8)

Abbreviation: SD, standard deviation.

phone or online thereafter. Due to difficulties in contacting participants via phone or online, the *n*'s are lower than expected for post-treatment participant-reported

outcomes. Because clinician-reported outcomes were collected during office visits, the *n*'s are higher for clinician-reported outcomes (DAS and clinician satisfaction). Note that because participant and physician satisfaction outcomes refer to the most recent treatment, there are no baseline values for either of these two measures.

Pain, disability, and QoL as measured on the DAS

Participants assessed their pain and levels of disability associated with functional impairments due to spasticity with the DAS. At treatment visit 1, the DAS was completed prior to injection with onabotA; thus treatment 1 (Tx 1) represents the baseline level of disability. Throughout the study, information was collected on treatment outcomes at each subsequent treatment visit. The DAS after treatment 8 was assessed via phone interview ~5 weeks after the last treatment. The fraction of participants reporting disability as none to mild on the DAS increased after the first treatment with onabotA; these levels did not return to baseline throughout the study (Figures 2 and 3, green bars). DAS model-estimated means (Figures 2 and 3, bottom panels), predicted based on a statistical model of the observed data demonstrated significant improvements in UL (Figure 2) and LL (Figure 3) disability levels across treatment sessions compared to baseline. For UL, there were significant improvements in the model-estimated mean DAS levels for pain, dressing, and limb posture compared to baseline across all treatments (Figure 2A,C,D). For LL, significant improvements were noted for pain and limb posture across most treatments (Figure 3A,D).

Pain and treatment satisfaction

Pain and treatment satisfaction were assessed ~4 to 6 weeks after each treatment via phone or online. Significant reductions in pain from baseline levels were noted on the NPRS after most treatment sessions (Figure 4). In addition to the NPRS, participants also responded to a series of questions related to pain and treatment satisfaction (Figure 5). Most participants were satisfied or extremely satisfied that their most recent treatment helped their spasticity (Figure 5A), with how long the treatment was working (Figure 5B), and with how the treatment has helped their spasticity-related pain (Figure 5C). The fraction of participants who responded "not applicable" regarding their spasticity-related pain (Figure 5C) ranged from 15.6% to 59.3% (see legend, Figure 5). Taking everything into consideration, most participants would continue to use onabotA to treat their spasticity (Figure 5D).

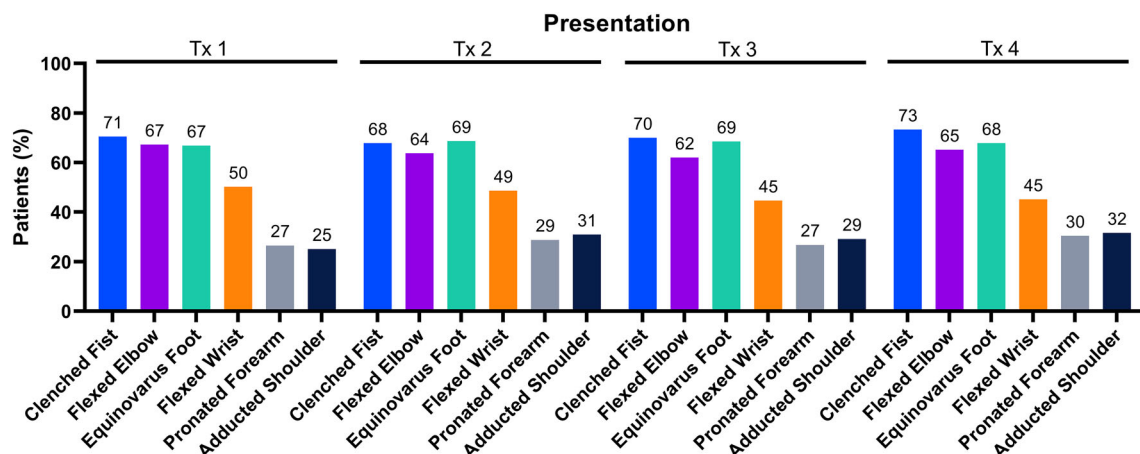


FIGURE 1 Predominant clinical presentations at treatments (Tx) 1 to 4. Clenched fist, equinovarus foot, and flexed elbow were the most common clinical presentations at baseline. Total number of participants at each treatment: Tx 1, $n = 275$; Tx 2, $n = 243$; Tx 3, $n = 213$; Tx 4, $n = 184$.

TABLE 4 Percentage of participants with upper, lower, or both upper and lower limbs treated at each session.

Location treated, n (%)	Tx 1 $n = 275$	Tx 2 $n = 243$	Tx 3 $n = 213$	Tx 4 $n = 184$	Tx 5 $n = 148$	Tx 6 $n = 109$	Tx 7 $n = 79$	Tx 8 $n = 27$
Lower limb	18 (6.5)	23 (9.5)	19 (8.9)	14 (7.6)	11 (7.4)	6 (5.5)	3 (3.8)	1 (3.7)
Upper limb	46 (16.7)	44 (18.1)	37 (17.4)	30 (16.3)	24 (16.2)	18 (16.5)	7 (8.9)	1 (3.7)
Upper and lower limb	211 (76.7)	176 (72.4)	157 (73.7)	140 (76.1)	113 (76.4)	85 (78.0)	69 (87.3)	25 (92.6)

Abbreviation: Tx, treatment.

TABLE 5 Location methods by treatment, all muscles.

Location method, n (%)	Tx 1 $n = 275$	Tx 2 $n = 242^a$	Tx 3 $n = 213$	Tx 4 $n = 184$	Tx 5 $n = 147^a$	Tx 6 $n = 109$	Tx 7 $n = 77^b$	Tx 8 $n = 27$
Anatomic + Guided	69 (25.1)	55 (22.7)	59 (27.7)	45 (24.5)	37 (25.2)	31 (28.4)	24 (31.2)	8 (29.6)
Anatomic	37 (13.5)	30 (12.4)	27 (12.7)	25 (13.6)	19 (12.9)	11 (10.1)	7 (9.1)	0 (0.0)
Guided	169 (61.5)	157 (64.9)	127 (59.6)	114 (62.0)	91 (61.9)	67 (61.5)	46 (59.7)	19 (70.4)

Abbreviation: Tx, treatment.

^aMissing data for one participant.

^bMissing data for two participants.

TABLE 6 Total dose of onabotA per treatment session.

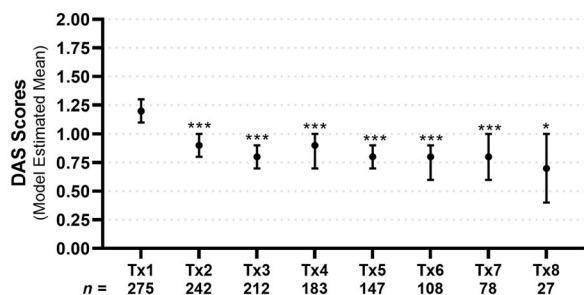
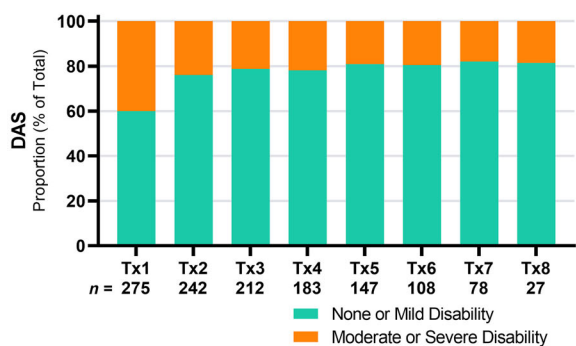
	Tx 1 $n = 275$	Tx 2 $n = 243$	Tx 3 $n = 213$	Tx 4 $n = 184$	Tx 5 $n = 148$	Tx 6 $n = 109$	Tx 7 $n = 79$	Tx 8 $n = 27$
Dose (total units)								
Mean (SD)	432.8 (199.1)	421.2 (195.3)	427.3 (188.1)	449.4 (193.4)	465.2 (192.5)	467.2 (192.6)	465.9 (182.6)	499.6 (188.6)
Min	62.0	50.0	80.0	80.0	110.0	150.0	180.0	225.0
Max	1000.0	1125.0	1100.0	1200.0	1200.0	1225.0	1200.0	1200.0

Abbreviations: SD, standard deviation; Tx, treatment.

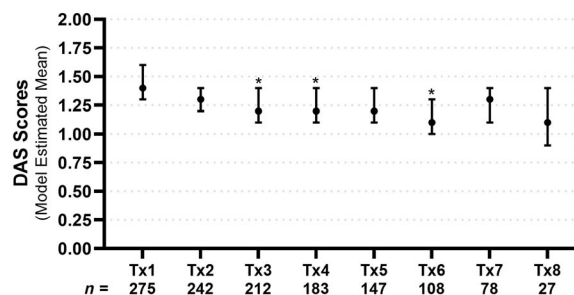
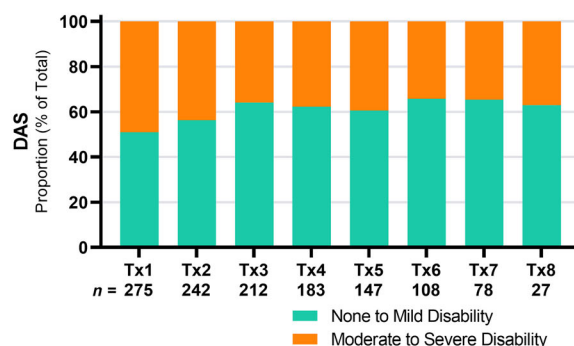
Physicians' treatment satisfaction after participants received treatment with onabotA is shown in Figure 6. Most physicians reported that they were satisfied or extremely satisfied with how the most recent treatment

helped manage the participants' spasticity (Figure 6A), with participants' sustained benefit of treatment (Figure 6B), and with how the most recent treatment helped manage participants' spasticity-related pain

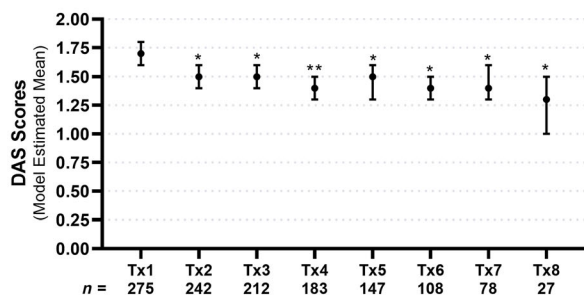
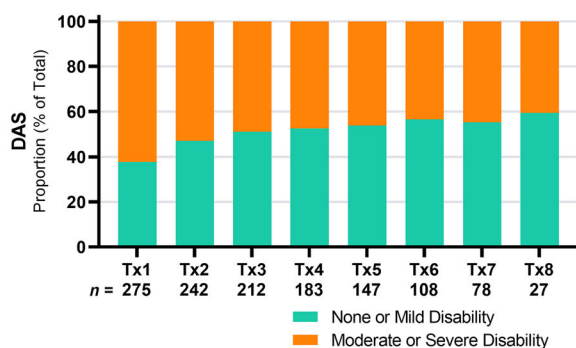
(A) Pain - UL



(B) Hygiene - UL



(C) Dressing - UL



(D) Posture - UL

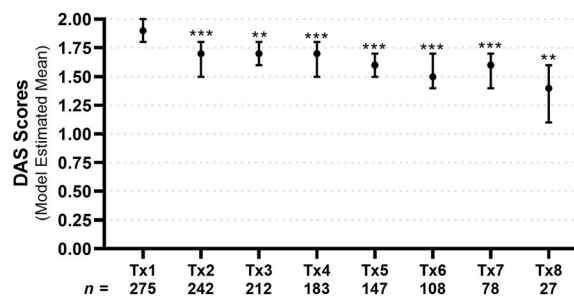
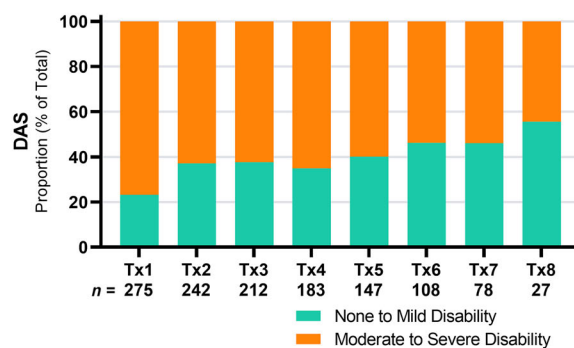


FIGURE 2 Upper limb disability. The baseline DAS was evaluated at office visit 1 (prior to treatment); treatments 2 to 8 reflect evaluation of the prior treatment (i.e., Tx 2 reflects the response to Tx 1). The DAS uses a 4-point rating scale, with 0 as no disability; 1, mild disability; 2, moderate disability; 3, severe disability. Missing or ambiguous responses resulted in variation in the number of n's for each panel. (A–D) Top panels: green, DAS scores of 0 to 1 (none to mild disability); orange, scores of 2 to 3 (moderate to severe). (A–D) Bottom panels: model-estimated means (95% confidence interval [CI]). *** $p \leq .0001$; ** $p \leq .001$; * $p \leq .05$. DAS, Disability Assessment Scale; Tx, treatment; UL, upper limb.

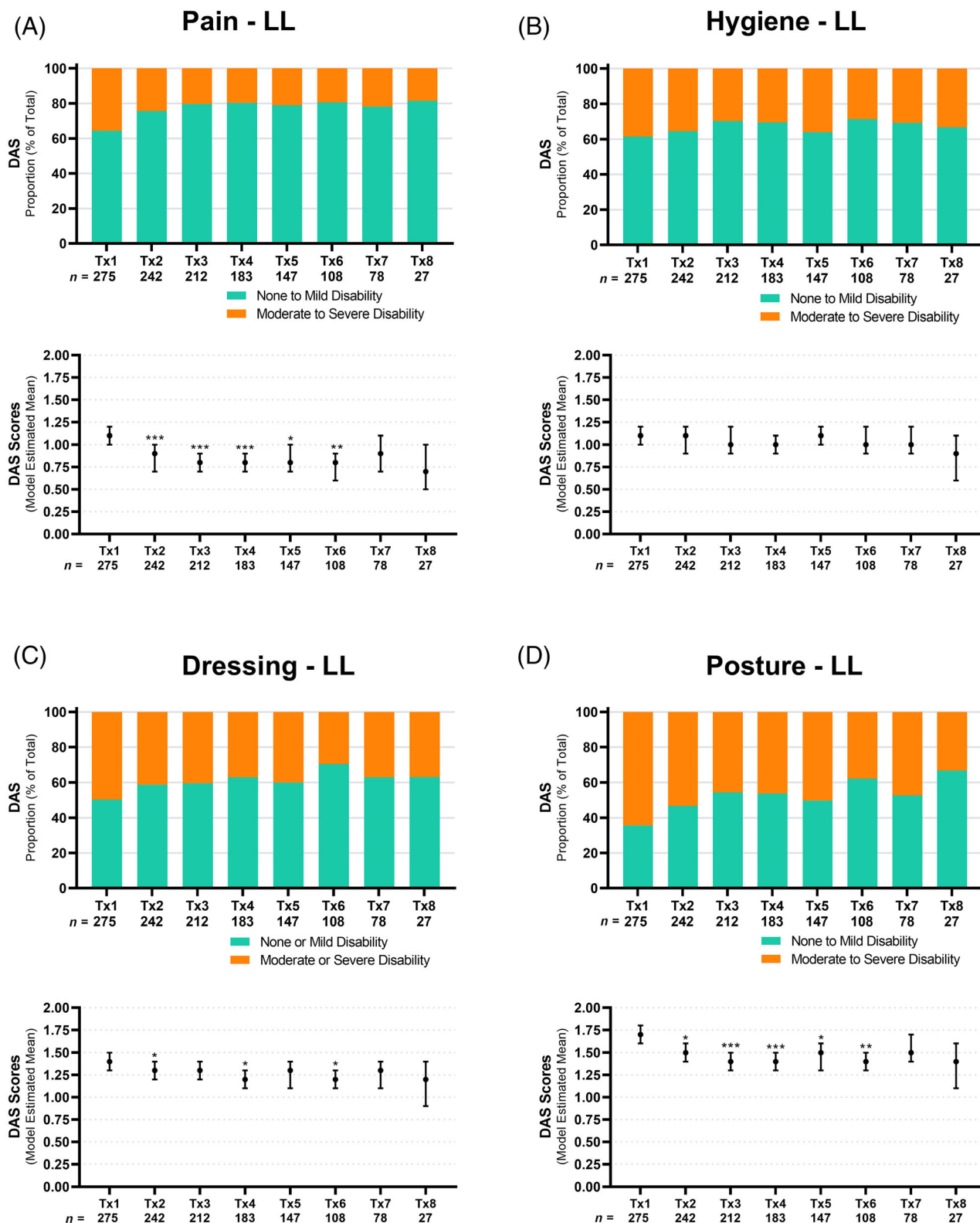


FIGURE 3 Lower limb disability. The baseline DAS was evaluated at office visit 1 (prior to treatment); treatments 2 to 8 reflect evaluation of the prior treatment (i.e., Tx 2 reflects the response to Tx 1). The DAS uses a 4-point rating scale, with 0 as no disability; 1, mild disability; 2, moderate disability; 3, severe disability. Missing or ambiguous responses resulted in variation in the number of *n*'s for each panel. (A–D) Top panels: green, DAS scores of 0 to 1 (none to mild disability); orange, scores of 2 to 3 (moderate to severe). (A–D) Bottom panels: model-estimated means (95% confidence interval [CI]). *** $p \leq .0001$; ** $p \leq .001$; * $p \leq .05$. DAS, Disability Assessment Scale; Tx, treatment; LL, lower limb.

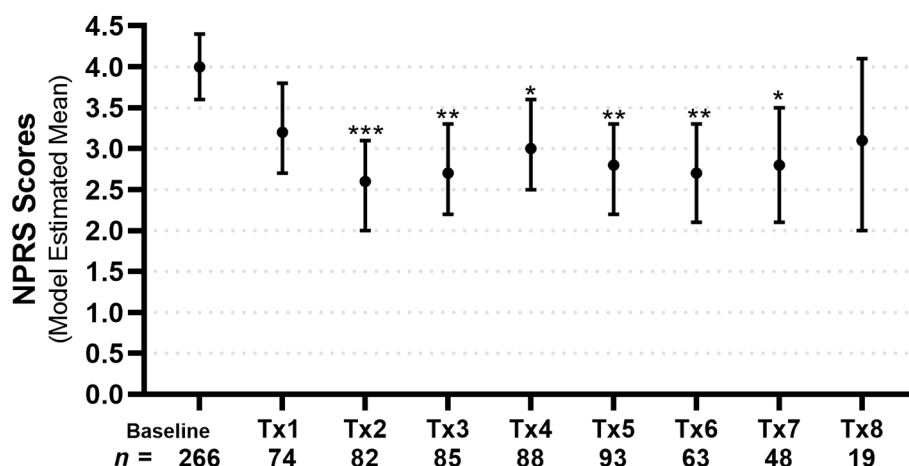


FIGURE 4 Pain on NPRS, model-estimated means (95% CI). NPRS rates the level of pain experienced in the last 24 hours from 0 (no pain) to 10 (highest pain imaginable). The baseline NPRS was evaluated at office visit 1; response to treatments 2 to 8 was collected by phone or online after each treatment. The baseline NPRS reflects the initial measurements available for the cohort participants treated at any subsequent time point. *** $p \leq .0001$; ** $p \leq .001$; * $p \leq .05$. NPRS, Numeric Pain Rating Scale; n (baseline), number of participants with NPRS values recorded at visit 1; n (Tx 1 to Tx 8), number of NPRS responses recorded via phone or online after each treatment; Tx, treatment.

(Figure 6C). The fraction of physicians who responded “not applicable” regarding participants’ spasticity-related pain (Figure 6C) ranged from 29.6% to 59.3% (see legend, Figure 6). Most physicians, taking everything into account, would continue to use onabotA to manage the participants’ spasticity (Figure 6D).

Functional impairments and QoL

At each treatment session, participants responded to questions regarding the effect of their spasticity on daily activities and QoL (SIA, Figure 7). The effect of UL spasticity was assessed with questions related to difficulty in showering/bathing, ability to complete household tasks (cooking and cleaning), and ability to participate in usual recreational activities. The proportion of participants who categorized UL activities as very or extremely difficult at baseline was reduced after one treatment and did not return to baseline throughout the study (Figure 7A–C). The effect of LL spasticity was assessed with questions related to the difficulty in participating in usual recreational activities, putting on shoes, or use of the leg to exercise. The proportion of participants categorizing LL activities as very or extremely difficult generally decreased after the first treatment, as compared to baseline (Figure 7D–F).

Safety data are presented in part in Table 7; full data are presented in Table S3. There were nine treatment-related AEs, shown according to MedDRA terms. Dysphagia, asthenia, drug tolerance, peripheral edema, and decreased grip strength were each reported by one participant. Four participants reported muscular weakness. A total of three treatment-related serious AEs were reported among two participants: dysphagia, muscular weakness, and slow speech.

DISCUSSION

Controlled trials have established the safety and efficacy of onabotA to treat UL^{37–40} and LL^{18,41,42} spasticity, most often in post-stroke participant populations. Stroke was the underlying etiology in nearly three-fourths of the participants concurrently treated for UL and LL spasticity in this sub-analysis. Clinician- and participant-reported outcomes reported here demonstrate improvements in pain, disability, and QoL in participants who received one or more concurrent treatments to UL and LL during the same treatment session over the 2-year study.

After treatment, the proportion of participants with none or mild disability on the DAS generally increased, with significant improvements pain, dressing, and posture, reflecting improvements in QoL. Although the DAS has been validated for UL spasticity only,³¹ it has also been used to evaluate LL spasticity.³² Our results (including those from LL DAS) are consistent with a recent study of UL and LL spasticity that divided the total BoNT/A recommended dose between UL and LL, with positive effects on gait.²⁴ Taken together, reductions in difficulty in completing everyday activities noted on the SIA, combined with improvements in pain, dressing, and posture on the DAS, are consistent with improved QoL in participants concurrently treated with onabotA for UL and LL spasticity.

Pain is also likely to play a central role in QoL in participants who experience pain due to spasticity.⁴³ Model-estimated NPRS scores revealed significant decreases in pain after treatment with onabotA across most treatments, consistent with reports from most participants that onabotA treatment improved their spasticity-related pain in this and other published studies.^{44,45} Although the precise mechanism by which

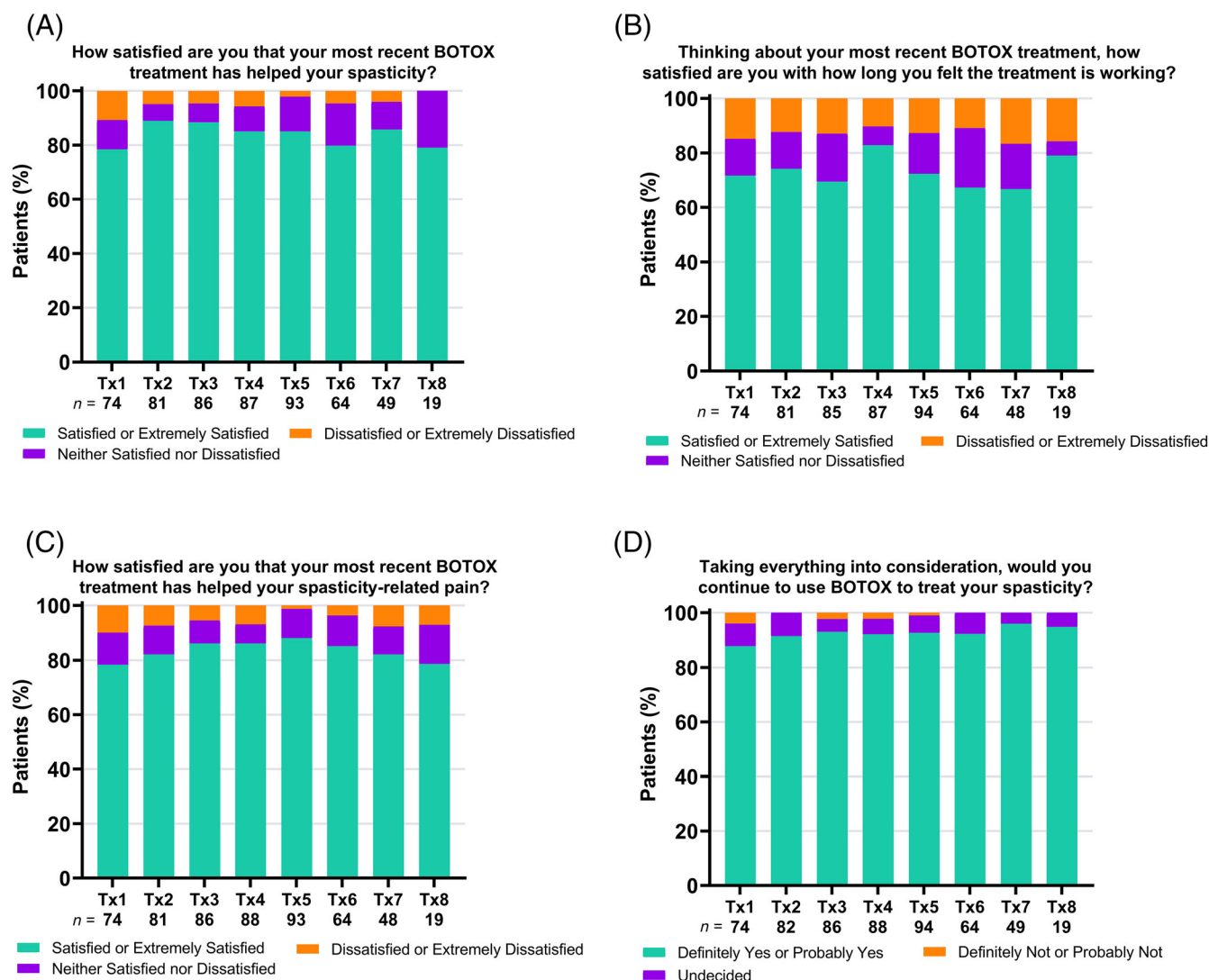


FIGURE 5 Pain reduction and treatment satisfaction reported by participants. N/A responses to panel C (the only question for which N/A could have been selected) are not included in vertical bars but are included in the total number of respondents below each treatment. N/A responses to the question posed in C were as follows: Tx 1 to Tx 3, $n = 14$; Tx 4, $n = 16$; Tx 5, $n = 17$; Tx 6, $n = 10$; Tx 7, $n = 9$; Tx 8, $n = 5$. Missing or ambiguous responses resulted in variation in the number of n 's for each panel. BOTOX, onabotulinumtoxinA; n , the number of participants responded to each question; N/A, not applicable; Tx, treatment.

onabotA reduces pain is not fully understood, several factors may contribute to its effect on pain: neurotransmitter and neuropeptide release from nociceptive terminals,^{46–48} modulation of surface expression of pain receptors and ion channels,⁴⁷ and anticholinergic effects at the neuromuscular junction that reduce excessive contractions and the painful spasms that often accompany such contractions.⁴⁹

The majority of participants and physicians indicated that they were satisfied with the duration of treatment, and that, taking everything into account, they would continue to use onabotA to treat their spasticity. A smaller proportion of participants than physicians indicated that spasticity-related pain was “not applicable,” suggesting that some participants either do not experience meaningful pain associated with their

spasticity or may not fully communicate the level of pain. Most participants and clinicians agree that, considering all factors, they would continue to use onabotA to manage spasticity.

The dosing, muscles selected (including any doses above 400 U and any muscles not specifically listed in the label³⁶), and location method were at the complete discretion of the provider. Consistent with our results, clinicians may choose to treat beyond the 400 U label in real-life practice because multiple muscles may need to be treated to address participant needs and optimize outcomes. Consistent with this idea, a recent report demonstrated that most doses above 400 U (up to and including those at 800 U and above) of onabotA for the treatment of spasticity were used in the concurrent treatment of UL and LL spasticity.⁵⁰ Our results

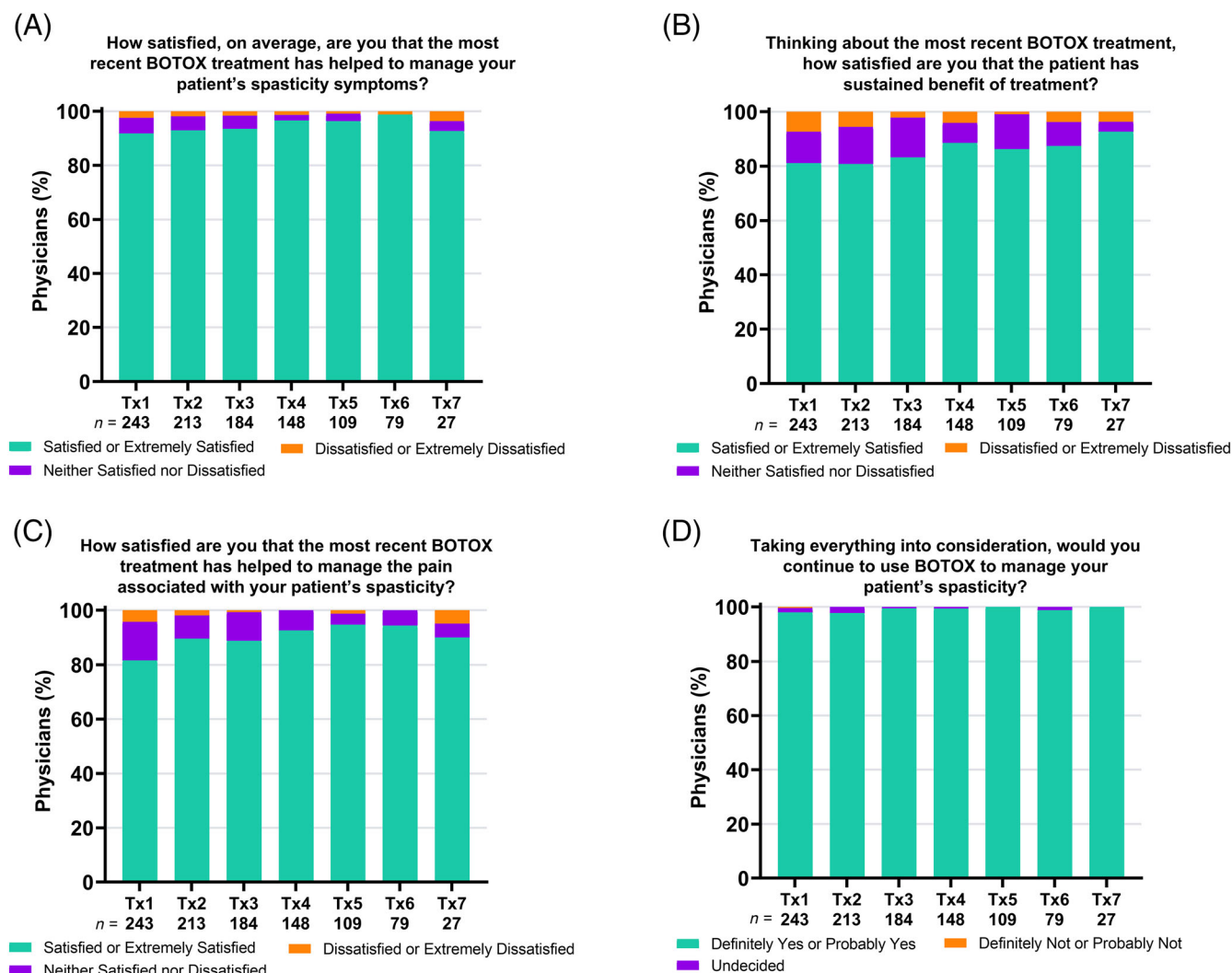


FIGURE 6 Pain reduction and treatment satisfaction reported by physicians. N/A responses to panel C (the only question for which N/A could have been selected) are not included in vertical bars but are included in the total number of respondents below each treatment. N/A responses to the question posed in C were as follows: Tx 1–2, $n = 59$; Tx 3, $n = 50$; Tx 4, $n = 41$; Tx 5, $n = 34$; Tx 6, $n = 26$; Tx 7, $n = 7$). BOTOX, OnabotulinumtoxinA; n , the number of participants responded to each question; N/A, not applicable; Tx, treatment.

demonstrate clinicians' ability to select and deliver a dose tailored according to each participant's clinical need while minimizing side effects, as evidenced by the relatively low number of treatment-related AEs and treatment-related serious AEs reported. Treatment with onabotA was well tolerated in this population, with no new safety signals identified.

Limitations

Due to the observational nature of this study, the study was non-blind and non-randomized, with relatively low sample sizes for some treatment sessions. This study consisted of predominantly White stroke survivors, many of whom were non-naïve to onabotA for the treatment of spasticity. Given these limitations, and along with the

broad inclusion criteria and range of doses employed in this study, the generality of this analysis is limited; results must be interpreted with caution. Participants unsatisfied with treatment may have elected to discontinue treatment with onabotA, creating a bias toward those who may have realized or anticipated a treatment benefit from onabotA. Although enrollment was limited to those who could answer questions (in the opinion of the treating HCP), some participants were either unable to answer questions or were otherwise unavailable to answer questions. Thus, participant-reported outcomes were generally fewer in number than clinician-reported outcomes. Studies such as this one cannot address any potential ceiling effect for onabotA injections over time, due to the observational nature of this study, along with variations in individual participant dosing, injection intervals, and possible concurrent adjunctive therapies.

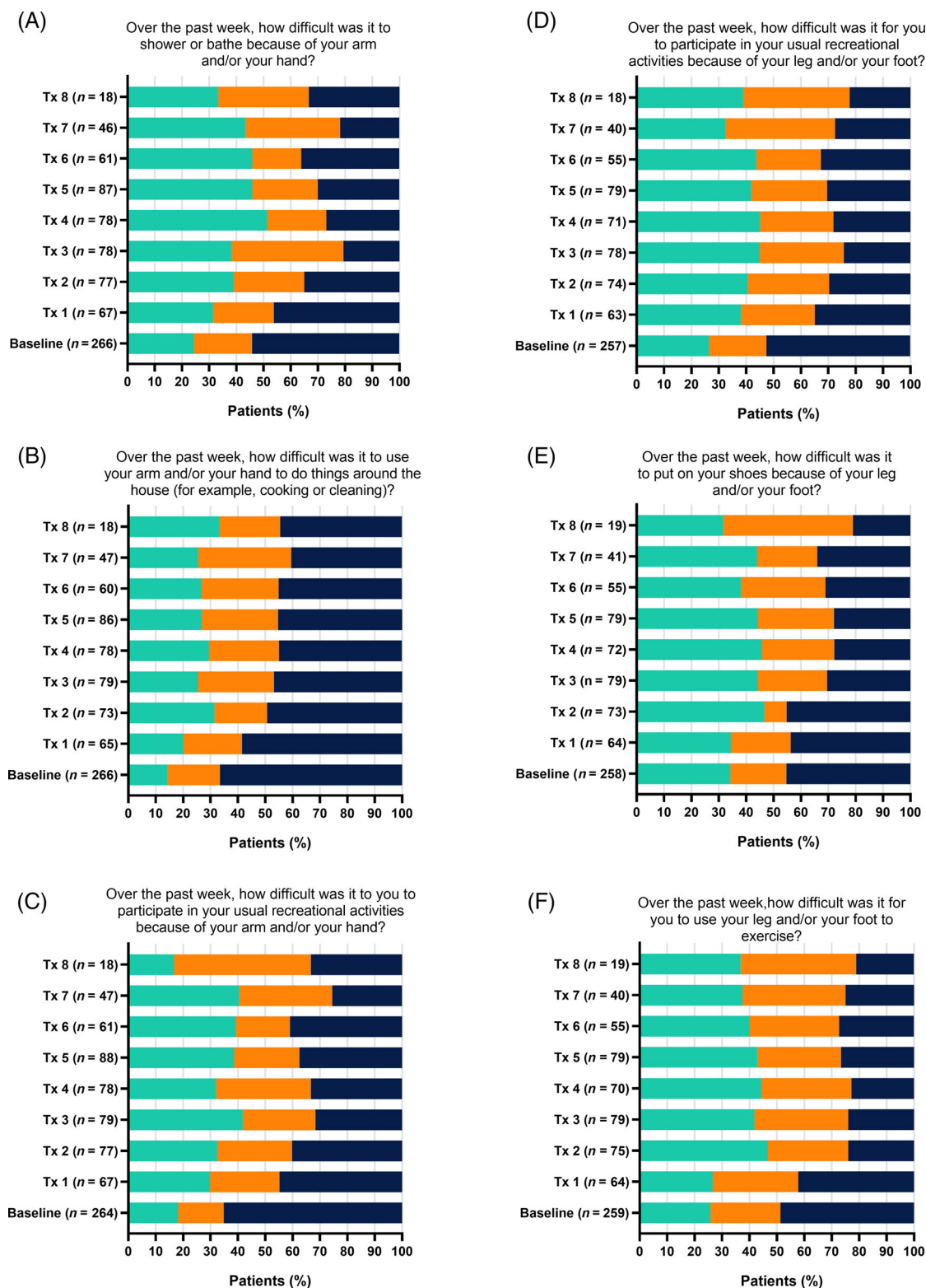


FIGURE 7 Spasticity Impact Assessment (SIA) of upper limb (A–C) and lower limb (D–F) before (baseline) and after indicated treatments. (A–F): Green, not at all or a little difficult; orange, somewhat difficult; navy blue, very or extremely difficult. The baseline SIA was evaluated at office visit 1 (prior to injection); treatments 2 to 8 reflect the evaluation of the prior treatment (i.e., Tx 2 reflects the response to Tx 1) and responses were collected by phone or online after each treatment. Missing or ambiguous responses resulted in variation in the number of *n*'s for each panel. Tx, treatment; *n*, baseline, number of participants with SIA responses recorded at visit 1; *n* (Tx 1 to Tx 8), number responses recorded via phone or online after each treatment.

TABLE 7 Participant- and event-based TRAEs and TRSAEs^a.

	Participants (N = 275)	
	Participants, N (%) ^b	Events, n
TRAEs		
Any event	9 (3.3)	9
Dysphagia	1 (0.4)	1
Asthenia	1 (0.4)	1
Drug tolerance ^c	1 (0.4)	1
Peripheral edema	1 (0.4)	1
Decreased grip strength	1 (0.4)	1
Muscular weakness	4 (1.5)	4
All TRSAEs		
Any event	2 (0.7)	3
Dysphagia	1 (0.4)	1
Muscular weakness	1 (0.4)	1
Slow speech	1 (0.4)	1

Abbreviations: TRAEs, treatment-related adverse events; TRSAEs, treatment-related serious adverse events.

^aAn event is categorized as treatment related if there is a reasonable possibility of a causal relationship between the event and treatment with onabotA.

^bIf a participant had the same event more than once, they are counted only once for the participant counts and percentages.

^cOne participant discontinued due to moderate immunity to onabotA.

CONCLUSIONS

Outcomes from participants across seven different countries are consistent with a significant and long-lasting benefit in the concurrent treatment of UL and LL spasticity with onabotA across a range of underlying etiologies and geographic regions. Concurrent treatment reduced functional impairment and pain associated with spasticity, resulting in improved QoL and a high degree of treatment satisfaction from participants and clinicians, with relatively few AEs overall, consistent with the established safety and efficacy of onabotA in the treatment of spasticity.^{26,28,36,39,51} Combined with randomized controlled clinical trial data, these results may help guide clinical use of onabotA and overall management of spasticity in the hemiparetic and hemiplegic population with both UL and LL spasticity.

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ETHICS STATEMENT

Before participation in this study, patients provided informed, written consent. This study was conducted in accordance with the Declaration of Helsinki and Guidelines for Good Pharmacoeconomics Practices, as outlined by the International Society for Pharmacoeconomics.^{38,39} The independent ethics committee or institutional review board (IRB) at each study site approved the study protocol, informed consent forms, and recruitment materials before patient enrollment. The studies were reviewed and approved by the following IRBs: Quorum IRB, University of Missouri IRB, Western IRB, Einstein Healthcare Network IRB, Medical University of South Carolina IRB, University of Maryland IRB, Wheaton Franciscan Healthcare IRB, University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects, Scott & White IRB, Loma Linda University IRB, Penn State Human Subjects Protection Office IRB, University of Pennsylvania IRB, Vanderbilt University IRB, Chang Gung Medical Foundation IRB, Taipei Medical University Joint IRB, Ethik-Kommission bei der Landesärztekammer Baden-Württemberg, Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelms-Universität, Ethik-Kommission Albert-Ludwigs-Universität Freiburg, Ethik-Kommission an der Medizinischen Fakultät der Universität Leipzig, Ethik-Kommission Universitätsklinikum Jena, Medizinische Hochschule Hannover Ethikkommission Vorsitzender, East Midlands-Derby Research Ethics Committee, Sección de Ordenación Farmacéutica Dirección General de Ordenación y Atención Sanitaria, Comité Autonómico de Ética de la Investigación de Galicia, CEIC. Parc de Recerca Biomèdica, Comité Etico de Investigación Clínica UASP. Programa de Qualitat Assistencial.

Subdirección Xeral de Farmacia e Produtos Sanitarios. Consellería de Sanidade Dirección, Comité Ético de Investigación Clínica Hospital Mútua de Terrassa, Comité Ético de Investigación Clínica Institut de Recerca, Comitato Ético Interaziendale Novara, Comitato Ético Interregionale Policlinico di Bari, Comitato Ético Ospedale San Raffaele Ufficio Ricerche Cliniche, Comitato Ético Fondazione Policlinico Universitario "Agostino Gemelli"- Università Cattolica del Sacro Cuore. The studies were conducted in accordance with the International Conference for Harmonization guidelines, applicable regulations, and the Declaration of Helsinki. All patients provided written informed consent before screening.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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