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Real-World Adherence to OnabotulinumtoxinA Treatment for Spasticity: Insights from the ASPIRE Study

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Conflicts of Interest

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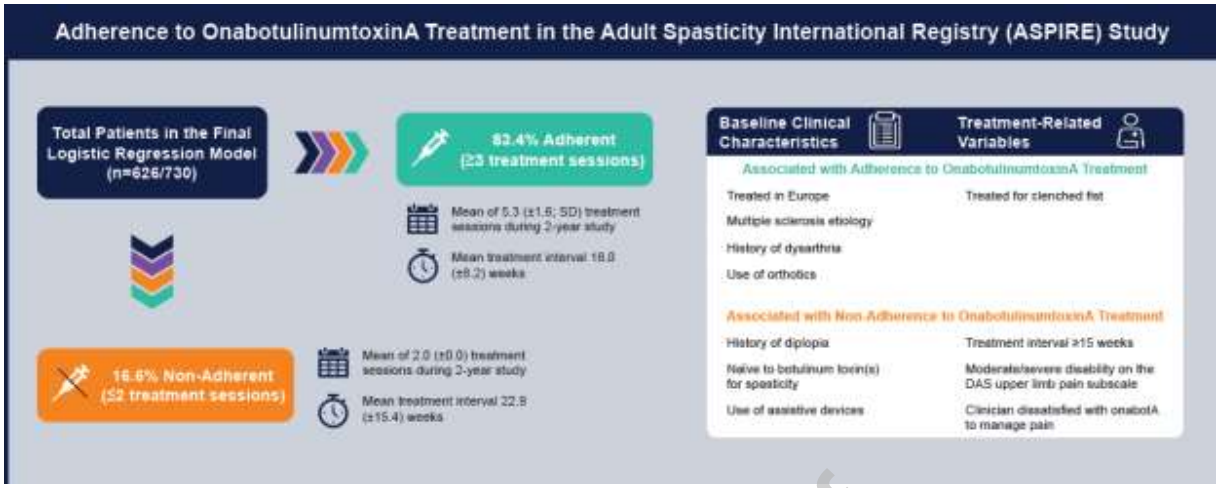
These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

Graphicla Abstract



Highlights

- Analyses reveal key clinical variables associated with onabotulinumtoxinA adherence
- Key adherent variables: used orthotics and treated in Europe
- Key non-adherent variables: re-treatment ≥15 wks, used assistive devices, DAS pain
- Most patients adhered to onabotulinumtoxinA, >5 sessions in 2 years for adherents
- Real-world evidence from ASPIRE can enhance spasticity patient care

Abstract

Objective: To identify baseline characteristics and treatment-related variables that impact adherence to onabotulinumtoxinA treatment from the Adult Spasticity International Registry (ASPIRE) study.

Design: Prospective, observational registry (NCT01930786).

Setting: International clinical sites.

Participants: Adults with spasticity.

Interventions: OnabotulinumtoxinA at clinician's discretion.

Main Outcome Measure(s): Clinically meaningful thresholds used for *treatment adherent* (≥3 treatment sessions during 2-year study) and *non-adherent* (≤2 sessions). Data analyzed using logistic regression and presented as odds ratios (OR) with 95% confidence intervals (CI). Treatment-related variables assessed at sessions 1 and 2 only.

Results*:* Of the total population (N=730), 523 patients (71.6%) were treatment adherent with 5.3 (1.6; mean [SD]) sessions; 207 (28.4%) non-adherent with 1.5 (0.5). In the final model (n=626/730), 522 patients (83.4%) were treatment adherent, 104 (16.6%) were non-adherent. Baseline characteristics associated with adherence: treated in Europe (OR:1.84, CI:1.06-3.21; *P*=0.030) and use of orthotics (OR:1.88, CI:1.15-3.08; *P*=0.012). Baseline characteristics associated with non-adherence: history of diplopia (OR:0.28, CI:0.09-0.89; *P*=0.031) and use of assistive devices (OR:0.51, CI:0.29-0.90; *P*=0.021). Treatment-related variables associated with non-adherence: treatment interval ≥15 weeks (OR:0.43, CI:0.26-0.72; *P*=0.001) and clinician dissatisfaction with onabotulinumtoxinA to manage pain (OR:0.18, CI:0.05-0.69; *P*=0.012). Of the stroke population (N=411), 288 patients (70.1%) were treatment adherent with 5.3 (1.6; mean [SD]) sessions; 123 (29.9%) non-adherent with 1.5 (0.5). In the final stroke model (n=346/411), 288 patients (83.2%) were treatment adherent, 58 (16.8%) were non-adherent. Baseline characteristics associated with adherence: treated in Europe (OR:2.99, CI:1.39-6.44; *P*=0.005) and use of orthotics (OR:3.18, CI:1.57-6.45; *P*=0.001). Treatment-related variables associated with non-adherence: treatment

interval ≥15 weeks (OR:0.42, CI:0.21-0.83; *P*=0.013) and moderate/severe disability on upper limb DAS pain subscale (OR:0.40, CI:0.19-0.83; *P*=0.015).

Conclusions: These ASPIRE analyses demonstrate real-world patient and clinical variables that impact adherence to onabotulinumtoxinA and provide insights to help optimize management strategies to improve patient care.

Keywords: Botulinum toxins, treatment adherence and compliance, stroke

Lists of Abbreviations

ASPIRE, Adult Spasticity International Registry

CI, Confidence interval

DAS, Disability Assessment Scale

MedDRA, Medical Dictionary for Regulatory Activities

MMAS, Modified Modified Ashworth Scale

MS, Multiple sclerosis

NPRS, Numeric Pain Rating Scale

OR, Odds ratio

UMN, Upper motor neuron

Spasticity is associated with several central nervous system disorders and can be defined as disordered sensorimotor control, stemming from an upper motor neuron (UMN) lesion, which presents as intermittent or sustained involuntary activation of muscles.[1, 2] OnabotulinumtoxinA (BOTOX®, Allergan, an AbbVie company, North Chicago, Illinois, USA)[3] is approved worldwide for the treatment of adult upper limb and lower limb spasticity. In combination with other therapies, onabotulinumtoxinA can

mitigate the deleterious effects of spasticity, including limited dexterity and mobility, limb pain, impaired activities of daily living, and reduced quality of life.[4-6]

To successfully meet patients' needs and goals, adherence to prescribed treatment is critical. However, little is known about the impact of patient and treatment-related variables on real-world adherence to onabotulinumtoxinA treatment for spasticity. An increased understanding of variables that impact treatment adherence is needed to inform clinical strategies to better manage spasticity and address knowledge gaps. The Adult SPasticity International REgistry (ASPIRE) study describes real-world onabotulinumtoxinA utilization to treat adult spasticity across multiple etiologies and geographic regions over 2 years.[8-11] The objective of this analysis was to identify baseline demographics, clinical characteristics, and treatment-related variables that impact adherence to onabotulinumtoxinA treatment for spasticity from the ASPIRE study.

Methods

Full methodological details for ASPIRE, including study dates and size, inclusion/exclusion criteria, and data collected, have been published.[8] Methods relevant to this analysis are described below.

Study Design

ASPIRE is an international (USA, Europe, and Taiwan), multicenter (54 sites), prospective, observational registry (NCT01930786) spanning 108 weeks (96-week study period; 12-week follow-up period).[8-11] OnabotulinumtoxinA treatments were

administered according to country-specific regulations and standard clinical practices, without intervention from the study sponsor. Time to re-treatment was not dictated by the sponsor, nor were the number of treatment sessions. Re-treatment with onabotulinumtoxinA was anticipated to occur approximately every 12 weeks.[3, 12] Financial support was not provided for any treatment or treatment-related costs. ASPIRE was conducted in agreement with all relevant regulatory requirements, including but not limited to the Guidelines for Good Pharmacoepidemiology Practices (issued by the International Society for Pharmacoepidemiology) and the Declaration of Helsinki.

Participants

Adult participants with spasticity related to UMN syndrome due to various etiologies were treated at the clinician's discretion with onabotulinumtoxinA during routine clinical practice. Participants were naïve (newly treated) or non-naïve (previously treated) to botulinum toxin for spasticity. All participants provided written informed consent prior to study participation. Institutional Review Board approval was granted at each study site.

For this analysis, two patient populations (total and stroke) from ASPIRE were assessed. The total population included all participants who received ≥1 onabotulinumtoxinA treatment during the 2-year study. The stroke population included all participants who received ≥1 onabotulinumtoxinA treatment during the 2-year study and identified stroke as their primary etiology at baseline.

Outcomes and Data Sources

To identify baseline clinical characteristics and treatment-related variables that impact adherence to onabotulinumtoxinA treatment in ASPIRE, clinically meaningful data-driven thresholds were established. *Treatment adherent* was defined as patients who received ≥3 treatment sessions with onabotulinumtoxinA during the 2-year study; *treatment non-adherent* was defined as patients who received ≤2 sessions. ASPIRE did not require a specific number of treatment sessions nor specify time to re-treatment; therefore, a patient could be labeled "non-adherent" according to our definition despite receiving their prescribed or desired number of treatments.

ASPIRE case report forms included original questionnaires developed through expert consensus (eg, clinician satisfaction) and published validated scales (eg, Disability Assessment Scale [DAS][13] and Modified Modified Ashworth Scale [MMAS][14, 15]). For this analysis, 12 baseline demographic and clinical characteristic categories and 7 treatment-related variable categories were assessed (**Table 1**). To assess treatment-related variables, data from treatment sessions 1 and 2 were compared (ie, earliest sessions after enrollment for both adherent and non-adherent patients). If patients did not have data from treatment session 2 (eg, patient no longer required treatment or patient failed to complete the assessment), data from treatment session 1 were used. Patient satisfaction and Numeric Pain Rating Scale (NPRS)[16, 17] were collected in ASPIRE but were not included in this analysis due to the extent of missing or invalid data (ie, >50% of patients did not respond to the questionnaire at treatment session 1 and/or 2).

Control for Bias

Control for bias in ASPIRE has been described previously.[8-11] Specific to this analysis, ASPIRE was designed for high generalizability to real-world clinical practice and included patients that were naïve or non-naïve to botulinum toxins. As treatment history likely impacts adherence to onabotulinumtoxinA, this variable was included in the analysis. Similarly, baseline severity scores (assessed via MMAS) and etiology were also included.

Variables and Statistical Methods

Baseline demographics, clinical characteristics, and treatment-related variables (**Table 1**) for the total and stroke populations were analyzed using a series of logistic regression models (**Figure 1**). Sample size limitations prevented etiologies other than stroke from being analyzed individually. Variables that achieved α level $P<0.2$ in the univariate binary logistic regression models, as well as variables of clinical interest (eg, concomitant medications for spasticity), were combined into blocks of similar variables and analyzed using multivariable binary logistic regression. All variables that achieved α level $P<0.2$ in the block models advanced to the final fully-adjusted multivariable model. For the final model, statistical significance was accepted at $P<0.05$; clinically meaningful non-significant variables of interest at $P<0.1$. Data are presented as odds ratios (OR) with 95% confidence intervals (CI). Missing data were minimal (<1%) and no imputation was performed. Statistical analyses were completed using IBM SPSS Statistics v24.0 (IBM; Armonk, NY, USA).

Results

Total Patient Population

Demographics

In ASPIRE, 730 patients received ≥1 onabotulinumtoxinA treatment for spasticity. Patients were on average 53.6 (15.4; mean [SD]) years of age at enrollment, nearly evenly distributed by gender (females: 52.1%), predominately Caucasian (77.0%), and 36.8% were naïve to botulinum toxin for spasticity. The most common etiology of spasticity was stroke (56.3%), followed by multiple sclerosis (MS; 16.3%).

Preliminary Logistic Regression Models

Of the total population (N=730), 523 patients (71.6%) were categorized as treatment adherent and 207 patients (28.4%) as non-adherent (**Table 2**). During the 2-year study, adherent patients had a mean (SD) of 5.3 (1.6) treatment sessions, while non-adherent patients had 1.5 (0.5) sessions. The mean (SD) treatment interval was 18.0 (8.2) weeks for adherent patients and 22.9 (15.4) weeks for non-adherent patients. The distribution of adherent and non-adherent patients across a range of treatment interval categories is shown in **Figure 2**. Variables associated with adherence/non-adherence in the preliminary univariate models (**Supplemental Table 1** and **Supplemental Table 2**) and block models (**Supplemental Table 3**) are shown in the supplementary material.

Variables Associated with Adherence/Non-Adherence in the Final Model

Of the total population (N=730), 626 patients had data for all variables and were included in the final model. Of those in the final model, 522 patients (83.4%) were categorized as treatment adherent and 104 patients (16.6%) as non-adherent. Adherent

patients had a mean (SD) of 5.3 (1.6) treatment sessions, while non-adherent patients had 2.0 (0.0) sessions. All variables that achieved α level *P*<0.2 in the block models (**Supplemental Table 3**) were carried forward into the final model (**Figure 3**). In the final total model, the following baseline clinical characteristics were associated with adherence: patient treated in Europe (OR:1.84, CI:1.06-3.21; *P*=0.030), etiology of MS (OR:2.06, CI:0.97-4.35; *P*=0.059), history of dysarthria (OR:2.28, CI:0.98-5.33; *P*=0.056), and use of orthotics (OR:1.88, CI:1.15-3.08; *P*=0.012). Baseline variables associated with non-adherence: history of diplopia (OR:0.28, CI:0.09-0.89; *P*=0.031), naïve to botulinum toxin for spasticity (OR:0.63, CI:0.39-1.01; *P*=0.056), and use of assistive devices (OR:0.51, CI:0.29-0.90; *P*=0.021). Treatment-related variables associated with adherence: treated for clenched fist (OR:1.64, CI:0.95-2.83; *P*=0.078). Treatment-related variables associated with non-adherence: treatment interval ≥15 weeks (OR:0.43, CI:0.26-0.72; *P*=0.001), moderate/severe disability on the upper limb DAS pain subscale (OR:0.56, CI:0.30-1.03; *P*=0.063), and clinician dissatisfaction with onabotulinumtoxinA to manage pain (OR:0.18, CI:0.05-0.69; *P*=0.012).

Stroke Patient Population

Demographics

In ASPIRE, 411 patients with spasticity resulting from stroke received ≥1 onabotulinumtoxinA treatment for spasticity. Patients were on average 58.7 (14.1; mean [SD]) years of age at enrollment, nearly evenly distributed by gender (males: 50.6%), predominately Caucasian (75.2%), and 39.4% were naïve to botulinum toxin for spasticity.

Preliminary Logistic Regression Models

Of the stroke population (N=411), 288 patients (70.1%) were categorized as treatment adherent and 123 patients (29.9%) as non-adherent (**Table 3**). During the 2-year study, adherent patients had a mean (SD) of 5.3 (1.6) treatment sessions, while non-adherent patients had 1.5 (0.5) sessions. The mean (SD) treatment interval was 18.1 (8.5) weeks for adherent patients and 23.6 (16.0) weeks for non-adherent patients. The distribution of adherent and non-adherent patients across a range of treatment interval categories is shown in **Figure 4**. As described above, variables associated with adherence/non-adherence in the preliminary univariate models (**Supplemental Table 4** and **Supplemental Table 5**) and block models (**Supplemental Table 6**) are shown in the supplementary material.

Variables Associated with Adherence/Non-Adherence in the Final Model

Of the stroke population (N=411), 346 patients had data for all variables and were included in the final model. Of those in the final model, 288 patients (83.2%) were categorized as treatment adherent and 58 patients (16.8%) as non-adherent. Adherent patients had a mean (SD) of 5.3 (1.6) treatment sessions, while non-adherent patients had 2.0 (0.0) sessions. All variables that achieved α level $P<0.2$ in the block models (**Supplemental Table 6**) were carried forward into the final model (**Figure 5**). In the final stroke model, the following baseline clinical characteristics were associated with adherence: patient treated in Europe (OR:2.99, CI:1.39-6.44; $P=0.005$), use of orthotics (OR:3.18, CI:1.57-6.45; $P=0.001$), and prior surgeries/procedures (OR:3.25, CI:0.93-

11.33; *P*=0.064). Baseline characteristics associated with non-adherence: higher age at enrollment (OR:0.98, CI:0.95-1.00; *P*=0.097) and use of assistive devices (OR:0.46, CI:0.20-1.03; *P*=0.058). Treatment-related variables associated with non-adherence: treatment interval ≥15 weeks (OR:0.42, CI:0.21-0.83; *P*=0.013), patient treated for thumb-in-palm (OR:0.48, CI:0.21-1.07; *P*=0.072), and moderate/severe disability on the upper limb DAS pain subscale (OR:0.40, CI:0.19-0.83; *P*=0.015).

Discussion

The ASPIRE study is one of the largest adult spasticity registries, with observational data gathered from 730 patients across 54 international sites.[8-10] ASPIRE data have increased generalizability to clinical settings and build upon evidence from previous controlled trials, in part due to the real-world study design (ie, non-interventional, observational) and patient etiologies examined (ie, stroke, MS, cerebral palsy, traumatic brain injury, and spinal cord injury). ASPIRE offers a unique opportunity to gain clinical insights into variables that can impact adherence to onabotulinumtoxinA treatment. The objective of this analysis was to identify baseline demographics, clinical characteristics, and treatment-related variables that impact adherence to onabotulinumtoxinA treatment for spasticity from the ASPIRE study.

Previous publications have explored adherence to spasticity treatments.[18-22] However, to the best of our knowledge (see **Supplemental Table 7** for search terms), this is one of the first publications to assess real-world adherence to botulinum toxin treatment for spasticity[21, 22] and the first to assess adherence to onabotulinumtoxinA specifically across multiple etiologies. Variables associated with adherence and non-

adherence to onabotulinumtoxinA treatment in the total and stroke logistic regression models from this analysis of ASPIRE are discussed below. We propose hypotheses for each variable based on our clinical experience, and where available, published literature. Any apparent literature gaps reveal a need for increased discussion in the medical field, as these variables are likely important for care pathways.

Variables Associated with Adherence and Non-Adherence to OnabotulinumtoxinA Treatment in the Final Total Model and Final Stroke Model

In both models, onabotulinumtoxinA treatment in Europe was associated with adherence, possibly due to different healthcare models than the USA. In Europe, onabotulinumtoxinA treatment costs are often fully covered by medical insurance, reducing the financial and logistical burdens for patients and clinicians, which may ultimately improve access to care and treatment persistence. The use of orthotics was also associated with adherence, which may indicate a desire by patients to reduce their dependency on, or need for, a splint or brace.

In contrast, the use of assistive devices at baseline was associated with non-adherence in both models. The use of assistive devices may indicate patients with more severe spasticity,[23] for which onabotulinumtoxinA treatment alone may not be sufficient, leading to reduced adherence. However, it should be noted that severe spasticity can also interfere with, or prevent the use of, assistive devices. Spasticity-related pain in the upper limb, as assessed by DAS,[13] was also associated with non-adherence in both models and could be due to a multifactorial or central driver.[24, 25] Notwithstanding, several trials have demonstrated the benefits of onabotulinumtoxinA for the

management of spasticity-related pain,[26-31] suggesting that pain relief may be an appropriate secondary goal of onabotulinumtoxinA treatment. A treatment interval ≥15 weeks between sessions 1 and 2 was associated with non-adherence. According to the package insert, onabotulinumtoxinA should be administered when the effect of the previous injection has diminished and is anticipated to occur approximately every 12 weeks.[3] Longer treatment intervals could be due to a patient's lack of logistical support to participate in treatment (eg, due to burdened caregivers) and/or other barriers to care (eg, medical complications or mental health factors) that make it difficult to adhere to, or participate in, treatment.[32] A previous study found that the second most common determinant for discontinuation in patients treated with botulinum toxin for MS-related spasticity was "logistic problems or barriers to reach the structure [MS center]".[21] Lee et al. supports this finding, suggesting that "incapability to return to the clinic owning to organizational issues (e.g., transportation, especially for more disabling disorders such as SPAS [spasticity])" may have negatively impacted long-term adherence to botulinum toxin treatment in their study.[22] Alternatively, longer treatment intervals may be consistent with the patient's prescribed treatment regimen.

Variables Associated with Adherence and Non-Adherence to OnabotulinumtoxinA Treatment in the Final Total Model Only

In the total model, which includes patients with stroke, MS, cerebral palsy, traumatic brain injury, and spinal cord injury, history of dysarthria was associated with adherence. Dysarthria could be indicative of medullary involvement leading to greater motor dysfunction,[33, 34] which may be more responsive to botulinum toxin treatment for

spasticity, leading to higher adherence. MS as the primary etiology of spasticity was also associated with adherence in the total model. Due to the early age of onset and the nature of their disease being chronic, as well as often progressive if not treated effectively,[35] MS patients may have higher motivation to adhere to prescribed treatment compared to the other etiologies in ASPIRE. Especially as older age and longer duration of MS have been associated with higher severity,[23] which in turn is associated with greater reductions in quality of life.[23, 36] Being treated for clenched fist, which is a common clinical presentation that can be improved with effective spasticity management,[37] was also associated with adherence in the total model.

In contrast, history of diplopia was associated with non-adherence in the total model, which could indicate a lesion involving the midbrain leading to ataxic movement disorders,[38, 39] that may not be as responsive to spasticity treatments. Clinician dissatisfaction with onabotulinumtoxinA to manage pain was associated with non-adherence in the total model, reinforcing that pain relief may be more appropriate as a secondary goal of onabotulinumtoxinA treatment for spasticity. Being naïve to botulinum toxin for spasticity was associated with non-adherence, which emphasizes the need for early patient education concerning onabotulinumtoxinA treatment goals and expectations.[40] Unrealistic expectations from patients, family members, and/or caregivers has been cited as one of the most common reasons for poor response to botulinum toxin therapy for spasticity management.[6]

Variables Associated with Adherence and Non-Adherence to OnabotulinumtoxinA Treatment in the Final Stroke Model Only

Prior surgeries or procedures were associated with adherence in the stroke model, which may indicate a patient's greater involvement with multi-modal spasticity management.[41, 42] In contrast, higher age, which has been shown to negatively impact rehabilitation outcomes,[43, 44] was associated with non-adherence. Lee et al. postulates that older age and disease progression (eg, additional strokes or other comorbidities) could be contributing factors to reduced long-term adherence to botulinum toxin treatment.[22] Patients being treated for thumb-in-palm, which can be a difficult clinical presentation to treat due to inaccessibility of the target muscles (especially if accompanied by clenched fist), was also associated with non-adherence in the stroke model.

Study Limitations

Limitations common to real-world observational studies were discussed in previous ASPIRE publicatons,[8-11] including the lack of control over study elements, patient drop-out due to study length, and the impact of confounding factors on data analysis and interpretation. Specific to this analysis, treatment-related variables were assessed at treatment sessions 1 and 2 only based on the treatment adherence/non-adherence definitions. Data gathered during this time frame may not fully represent treatment outcomes at later timepoints. In addition, ASPIRE was designed to include approximately one-third of patients that were naïve to botulinum toxin for spasticity and two-thirds that were non-naïve/continuing botulinum toxin treatment,[8] which may have skewed the patient population in favor of those adherent to onabotulinumtoxinA treatment. Due to sample size limitations, separate analyses for specific etiologies other

than stroke were not done. Lastly, a less stringent threshold was applied at the univariate and multivariable block phases of the analysis (P<0.2) to ensure that potentially important variables were not prematurely removed from the model due to low sample size or heterogeneity in the dataset. Importantly, the more stringent P<0.05 was applied at the final model stage to ensure the robust identification of variables that impacted onabotulinumtoxinA treatment adherence in this study.

Conclusions

In ASPIRE, the majority of patients adhered to onabotulinumtoxinA treatment for spasticity, with adherent patients having an average >5 treatment sessions during the 2-year study. These analyses provide real-world insights to improve adherence to onabotulinumtoxinA treatment, including use of orthotics and treatment in Europe. In addition, these analyses further elucidate variables associated with non-adherence, including a re-treatment interval ≥15 weeks, use of assistive devices, and moderate/severe disability on the upper limb DAS pain subscale, for which clinicians should pay particular attention to better support their patients. Increased knowledge of variables that impact onabotulinumtoxinA treatment adherence can help to optimize spasticity management strategies to improve patient care.

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Figure Legends

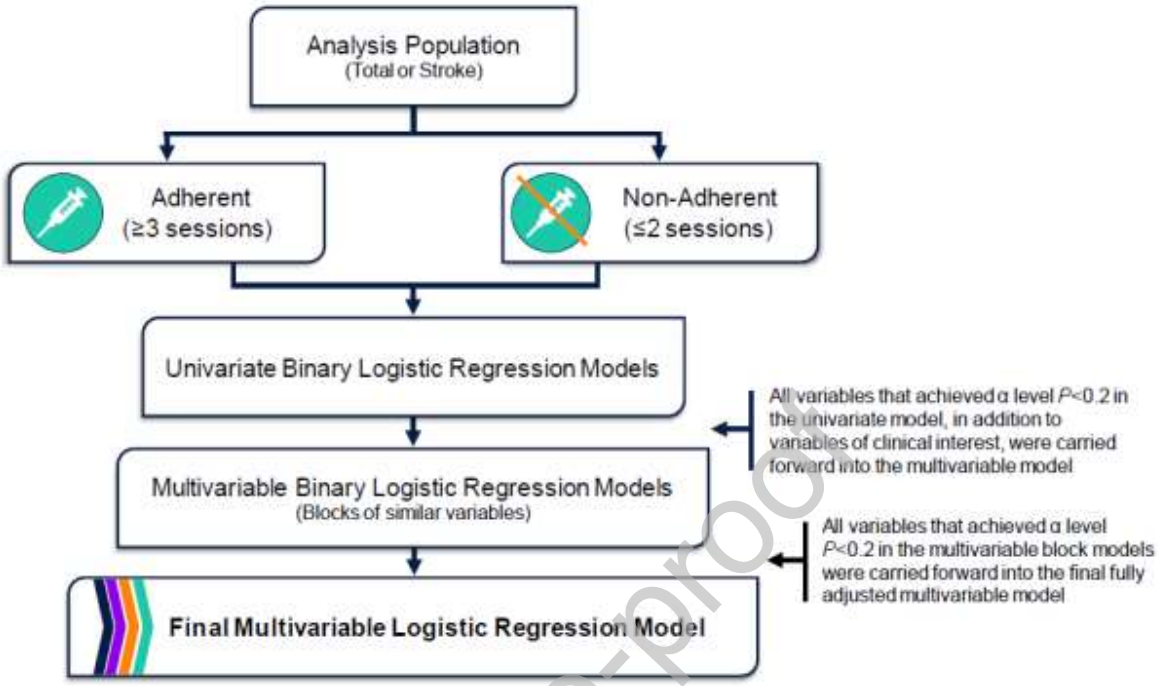

Figure 1. Logistic Regression Statistical Analysis. Data for the total and stroke patient populations were analyzed using a series of univariate and multivariable logistic regression models to obtain a final model, which idenfified variables that impacted adherence to onabotulinumtoxinA treatment from the ASPIRE study.

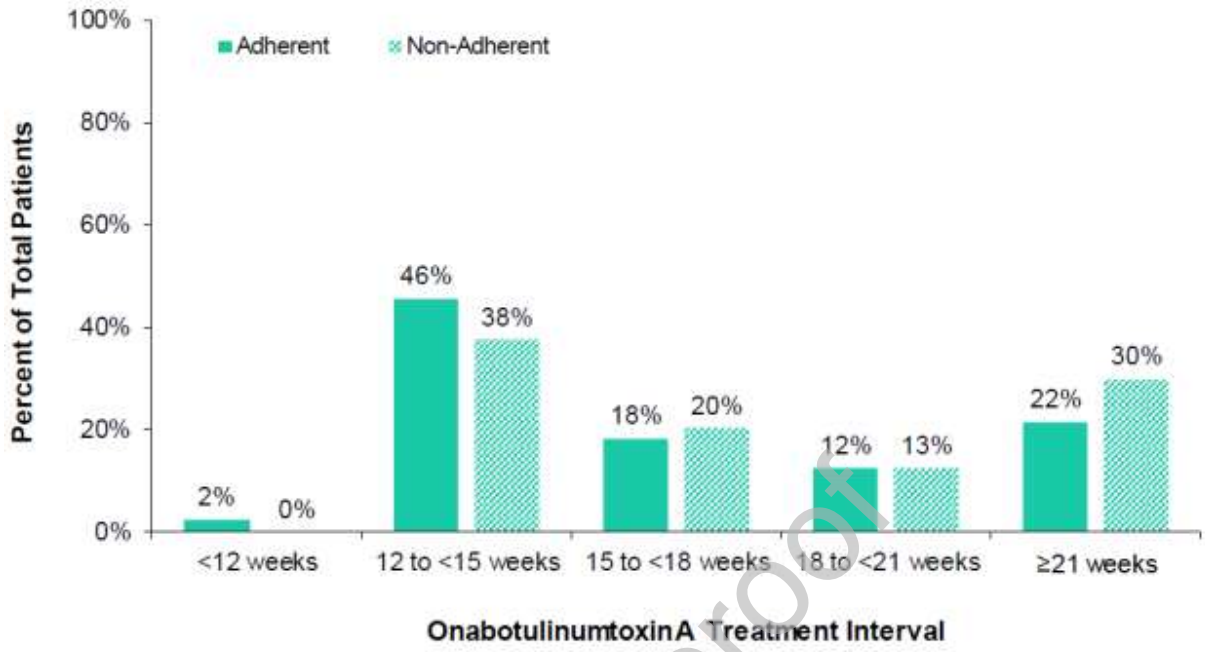

Figure 2. OnabotulinumtoxinA Treatment Interval for the Total Patient Population. Data shown represents the distribution of total patients across treatment interval categories (ie, length of time between treatment sessions 1 and 2 in weeks) for adherent and non-adherent patients.

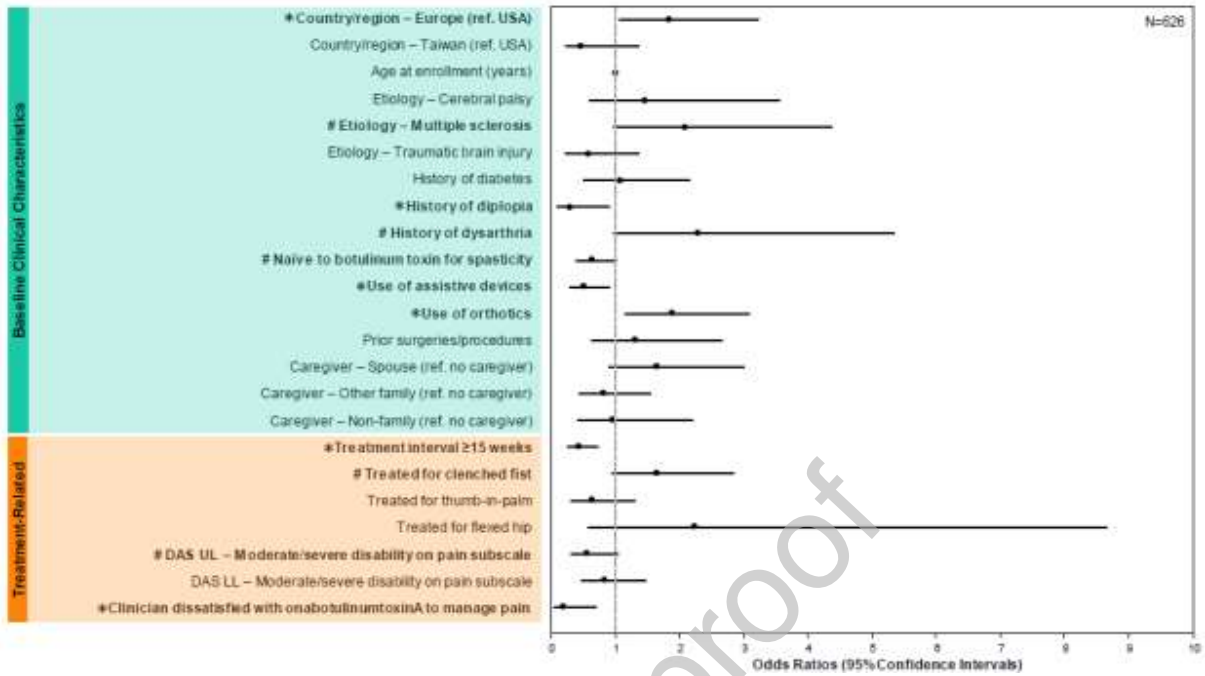

Figure 3. Final Model for the Total Patient Population. Baseline demographics, clinical chracteristics, and treatment-related variables that maintained α *P*<0.2 in the block models (**Supplemental Table 3**) were carried forward into the final model shown here. Reference (abbreviated as "ref.") indicates the comparator value used for analysis. Treatment-related variables were assessed at sessions 1 and 2 only. For interpretation of the figure, if both the upper and lower confidence intervals are less than 1 (indicated with a dashed gray vertical line), the variable has a significant impact on treatment non-adherence. If both the upper and lower confidence intervals are greater than 1, the variable has a significant impact on treatment adherence. Statistical significance was accepted at **P*<0.05 and clinically meaningful non-significant variables of interest at $^{\#}$*P*<0.1. LL, lower limb; Tx, treatment session; UL, upper limb.

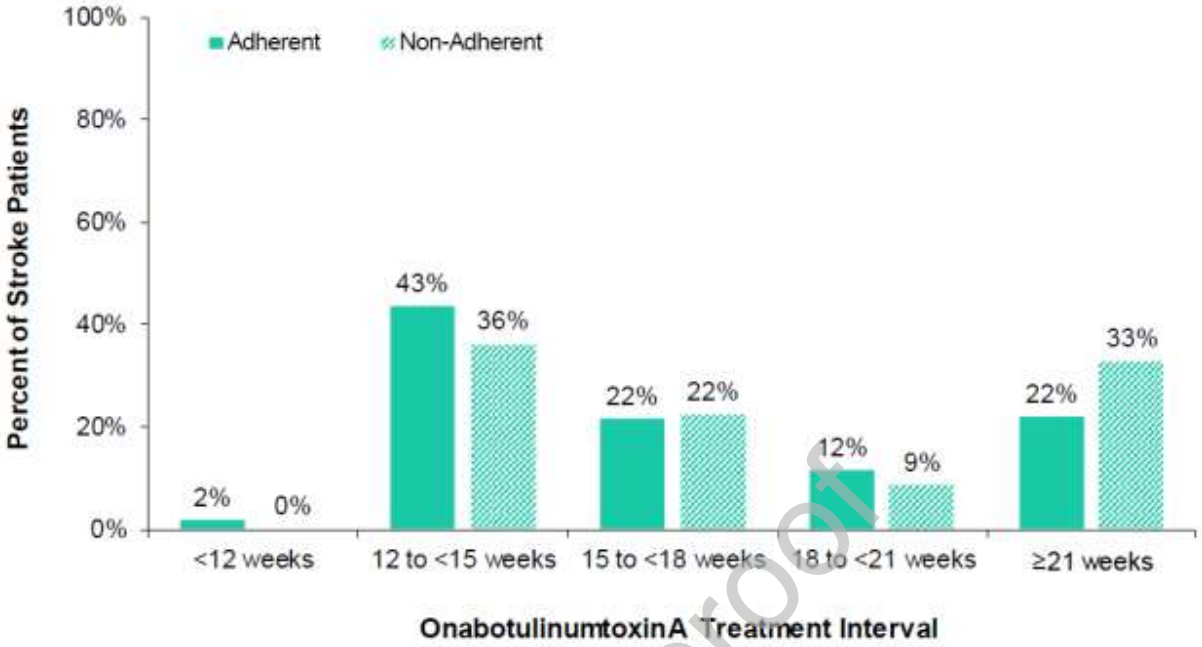

Figure 4. OnabotulinumtoxinA Treatment Interval for the Stroke Patient Population. Data shown represents the distribution of stroke patients across treatment interval categories (ie, length of time between treatment sessions 1 and 2 in weeks) for adherent and non-adherent patients.

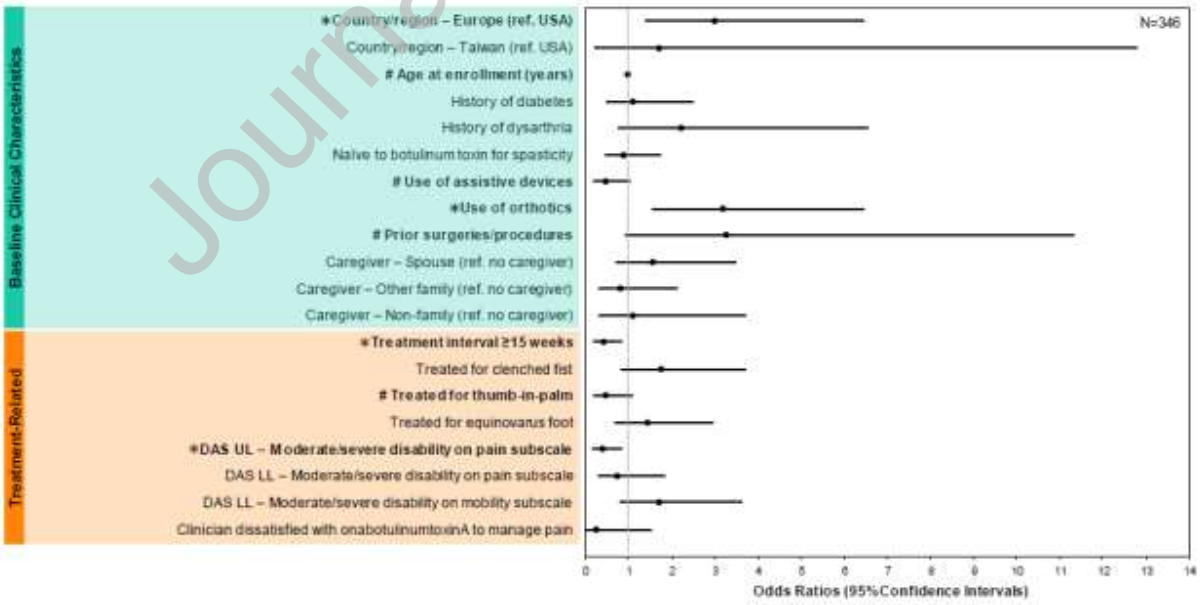

Figure 5. Final Model for the Stroke Patient Population. Baseline demographics, clinical chracteristics, and treatment-related variables that maintained α *P*<0.2 in the block models (**Supplemental Table 6**) were carried forward into the final model shown here. Reference (abbreviated as "ref.") indicates the comparator value used for analysis. Treatment-related variables were assessed at sessions 1 and 2 only. For interpretation of the figure, if both the upper and lower confidence intervals are less than 1 (indicated with a dashed gray vertical line), the variable has a significant impact on treatment non-adherence. If both the upper and lower confidence intervals are greater than 1, the variable has a significant impact on treatment adherence. Statistical significance was accepted at **P*<0.05 and clinically meaningful non-significant variables of interest at $^{\#}$*P*<0.1. LL, lower limb; Tx, treatment session; UL, upper limb.

Table 1: Logistic Regression Model Variables

Baseline Demographics and Clinical Characteristics	**Treatment-Related Variables**[‡]
Age at enrollment	Adverse events[§]
Caregiver relation to patient	Any adverse event
Spouse	Any serious adverse event
Other family	Any treatment-related adverse event
Non-family	Clinician satisfaction[‖]
No caregiver	OnabotulinumtoxinA helped manage spasticity
Concomitant medication(s) use	OnabotulinumtoxinA helped manage pain
Country/region	Sustained benefit of onabotulinumtoxinA treatment
Europe*	OnabotulinumtoxinA helped PT/OT or exercise
Taiwan	Continue to use onabotulinumtoxinA for spasticity
USA	DAS – Upper limb[¶]
Employment status	Dressing
Employed full- or part-time	Hygiene
Not employed	Limb posture
Gender	Pain
Female	DAS – Lower limb[¶]
Male	Dressing
Medical history	Hygiene
Aspiration/aspiration pneumonia	Limb posture
Cardiac disease	Pain
Cervical dystonia	Mobility
Connective tissue disease	Treatment interval
Constipation	< 12 weeks or ≥ 12 weeks
Dementia	< 15 weeks or ≥ 15 weeks
Depression	Treated upper limb clinical presentations[1, 2]
Diabetes	Adducted/internally rotated shoulder

- Diplopia
- Dysarthria
- Overactive bladder (idiopathic)
- Overactive bladder (neurogenic)
- Chronic/transformed migraine
- Myalgia
- Neuromuscular disorder(s)
- Urinary tract infection(s)

Naïve to botulinum toxin for spasticity

Pattern of spasticity
- Upper limb
- Lower limb
- Upper and lower limbs

Primary underlying etiology of spasticity
- Cerebral palsy
- Multiple sclerosis
- Spinal cord injury
- Stroke
- Traumatic brain injury

Severity of spasticity†
- Total mean upper limb MMAS score
- Total mean lower limb MMAS score
- Total mean upper limb and lower limb MMAS score

Treatment modalities
- Acupuncture
- Assistive devices
- Casting
- Chemodenervation
- Intrathecal therapy
- Clenched fist
- Flexed elbow
- Flexed wrist
- Intrinsic plus hand
- Pronated forearm
- Thumb-in-palm

Treated lower limb clinical presentations[2, 3]
- Adducted thigh
- Equinovarus foot
- Flexed hip
- Flexed knee
- Flexed toes
- Hitchhiker toe
- Stiff extended knee

Orthotics
Physio or occupational therapy
Surgeries or procedures

*Europe includes France, Germany, Italy, Spain, and the United Kingdom. †Severity of spasticity was assessed using the Modified Modified Ashworth Scale (MMAS), a validated and reliable measure of the intensity of spasticity.[4, 5] At baseline, each clinical presentation was scored on a 5-point scale from 1 (no increase in tone) to 5 (limb rigid in flexion or extension) by the clinician. For analysis, the mean MMAS score for all presentations in the upper limb, lower limb, or both limbs were utilized. ‡Treatment-related variables were assessed at sessions 1 and 2 only. §Adverse event data were captured for up to 108 weeks in ASPIRE and were summarized using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 by system organ class and preferred term. Relationship to onabotulinumtoxinA treatment was adjudicated by a panel of safety clinicians. ‖Clinicians were asked a series of five questions to determine their satisfaction with onabotulinumtoxinA treatment for spasticity at each subsequent treatment session. For analysis, satisfaction was categorized into the following binary variables: extremely satisfied/satisfied/neither/not applicable or dissatisfied/extremely dissatisfied. ¶Functional impairment was assessed using the Disability Assessment Scale (DAS)[6]. Four subscales in the upper limb (ie, dressing, hygiene, limb posture, and pain) and five subscales in the lower limb (ie, dressing, hygiene, limb posture, pain, and mobility) were scored on a 4-point scale from 0 (no disability) to 3 (severe disability [normal activities limited]) by the clinician at treatment session 1 and at each subsequent treatment session. For analysis, DAS scores were categorized into the following binary variables: no/mild disability or moderate/severe disability.

Table 2: Composition of the Total Patient Population by Adherent and Non-Adherent Status*

	Non-Adherent (n=207)	Adherent (n=523)
Country/region†		
France	3.9	6.1
Germany	1.0	5.4
Italy	8.2	9.4
Spain	3.4	3.1
Taiwan	15.5	1.5
United Kingdom	8.2	13.6
USA	59.9	61.0
Age at enrollment (years), mean (SD)	54.1 (16.8)	53.4 (14.8)
Gender		
Female	51.2	52.4
Male	48.8	47.6
Caregiver relation		
Spouse	27.1	32.3
Other family	20.8	15.7
Non-family	14.5	9.0
No caregiver	37.7	43.0
Employment status		
Employed full- or part-time	15.0	17.2
Not employed	85.0	82.8
Treatment history		
Naïve	47.3	32.7
Non-naïve	52.7	67.3
Etiology		
Stroke	59.4	55.1
Multiple sclerosis	13.0	17.6
Cerebral palsy	7.2	11.9
Traumatic brain injury	9.2	5.0
Spinal cord injury	5.8	5.7
Pattern of spasticity		
Upper limb	17.9	14.0
Lower limb	26.1	28.0
Upper and lower limbs	56.0	58.0
Severity of spasticity, mean (SD)		
Upper limb	3.4 (0.8)	3.3 (0.8)
Lower limb	3.2 (0.9)	3.3 (0.8)
Upper and lower limbs	3.3 (0.8)	3.3 (0.7)
Concomitant medication(s) used for spasticity	58.9	60.4
Treatment modalities		
Acupuncture‡	7.2	7.8
Right upper limb	33.3	24.4

Left upper limb	66.7	36.6
Right lower limb	26.7	39.0
Left lower limb	60.0	53.7
Head/neck	33.3	24.4
Unknown	0.0	4.9
Other	0.0	19.5
Assistive devices‡	71.0	66.3
Cane	43.5	53.3
Crutch	6.1	7.5
Walker	22.4	27.4
Wheelchair	66.0	64.3
Unknown	0.7	0.3
Other	6.1	10.4
Casting‡	8.7	10.3
Right upper limb	38.9	22.2
Left upper limb	27.8	27.8
Right lower limb	16.7	44.4
Left lower limb	38.9	37.0
Unknown	5.6	3.7
Chemodenervation‡	3.4	4.4
Right upper limb	14.3	26.1
Left upper limb	28.6	43.5
Right lower limb	14.3	34.8
Left lower limb	14.3	52.2
Neck	0.0	4.3
Unknown	0.0	4.3
Intrathecal therapy	10.1	10.3
Orthotics‡	46.9	53.5
Wrist + hand	39.2	29.6
Wrist	4.1	8.2
Elbow	5.2	3.9
Shoulder	2.1	2.9
Ankle + foot	59.8	70.0
Knee + ankle + foot	6.2	5.4
Knee	3.1	4.3
Unknown	4.1	1.4
Physio or occupational therapy‡	79.2	78.6
Activities of daily living (ADL) retraining	45.7	46.0
Aerobic exercise	14.6	19.0
Exercise for motor control and strength	62.2	64.2
Gait retraining	53.0	62.0
Passive stretching	54.3	65.2
Physical modalities	17.7	19.7
Posture and balance retraining	48.8	50.4
Transfer and mobility retraining	38.4	49.6
Unknown	7.3	7.8
Other	6.1	7.5
Surgeries or procedures‡	9.2	14.1
Orthopedic operations	68.4	67.6

Selective rhizotomy	0.0	4.1
Unknown	10.5	2.7
Other	21.1	25.7
Medical history		
Aspiration/aspiration pneumonia	6.3	5.5
Cardiac disease	46.4	44.7
Cervical dystonia	2.4	1.3
Connective tissue disease	1.9	2.1
Constipation	24.2	26.4
Dementia	1.0	0.8
Depression	41.1	42.3
Diabetes	16.9	11.3
Diplopia	4.3	2.3
Dysarthria	8.2	13.4
Overactive bladder (idiopathic)	4.8	4.0
Overactive bladder (neurogenic)	16.4	18.7
Chronic/transformed migraine	7.2	8.6
Myalgia	12.1	9.4
Neuromuscular disorder(s)	14.0	14.7
Urinary tract infection(s)	12.1	12.6
Treated upper limb clinical presentations		
Adducted/internally rotated shoulder	19.8	22.9
Clenched fist	44.0	50.7
Flexed elbow	48.3	45.5
Flexed wrist	36.2	36.9
Intrinsic plus hand	10.6	11.9
Pronated forearm	24.2	22.0
Thumb-in-palm	17.4	12.8
Treated lower limb clinical presentations		
Adducted thigh	12.6	13.0
Equinovarus foot	49.3	54.9
Flexed hip	1.9	4.8
Flexed knee	15.5	17.0
Flexed toes	9.7	13.6
Hitchhiker toe	6.3	7.8
Stiff extended knee	13.5	13.4
DAS upper limb - Moderate/severe disability		
Dressing	43.1	35.8
Hygiene	37.7	30.1
Limb posture	47.1	43.7
Pain	33.3	14.6
DAS lower limb - Moderate/severe disability		
Dressing	39.5	37.7
Hygiene	34.1	29.8
Limb posture	46.8	48.6
Pain	35.1	22.4
Mobility	60.5	63.7

Clinician dissatisfied/extremely dissatisfied or probably not/definitely not		
OnabotulinumtoxinA helped manage spasticity	4.8	2.1
OnabotulinumtoxinA helped manage pain	5.8	1.0
Sustained benefit of onabotulinumtoxinA treatment	6.7	4.0
OnabotulinumtoxinA helped PT/OT or exercise	3.8	1.3
Continue to use onabotulinumtoxinA for spasticity	1.9	0.2
Adverse events		
Any adverse event	26.6	24.1
Any serious adverse event	10.1	7.5
Any treatment-related adverse event	1.4	1.1

n, sample size; OT, occupational therapy; PT, physical therapy

*Data presented as percent of patients, unless otherwise indicated. Treatment-related variables were assessed at sessions 1 and 2 only. †For analysis, France, Germany, Italy, Spain, and the United Kingdom were grouped under “Europe”. ‡Sub-categories (shown in italics) may not add up to 100%, as more than one response was allowed.

Table 3: Composition of the Stroke Patient Population by Adherent and Non-Adherent Status*

	Non-Adherent (n=123)	**Adherent (n=288)**
Country/region†		
France	0.8	4.2
Germany	1.6	6.9
Italy	4.1	10.8
Spain	5.7	5.2
Taiwan	18.7	2.4
United Kingdom	8.9	11.8
USA	60.2	58.7
Age at enrollment (years), mean (SD)	60.5 (15.2)	57.9 (13.5)
Gender		
Female	49.6	49.3
Male	50.4	50.7
Caregiver relation		

Spouse	33.3	43.1
Other family	22.8	14.9
Non-family	14.6	7.6
No caregiver	29.3	34.4
Employment status		
Employed full- or part-time	7.3	12.2
Not employed	92.7	87.8
Treatment history		
Naïve	47.2	36.1
Non-naïve	52.8	63.9
Pattern of spasticity		
Upper limb	22.8	18.1
Lower limb	4.1	9.8
Upper and lower limbs	73.2	72.1
Severity of spasticity, mean (SD)		
Upper limb	3.4 (0.9)	3.4 (0.8)
Lower limb	3.1 (0.9)	3.2 (0.8)
Upper and lower limbs	3.3 (0.8)	3.3 (0.7)
Concomitant medication(s) used for spasticity	52.0	55.6
Treatment modalities		
Acupuncture‡	8.1	6.9
Right upper limb	30.0	30.0
Left upper limb	70.0	50.0
Right lower limb	30.0	25.0
Left lower limb	60.0	45.0
Head/neck	30.0	25.0
Unknown	0.0	0.0
Other	0.0	10.0
Assistive devices‡	72.4	67.0
Cane	57.3	66.3
Crutch	4.5	6.7
Walker	19.1	25.4
Wheelchair	66.3	65.3
Unknown	0.0	0.5
Other	6.7	7.8
Casting‡	10.6	10.1
Right upper limb	46.2	24.1
Left upper limb	30.8	31.0
Right lower limb	7.7	31.0
Left lower limb	30.8	27.6
Unknown	7.7	3.4
Chemodenervation‡	3.3	5.6
Right upper limb	25.0	25.0
Left upper limb	50.0	50.0
Right lower limb	75.0	18.8
Left lower limb	25.0	43.8
Neck	0.0	0.0
Unknown	0.0	0.0
Intrathecal therapy	8.9	9.0
Orthotics‡	48.8	62.8

Wrist + hand	51.7	33.1
Wrist	6.7	8.3
Elbow	6.7	4.4
Shoulder	3.3	4.4
Ankle + foot	51.7	69.1
Knee + ankle + foot	6.7	5.0
Knee	0.0	3.3
Unknown	3.3	1.1
Physio or occupational therapy‡	80.5	81.3
Activities of daily living (ADL) retraining	58.6	58.5
Aerobic exercise	13.1	21.8
Exercise for motor control and strength	66.7	68.4
Gait retraining	57.6	69.2
Passive stretching	49.5	64.5
Physical modalities	22.2	26.1
Posture and balance retraining	52.5	53.8
Transfer and mobility retraining	42.4	56.4
Unknown	5.1	7.7
Other	6.1	7.7
Surgeries or procedures‡	4.9	10.8
Orthopedic operations	66.7	71.0
Selective rhizotomy	0.0	0.0
Unknown	16.7	3.2
Other	16.7	25.8
Medical history		
Aspiration/aspiration pneumonia	5.7	7.3
Cardiac disease	63.4	61.8
Cervical dystonia	2.4	1.0
Connective tissue disease	2.4	2.8
Constipation	25.2	25.0
Dementia	1.6	0.7
Depression	39.8	44.8
Diabetes	26.0	17.0
Diplopia	3.3	1.7
Dysarthria	9.8	15.6
Overactive bladder (idiopathic)	4.9	5.2
Overactive bladder (neurogenic)	7.3	8.3
Chronic/transformed migraine	7.3	7.3
Myalgia	15.4	11.5
Neuromuscular disorder(s)	12.2	10.1
Urinary tract infection(s)	12.2	10.1
Treated upper limb clinical presentations		
Adducted/internally rotated shoulder	28.5	34.0
Clenched fist	61.8	70.5
Flexed elbow	64.2	63.9
Flexed wrist	49.6	51.7
Intrinsic plus hand	15.4	15.6

Pronated forearm	35.0	31.3
Thumb-in-palm	26.0	18.4
Treated lower limb clinical presentations		
Adducted thigh	4.1	4.9
Equinovarus foot	43.1	52.8
Flexed hip	0.8	3.1
Flexed knee	6.5	10.1
Flexed toes	8.9	13.5
Hitchhiker toe	8.1	7.6
Stiff extended knee	6.5	9.0
DAS upper limb - Moderate/severe disability		
Dressing	58.2	46.5
Hygiene	48.4	39.9
Limb posture	63.1	58.3
Pain	46.7	19.4
DAS lower limb - Moderate/severe disability		
Dressing	32.0	32.6
Hygiene	26.2	24.7
Limb posture	41.0	42.7
Pain	31.1	15.6
Mobility	52.5	58.7
Clinician dissatisfied/extremely dissatisfied or probably not/definitely not		
OnabotulinumtoxinA helped manage spasticity	1.7	3.5
OnabotulinumtoxinA helped manage pain	5.2	1.4
Sustained benefit of onabotulinumtoxinA treatment	5.2	6.3
OnabotulinumtoxinA helped PT/OT or exercise	3.4	2.4
Continue to use onabotulinumtoxinA for spasticity	0.0	0.3
Adverse events		
Any adverse event	30.9	23.3
Any serious adverse event	12.2	6.9
Any treatment-related adverse event	1.6	1.0

n, sample size; OT, occupational therapy; PT, physical therapy

*Data presented as percent of patients, unless otherwise indicated. Treatment-related variables were assessed at sessions 1 and 2 only. †For analysis, France, Germany, Italy, Spain, and the United Kingdom were grouped under “Europe”. ‡Sub-categories (shown in italics) may not add up to 100%, as more than one response was allowed.