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Primary results from the Cervical Dystonia Patient Registry for Observation of OnabotulinumtoxinA Efficacy (CD PROBE)

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ABSTRACT

Background: The Cervical Dystonia Patient Registry for Observation of OnabotulinumtoxinA Efficacy (CD PROBE; NCT00836017) is a prospective, observational, multicenter, real-world registry designed to assess the safety, effectiveness, and treatment utilization following multiple treatments of onabotulinumtoxinA.
Methods: Subjects were naïve to botulinum toxin, new to practice, or had not received toxin in ≥16 weeks if in a clinical trial. Dosages and treatment intervals varied due to the real-world design. Descriptive and inferential statistics evaluated changes over 3 treatments.
Results: 1046 subjects enrolled. Subjects were 74.4% female, 63.5% toxin-naïve, mean age 58.0 ± 14.7 years. The mean dose over 2481 treatment sessions was 189.8 ± 87.1 U, with average treatment intervals of 14.6 and 15.1 weeks. The mean Toronto Western Spasmodic Torticollis Rating Scale Total score in subjects who completed all assessments (n = 479) decreased from 39.2 at baseline to 27.1 at final visit ($P < .0001$). A high percentage of physicians reported improvement in Clinician Global Impression of Change after initial assessment; this significantly increased at final assessment (n = 479, 91.2% vs 95.0%; $P < .0001$). Similarly, a high percentage of subjects reported improvement in Patient Global Impression of Change after initial assessment, which significantly increased at final assessment (n = 470, 83.0% vs 91.7%; $P < .0001$). Significant reductions in all Cervical Dystonia Impact Profile-58 scores were observed (n = 407). Overall, 26.2% of subjects reported adverse events, including muscular weakness (7.0%) and dysphagia (6.4%).
Conclusions: Results indicate robust improvement in clinical ratings and excellent tolerability following onabotulinumtoxinA treatment of CD.

1. Introduction

Cervical dystonia (CD), the most common form of focal dystonia, is manifested by involuntary muscular contractions, resulting in abnormal head and shoulder movements and/or postures that can involve tremor and pain [1,2]. Several studies have demonstrated that CD can be potentially stigmatizing and has a negative impact on quality of life (QOL) [3–5]. Botulinum toxin (BoNT) is considered the treatment of choice for CD [6,7]. Although its safety and efficacy have been well established by controlled clinical trials [8,9], there are few long-term studies to determine the impact of BoNT treatments on QOL and other outcome measures in real-world practice.

Evidence-based practice is strongly encouraged and increasingly mandated by regulatory agencies and payer policies. While placebo-controlled trials remain the gold standard in assessing response to a therapeutic intervention, they often involve a relatively homogenous population of patients with pre-specified duration of symptoms, age, comorbidities, and restricted concomitant medications. Furthermore, placebo-controlled trials are usually short-term and are not suitable to determine long-term efficacy and safety. Observational studies are designed to address such concerns, and if designed to collect data in a pre-specified fashion, may provide important insight into the effects of medical treatments on disease state [10,11].

The Cervical Dystonia Patient Registry for Observation of OnabotulinumtoxinA Efficacy (CD PROBE) is an observational,

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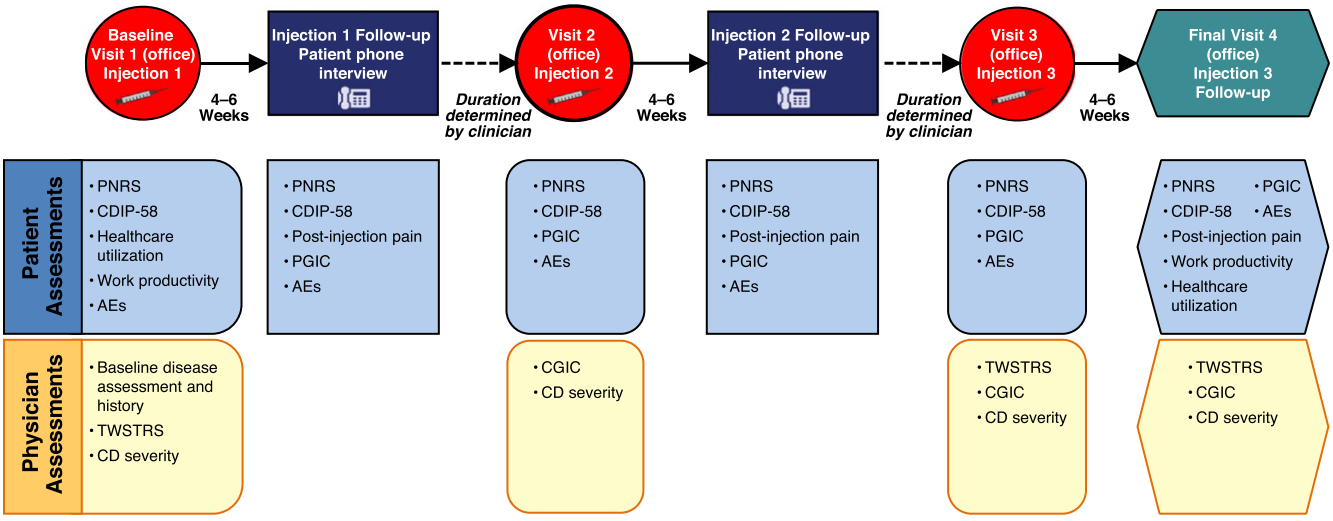


Fig. 1. Study design of CD PROBE and timing of physician- and subject-reported assessments. Abbreviations: AE, adverse event; CD, cervical dystonia; CDIP-58, Cervical Dystonia Impact Profile-58; CGIC, Clinician Global Impression of Change; PGIC, Patient Global Impression of Change; PNRS, Pain Numeric Rating Scale; TWSTRS, Toronto Western Spasmodic Torticollis Scale. Fig. 1 is reprinted with permission from Jankovic J, Adler CH, Charles PD, et al. Rationale and design of a prospective study: Cervical Dystonia Patient Registry for Observation of OnaBotulinumtoxinA Efficacy (CD PROBE). *BMC Neurol.* 2011;11:140. Copyright 2011 *BMC Neurology*.

multicenter, prospective clinical registry designed to describe current treatment practices and summarize the safety and effectiveness profile, including QOL outcomes, for onabotulinumtoxinA treatment of CD [12]. This is the first report of primary outcomes in CD PROBE.

2. Methods

2.1. Study design and subjects

Full methods, including detailed descriptions of inclusion and exclusion criteria, of CD PROBE (ClinicalTrials.gov identifier: NCT00836017) have been previously described [12]. Briefly, subjects diagnosed with CD were identified by the enrolling physician as candidates for onabotulinumtoxinA therapy. Participants also had to meet ≥1 of the following criteria: new to the physician practice, new to BoNT therapy, and/or if previously treated with BoNT in a clinical trial, must not have received BoNT for ≥16 weeks. CD PROBE complied with the ethical principles described in the current revision of the Declaration of Helsinki. Institutional review boards reviewed the study protocol and the informed consent form prior to initiating the study. Informed consent was obtained for each subject. The study size was determined as the number of subjects who could be reasonably recruited at the 88 US sites within the enrollment time frame of January 12, 2009 to August 31, 2012.

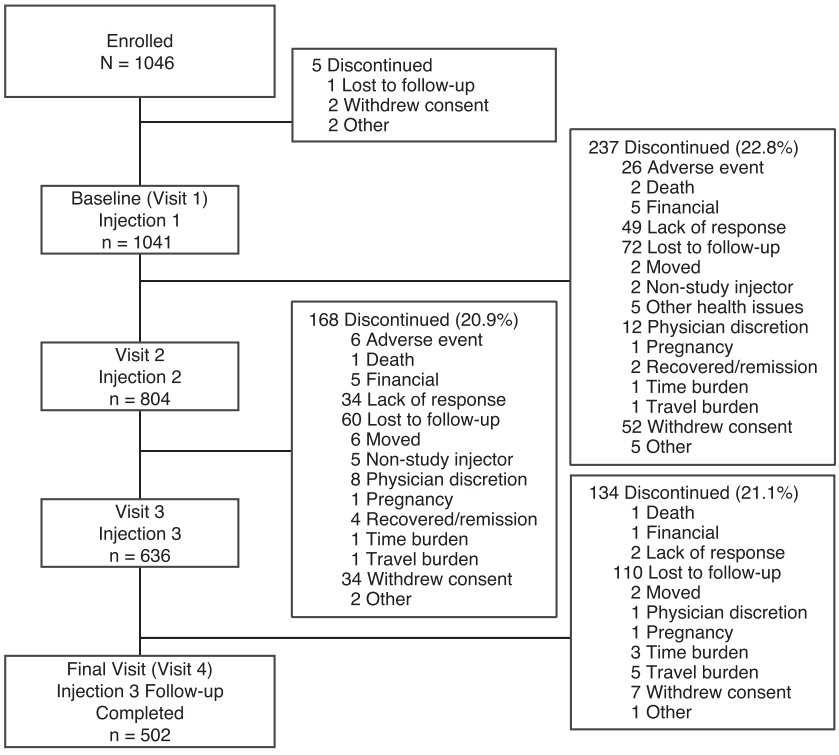


Fig. 2. Subject disposition.

Enrolled subjects could receive up to 3 onabotulinumtoxinA (BOTOX®, Allergan, Inc., Irvine, CA, USA) treatment sessions: at baseline/visit 1, visit 2, and visit 3 (Fig. 1). Treatment interval, dilution, dosing, injection guidance, and muscles injected with onabotulinumtoxinA were at the full discretion of the treating physician. Phone interviews were conducted 4–6 weeks post-injection, and the time to the next treatment session was determined by standard of care at each

Table 1
Baseline subject demographics and disease characteristics.

	Overall N = 1041
Demographics	
Age, years	58.0 ± 14.7
Gender, n (%)	
Female	774 (74.4)
Race, n (%)	
White	961 (92.3)
Non-white	80 (7.7)
Employment status, n (%)	
Retired	340 (32.7)
Employed full time	311 (29.9)
Employed part time	67 (6.4)
Disabled	123 (11.8)
Self-employed	61 (5.9)
Other[a]	139 (13.4)
Educational level, n (%)	
High school or less	357 (34.3)
Any college	519 (49.9)
Advanced degree	147 (14.1)
Other	17 (1.6)
Data not available, n	1
Clinical characteristics	
Predominant subtype, n (%)	
Anterocollis	59 (5.7)
Laterocollis	404 (38.9)
Retrocollis	55 (5.3)
Torticollis	494 (47.5)
Other	27 (2.6)
Data not available, n	2
Severity, n (%)	
Mild	345 (33.2)
Moderate	548 (52.7)
Severe	146 (14.1)
Data not available, n	2
Age at symptom onset, years	49.0 ± 16.7
Time from CD onset to diagnosis, years	5.0 ± 8.1
Time from diagnosis to treatment, years	1.1 ± 4.5
Prior treatment with botulinum toxin, n (%)	
Yes	380 (36.5)
No	661 (63.5)
Common comorbid conditions, n (%)	
Unspecified essential hypertension	340 (32.7)
Depressive disorder not elsewhere classified	207 (19.9)
Pure hypercholesterolemia	164 (15.8)
Anxiety state unspecified	125 (12.0)
Esophageal reflux	121 (11.6)
Unspecified acquired hypothyroidism	111 (10.7)
Other and unspecified hyperlipidemia	97 (9.3)
Migraine	95 (9.1)
Unspecified arthropathy	67 (6.4)
Parkinson's disease	60 (5.8)
Concomitant medications, n (%)	
Vitamins and combinations	373 (35.8)
Analgesics, miscellaneous	230 (22.1)
Antilipidemic agents, HMG-CoA reductase inhibitors	168 (16.1)
Antidepressants, selective serotonin reuptake inhibitors	162 (15.6)
β-adrenergic blocking agents	154 (14.8)
Thyroid preparations	139 (13.4)
Antianxiety agents, benzodiazepines and combinations	131 (12.6)
Antidepressants, miscellaneous	123 (11.8)
Proton pump inhibitors	119 (11.4)

All values are means with standard deviation unless stated otherwise.
[a] Other includes homemaker, never employed, student, and unemployed.

Table 2
Summary of treatment characteristics for each session and overall.

	Treatment session 1 (n = 1041)	Treatment session 2 (n = 804)	Treatment session 3 (n = 636)	Overall (N = 2481)
Total number of injections, n				
Mean ± SD	8.7 ± 5.2	9.5 ± 5.8	10.0 ± 6.2	9.3 ± 5.7
Range	1.0–45.0	1.0–41.0	0.0–40.0	0.0–45.0
Total number of muscles injected				
Mean ± SD	4.0 ± 1.4	4.1 ± 1.5	4.3 ± 1.5	4.1 ± 1.4
Range	0.0–11.0	1.0–11.0	0.0–13.0	0.0–13.0
Total dose, U				
Mean ± SD	171.6 ± 78.9	199.6 ± 88.3	207.2 ± 93.0	189.8 ± 87.1
Range	15.0–500.0	20.0–517.7	25.0–519.5	15.0–519.5
Data not available, n	64	49	37	150
Dilution, n (%)				
1 mL/100 U vial	681 (69.7)	538 (71.3)	424 (70.8)	1643 (70.5)
2 mL/100 U vial	257 (26.3)	187 (24.8)	146 (24.4)	590 (25.3)
Other	39 (4.0)	30 (4.0)	29 (4.8)	98 (4.2)
Data not available, n	64	49	37	150
Injection guidance, n (%)				
Anatomical[a]	269 (25.8)	217 (27.0)	174 (27.4)	660 (26.6)
Electromyography	772 (74.2)	585 (72.8)	459 (72.4)	1816 (73.3)
Ultrasound	0 (0)	0 (0)	0 (0)	0 (0)
Other	0 (0)	2 (0.2)	1 (0.2)	3 (0.1)
Data not available, n	0	0	2	2
Muscle injected, n (%)				
Splenius capitus	901 (86.6)	683 (85.0)	551 (86.6)	2135 (86.1)
Sternocleidomastoid	788 (75.7)	621 (77.2)	499 (78.5)	1908 (76.9)
Levator scapulae	693 (66.6)	543 (67.5)	433 (68.1)	1669 (67.3)
Trapezius	654 (62.8)	517 (64.3)	407 (64.0)	1578 (63.6)
Scalenes	319 (30.6)	268 (33.3)	227 (35.7)	814 (32.8)
Semispinalis	299 (28.7)	236 (29.4)	199 (31.3)	734 (29.6)
Longissimus	188 (18.1)	148 (18.4)	128 (20.1)	464 (18.7)
Splenius cervicis	107 (10.3)	80 (10.0)	67 (10.5)	254 (10.2)
Other[b]	187 (18.0)	230 (28.6)	225 (35.4)	642 (25.9)

[a] Inspection and palpation.
[b] Includes muscles written in by physician (cervical paraspinal muscles, corrugator supercilii, frontalis, masseter, obliquus capitis inferior muscle, pectoralis, platysma, procerus, rhomboids, suboccipitalis, and temporalis); each was <10%.

Table 3
Treatment paradigm.

	Total subjects (N = 1041)	Total treatment sessions (N = 2481)
Dose, U		
≤100	315 (31.8)	486 (20.8)
101–200	631 (63.7)	1085 (46.5)
201–300	344 (34.7)	566 (24.3)
>300	108 (10.9)	176 (7.6)
Data not available, n	50	150
Injection sites		
<7	510 (49.0)	957 (38.6)
7–12	585 (56.2)	1032 (41.6)
>12	253 (24.3)	492 (19.8)
Injected muscles		
<3	176 (16.9)	297 (12.0)
3–5	866 (83.2)	1839 (74.1)
>5	196 (18.8)	345 (13.9)
Dosing interval, weeks		
<11	38 (4.7)	46 (3.2)
>13	627 (78.0)	879 (61.0)
>16	207 (25.7)	246 (17.1)

Data are presented as n (%). Groups are not mutually exclusive because a patient could be represented more than once.

physician's practice. Treatment intervals, and thus assessment intervals, varied due to the real-world design. Visit 4 was the final office visit and did not include a treatment.

Treatment data were verified throughout the study. Missing or inconsistent data were queried and corrected by the sites as needed. Additional monitoring was conducted after entry of all data and focused on high- (≥600 U) and low- (<50 U) dose outliers.

2.2. Outcome variables

Baseline information collected prior to initial study treatment at visit 1 included demographic information, history of CD diagnosis and past treatments, physician classification of predominant CD subtype and severity, comorbidities, and concomitant medications. Investigators also answered a questionnaire that included type of practice and receipt of formal BoNT training.

For this primary analysis, effectiveness assessments included the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), Clinician and Patient Global Impression of Change (CGIC and PGIC, respectively) and the Cervical Dystonia Impact Profile-58 (CDIP-58) (Fig. 1).

TWSTRS, a validated, widely used rating scale for CD [13,14], was assessed at baseline, treatment session 3, and final office visit. The TWSTRS Total score is the sum of the 3 subscales: Severity, Disability, and Pain; higher scores indicate greater impairment [15]. The CGIC is a 7-item scale ranging from "very much improved" to "very much worse," in which the physician assesses clinically meaningful change in the health of the subject since the start of study treatment [16]. CGIC was assessed at treatment sessions 2 and 3 and final office visit. The PGIC is 7-item scale, similar to the CGIC, in which the subject assesses the change in his/her health status since the start of study treatment and provides insight into value of treatment to the subject [17]. PGIC was assessed at each office visit and phone interview except at baseline/visit 1. The CDIP-58, assessed at each office visit and phone interview, is a validated, disease-specific, QOL questionnaire that can measure the impact of BoNT treatment in CD [14,18,19]. It consists of 58 questions comprising 8 subscales, with higher scores more impaired.

Safety was evaluated by reported adverse events (AEs), each assessed by the investigator regarding severity (mild, moderate, severe), treatment relatedness, and whether it was serious. At each office visit, the physician answered the question "Has the patient experienced any adverse events since the last registry visit?" All AEs were coded using the Medical Dictionary for Regulatory Activities, version 13.1 [20].

2.3. Statistical analyses

Descriptive statistics were utilized to define the sociodemographics and disease characteristics and to analyze treatment patterns. Descriptive and inferential statistics, analysis of variance (ANOVA), and analysis of covariance (ANCOVA) were used when appropriate to evaluate any change in outcome measures over study treatment sessions. Data were generated for 2 subpopulations: (1) the as-treated population, comprised of subjects who completed the first treatment session and reported whether they were naïve or non-naïve to BoNT treatment at baseline (N = 1041), and (2) the subset of the as-treated population who completed all assessments for a given measure (numbers vary by outcome measures). A P value of ≤ .05 was considered statistically significant within the subpopulation with complete data.

AEs were reported per rates of total population and per total AEs. AE incidence rate was calculated as: ([total unique events] × [365.25 days per year]) / sum of exposure time in days, where the time of exposure for each subject was the time from enrollment until the latest of the available dates of treatment, peak effect contact, or withdrawal.

3. Results

3.1. Subject disposition

The as-treated population included those who reported whether they had prior exposure to BoNT and completed the first treatment session (N = 1041); 5 subjects enrolled but did not receive treatment (Fig. 2). Of the enrolled subjects, 60.8% (n = 636) completed all 3 treatment sessions, and 48.0% (n = 502) completed all 3 treatment sessions and the final assessment visit; 410 subjects withdrew before the final visit.

Of the enrolled subjects, 22.8% withdrew after the first visit, 20.9% after the second, and 21.1% after the third (Fig. 2). The most common reasons for discontinuation were loss to follow-up (n = 243, 23.2%), consent withdrawal (n = 95, 9.1%), lack of response after any of the 3 treatment sessions (n = 85, 8.1%), and AE (n = 32, 3.1%).

Comparison of the demographics and baseline disease characteristics between those who discontinued for any reason and those who completed the study indicated that the demographic profiles were similar. There were no significant differences across the 2 groups in TWSTRS, physician assessment of severity, predominant subtype of CD, or whether they had received BoNT in the past. The Head and Neck subscale of the CDIP-58 was significantly higher at baseline in those who completed the study compared with those who withdrew (71.7 vs 68.4, respectively; P = .0079). In addition, the total dose at treatment session 1 was significantly higher for those who completed compared with those who withdrew (178.4 U vs 165.5 U; P = .0108). Those who completed the study were more likely to have been treated by an investigator with formal BoNT training compared with those who withdrew (96.2% vs 92.5%; P = .0118).

3.2. Baseline demographics and disease characteristics

The mean age of the 1041 as-treated subjects was 58.0 ± 14.7 years; 74.4% were female (Table 1). The mean time from diagnosis to treatment was 1.1 ± 4.5 years. The most predominant postures were torticollis (47.5%) and laterocollis (38.9%), and 63.5% of subjects were toxin-naïve at baseline. Over half of subjects' CD (52.7%) was rated as moderately severe.

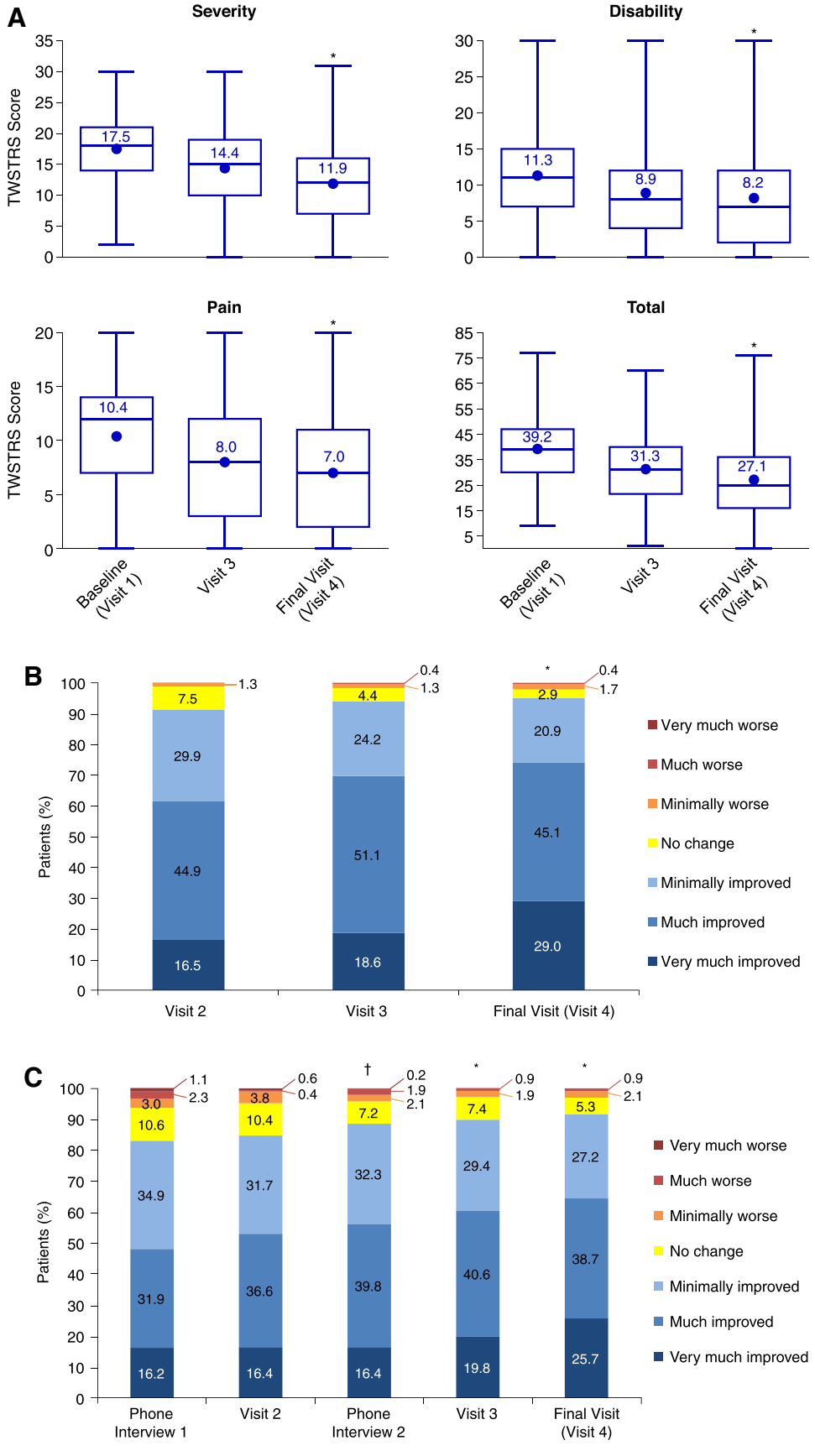
Out of 85 responding treating physicians in CD PROBE, 76 (89.4%) were neurologists, 8 (9.4%) were physical medicine and rehabilitation physicians, and 1 (1.2%) was a pain specialist. Most (91.7%) had received formal BoNT training.

3.3. Treatment characteristics and paradigm

Data from 2481 onabotulinumtoxinA treatment sessions were captured (Table 2). The mean total dose across all 3 treatment sessions was 189.8 ± 87.1 U and ranged from 15 to 519.5 U. Mean doses increased over the treatment sessions (171.6 U, 199.6 U, and 207.2 U for sessions 1–3, respectively). Similarly, the mean number of total injections increased from 8.7 ± 5.2 to 10.0 ± 6.2 over treatment sessions 1–3. About 70% of treatment sessions utilized the 1 mL/100 U dilution of onabotulinumtoxinA, and in about 75% of treatment visits, electromyography was used to guide the injection into the intended target muscle. The mean time between treatments increased from 14.6 ± 4.1 weeks following treatment session 1 to 15.1 ± 5.2 weeks after treatment session 2.

Doses of <50 U, considered low-dose outliers, were administered to 19 subjects over 25 treatment sessions. All doses <50 U were verified by the study site; 19/25 of these doses were administered at the same center. When examining treatment interval outliers, 7 subjects had treatment intervals <60 days (5, 26, 34, 36, 51, 53, and 56 days, respectively). Only 2 of the 7 subjects with short treatment intervals were administered low doses (30 U, 50 U).

Examination of the treatment paradigm showed that the majority of subjects (63.7%) received 101–200 U, and 31.8% (n = 315) of subjects received a dose ≤100 U. Most subjects (56.2%) received 7–12 injections per treatment session, which most commonly involved 3–5 muscles (83.2%). Additionally, most subjects (78.0%) and treatment sessions (61.0%) had a treatment interval of >13 weeks. Less



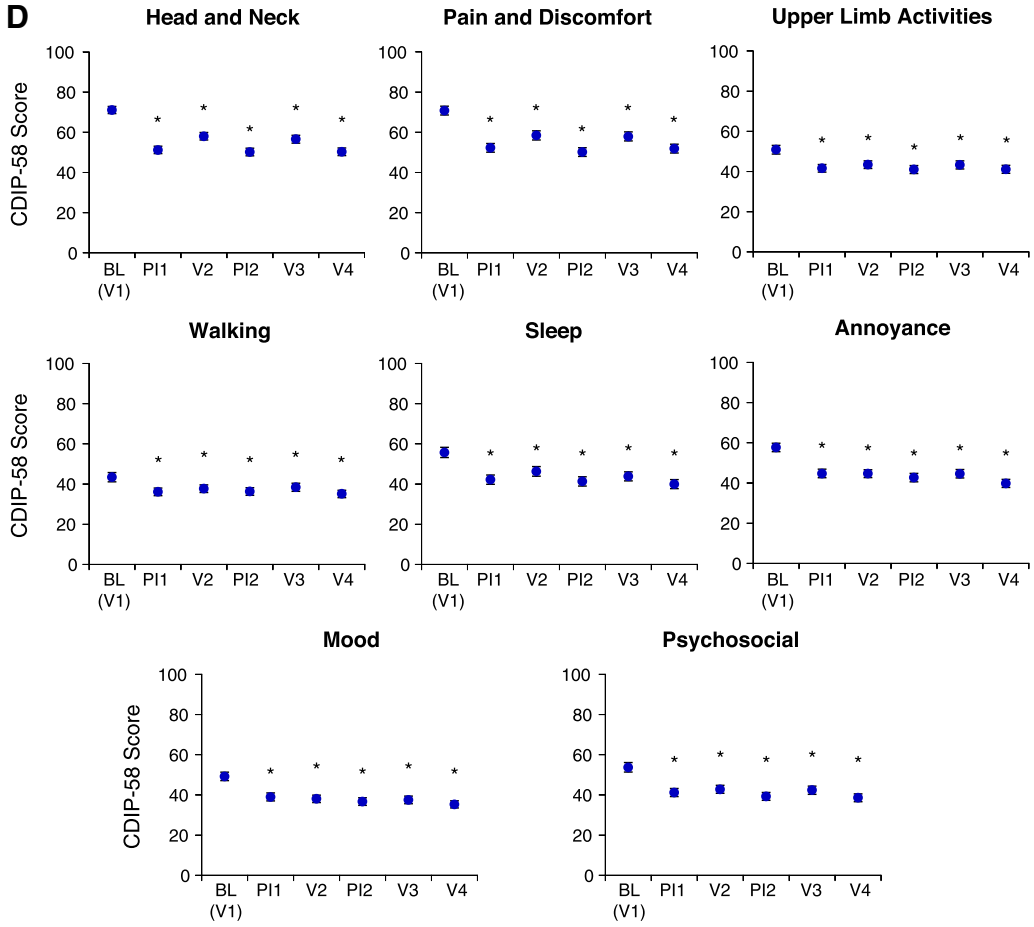


Fig. 3. Effectiveness assessments from CD PROBE for subjects with complete data for each assessment. (A) Toronto Western Spasmodic Torticollis Rating Scale (n = 479), (B) Clinical Global Impression of Change (n = 479), (C) Patient Global Impression of Change (n = 470), and (D) Cervical Dystonia Impact Profile-58 (n = 407). Abbreviations: BL, baseline; CD PROBE, Cervical Dystonia Patient Registry for Observation of OnabotulinumtoxinA Efficacy; CI, confidence interval; dot, mean; line in box, median; PI, phone interview; top and bottom of box, interquartile range; V, visit; whiskers, minimum and maximum. (A). n = 479 for all visits. Scales range as follows: Severity, 0–35; Disability, 0–30; Pain, 0–20; and Total, 0–85. *$P < .0001$ vs baseline. (B). n = 479 for all visits. *$P < .0001$ vs visit 2. (C). n = 470 for all visits. *$P < .0001$ vs phone interview 1. †$P < .01$ vs phone interview 1. (D). n = 407 for all visits. Data are mean ± 95% CI. Scores for each domain range from 0 to 100. *$P < .0001$ vs baseline.

than 5% of subjects and treatment sessions had a treatment interval of <11 weeks (Table 3).

3.4. Effectiveness outcomes

There was a significant and sustained improvement in all TWSTRS domains after onabotulinumtoxinA treatments (Fig. 3A). When evaluating the subpopulation of subjects who completed all TWSTRS assessments (n = 479), the mean TWSTRS total score significantly decreased from a baseline score of 39.2 to 27.1 at final assessment ($P < .0001$) (Fig. 3A). Furthermore, each TWSTRS subscale significantly decreased from baseline to final visit (each $P < .0001$). Improvements were sustained over time. Results were similar to those from the as-treated population: mean TWSTRS total score of 38.8 at baseline (visit 1), 31.5 at visit 3, and 27.1 at final visit (Fig. 4A).

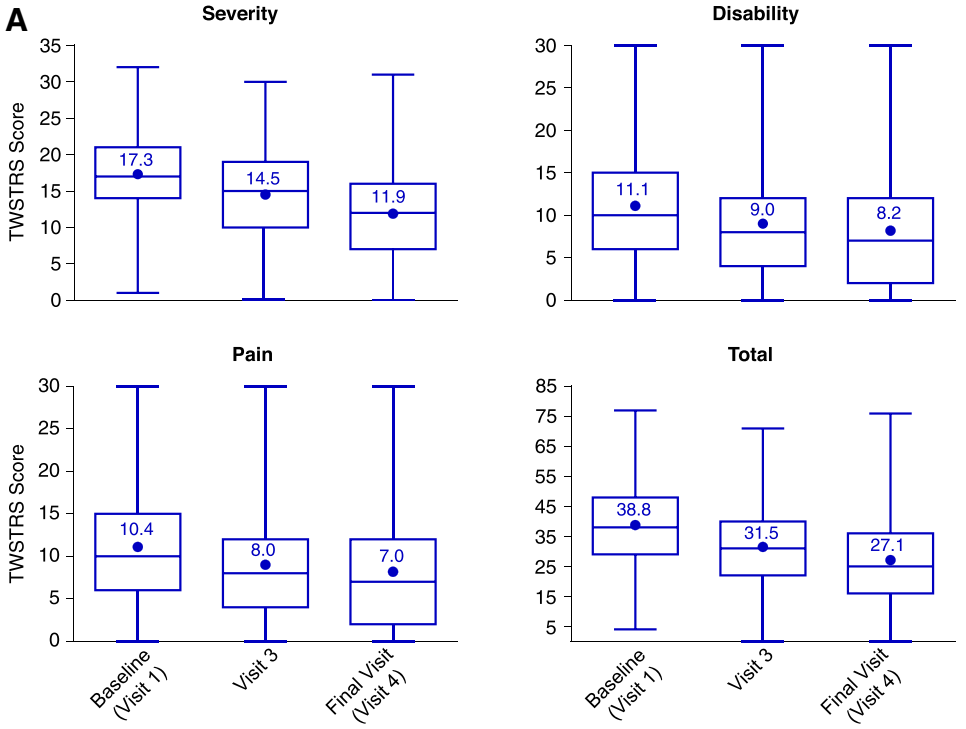
In the subpopulation of subjects with all CGIC assessments (n = 479), a significantly higher percentage of physicians reported subject CD as minimally, much, or very much improved at final visit compared with visit 2; 95.0% vs 91.2%, respectively ($P < .0001$) (Fig. 3B). Results were similar to those from the as-treated population: at visit 2, 89.5% of physicians rated subject CD as minimally, much, or very much improved, which increased to 93.5% at visit 3 and 94.8% at the final assessment (Fig. 4B). Similarly, when evaluating the subpopulation of subjects who had all PGIC assessments (n = 470), a significantly higher percentage of subjects reported improvement at final visit compared with phone interview 1: 91.7% vs 83.0% of subjects reported CD symptoms as minimally, much, or very much improved ($P < .0001$) (Fig. 3C). Results were similar to those from the as-treated population (Fig. 4C).

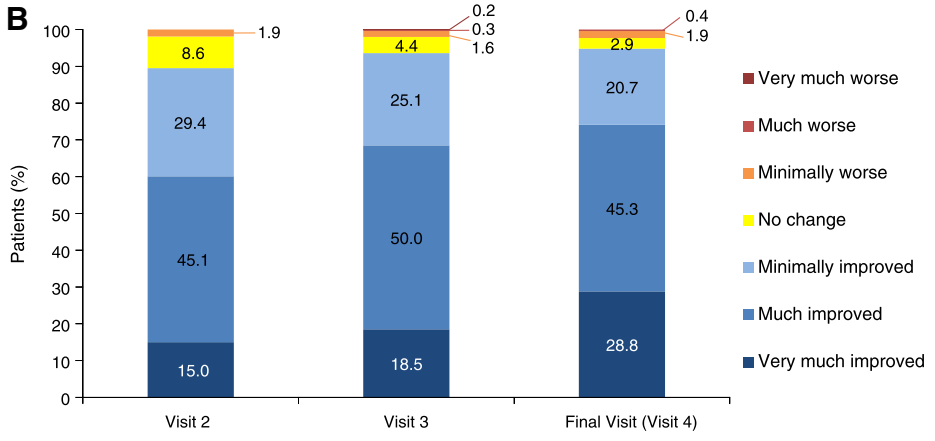
Among the CDIP-58 domains, the Head and Neck and Pain and Discomfort subscale scores were the highest (i.e., most impacted) at baseline (Fig. 3D). Significant reductions in all CDIP-58 subscale scores were observed following onabotulinumtoxinA treatment for the subpopulation with complete data (n = 407) and were sustained over time (each $P < .0001$) (Fig. 3D). Head and Neck subscale scores decreased from 71.1 at baseline to 50.3 at final visit; Pain and Discomfort, 70.8 to 51.9; Upper Limb Activities, 50.9 to 41.1; Walking, 43.4 to 35.1; Sleep, 55.7 to 39.9; Annoyance, 57.7 to 39.8; Mood, 49.2 to 35.3; and Psychosocial, 53.7 to 38.6 (each $P < .0001$). For most subscales, improvements were most robust at phone interviews (peak effect) and slightly decreased prior to the next treatment session. Similar results were observed in the as-treated population (Fig. 4D).

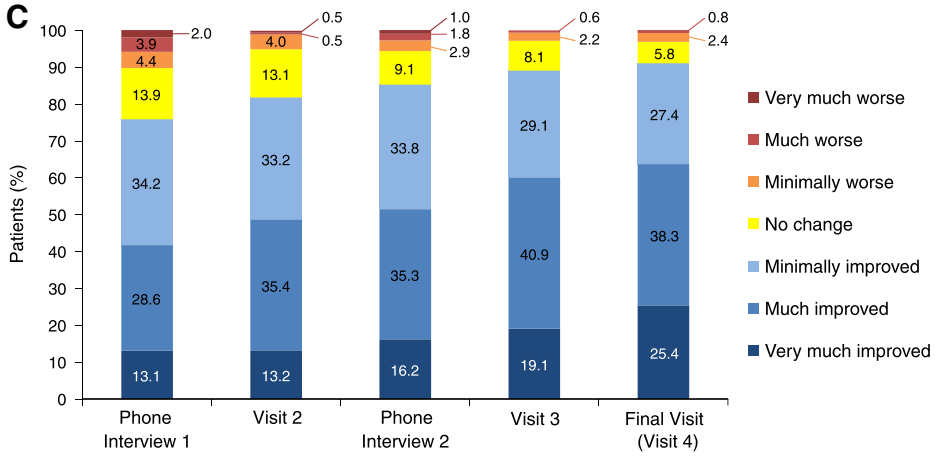
3.5. Safety outcomes

A total of 515 AEs were reported in 273 (26.2%) unique subjects (Table 4). The overall incidence rate of AEs was 0.6 per subject per year. Most AEs (88.3%, n = 455) were mild to moderate in severity. Muscular weakness (n = 9) and dysphagia (n = 7) were the most common AEs in those who withdrew due to AE. AEs reported in ≥2.0% of subjects were muscular weakness (7.0%), the majority of which were local; dysphagia (6.4%; of which 2.8% was moderate to severe); and neck pain (2.7%).

There were 315 treatment-related AEs reported in 185 subjects (17.8%). The most common events were muscular weakness (6.9%), dysphagia (6.2%), and neck pain (2.3%). There were 46 serious AEs (SAEs) reported in 33 subjects (3.2%), with an overall incidence of 0.1 per subject per year. Four treatment-related SAEs were reported in 4 subjects (0.4%). Four deaths were reported; none were considered to be treatment-related.







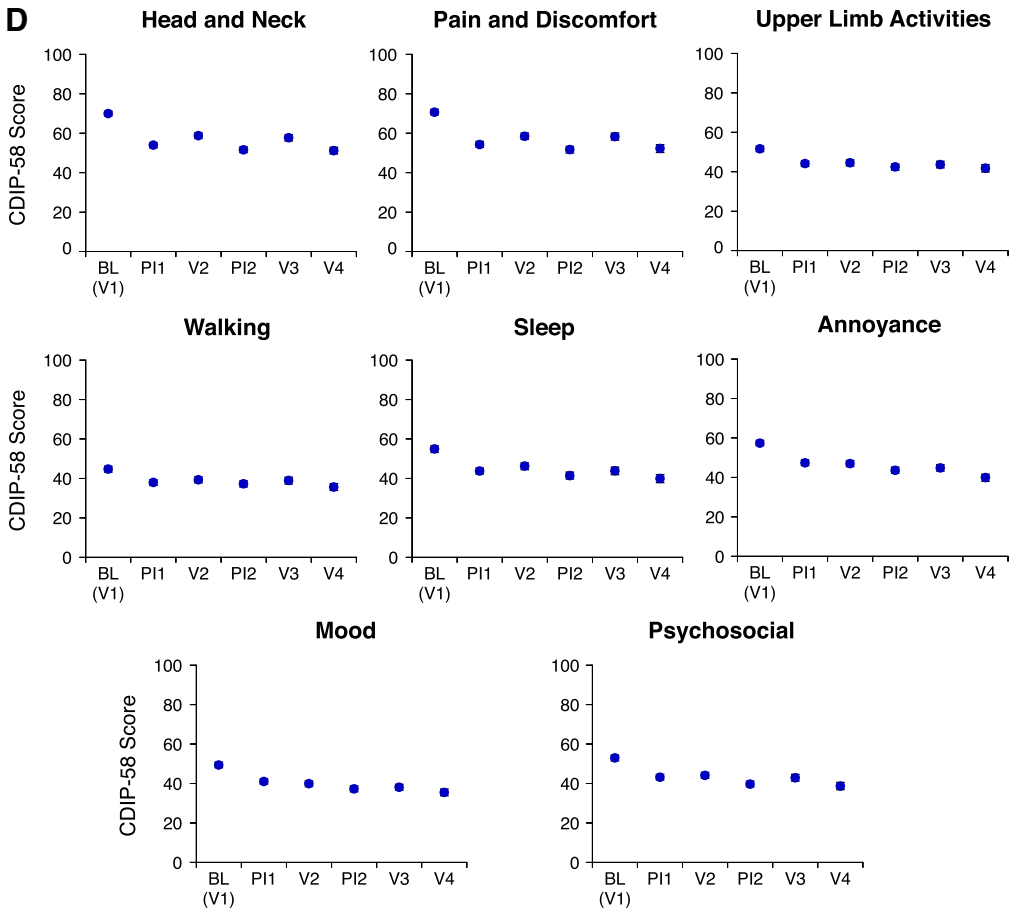


Fig. 4. As-treated data for effectiveness assessments from CD PROBE. (A) Toronto Western Spasmodic Torticollis Rating Scale, (B) Clinical Global Impression of Change, (C) Patient Global Impression of Change, and (D) Cervical Dystonia Impact Profile-58. Abbreviations: BL, baseline; CD PROBE, Cervical Dystonia Patient Registry for Observation of OnabotulinumtoxinA Efficacy; dot, mean; line in box, median; PI, phone interview; top and bottom of box, interquartile range; V, visit; whiskers, minimum and maximum. (A). n = 1038 for baseline (visit 1), n = 635 for visit 3, and n = 480 for final visit (visit 4). Scales range as follows: Severity, 0–35; Disability, 0–30; Pain, 0–20; and Total, 0–85. (B). n = 799 for visit 2, n = 634 for visit 3, and n = 483 for final visit (visit 4). (C). n = 959 for phone interview 1, n = 800 for visit 2, n = 717 for phone interview 2, n = 633 for visit 3, and n = 504 for final visit (visit 4). (D). n = 1037 for baseline (visit 1), n = 953 for phone interview 1, n = 797 for visit 2, n = 716 for phone interview 2, n = 632 for visit 3, and n = 502 for final visit (visit 4). Scores for each domain range from 0 to 100.

4. Discussion

CD PROBE, with 1046 subjects enrolled by 88 investigators and data from 2481 treatment sessions, was designed and implemented to assess the safety and effectiveness of BoNT in patients with CD. This real-world information on treatment outcomes provides support for the conclusion that onabotulinumtoxinA significantly and safely decreases CD symptoms and improves QOL of patients with CD. OnabotulinumtoxinA appears to be well tolerated, and no new safety concerns emerged.

Baseline demographics of subjects were similar to those of subjects in other large trials [8,21–25]. Baseline TWSTRS Total scores were slightly lower in CD PROBE compared with those from registration trials for other BoNTs (mean of 39.2 in CD PROBE and low to mid-40s for registration trials) [21–24].

Although the mean onabotulinumtoxinA doses increased over the treatment sessions from 171.6 U to 207.2 U, the mean dose of 189.8 ± 87.1 U is lower than the maximum recommended dose [26], is comparable to the mean dose of 187.0 ± 76.5 U in another observational study [9], and is less than doses previously reported as typical in clinical practice [7]. This is possibly because 63.5% were BoNT-naïve. Consistent with other longitudinal studies, the treatment interval also increased with subsequent treatment sessions [27].

CD PROBE aimed to represent the "real-world" experience and reflects a broad range of treatment practices. As a result, outliers were identified. For example, the few cases of low doses and short treatment intervals may be due to physicians testing tolerability to onabotulinumtoxinA, since these were mostly observed during the first treatment session. Some practitioners may have used "touch-up" sessions, whereby a low dose of onabotulinumtoxinA was injected into a specific area to optimize benefit, thus accounting for the short treatment interval in limited cases. Such "booster" injections are generally not recommended, as this practice has been associated with increased risk of immunoresistance [27].

In CD PROBE, onabotulinumtoxinA treatment showed significant and sustained improvements in CD symptoms, as measured via both physician- and subject-reported outcomes, including TWSTRS, CGIC, PGIC, and CDIP-58. There is no defined minimal important difference (MID) for TWSTRS [10], but BoNT trials have defined a responder as a subject with a decrease in the TWSTRS Total score of ≥30% and/or ≥10 points [21,25]. In CD PROBE, the mean change in TWSTRS Total score from baseline to final visit was 12.1, which is 30.9% lower than the baseline score (median change from baseline to final visit is 14.0, a 35.9% reduction). The CDIP-58 also has no defined MID [10], but the changes from baseline to peak effect for each subscale in CD PROBE were comparable to or better than those in a smaller clinical trial [19].

We recognize that the frequency of discontinuations (n = 544, 52.0%) was relatively high, which reduced the sample size available for outcome-related analyses. This is, however, not entirely unexpected, as CD PROBE is an observational, naturalistic study rather than a randomized clinical trial. Registries generally have higher discontinuation rates than randomized clinical trials, as these studies often enroll a broader subject population, have a longer study duration, and do not have a protocol-defined treatment schedule [11]. Registries also do

not provide study drug, and so are limited by reimbursement and other financial challenges that may adversely impact retention. In comparison to CD PROBE's retention rate (48.0% of subjects completed the study), 72–96% of subjects in the BoNT registration trials completed the respective studies [8,21–24], with the exception of 1 trial in which 26.3% of subjects remained in the study after week 12 [25]. The retention rate in CD PROBE was lower than those of other registries, which range from 65.4 to 77.5% [28,29]. We performed additional analyses in order to better understand the reasons for discontinuation and the potential impact on the study conclusions. Most (110/134) of the subjects who withdrew between treatment session 3 and final visit were lost to follow-up; this accounts for almost half of those who were lost to follow-up over the entire course of the study. Therefore, 60.8% completed all 3 treatment cycles. We hypothesize that the high rates of withdrawal prior to the final visit may have been due to subject unwillingness to take the time for a non-treatment office visit, particularly since it was the final visit for the study. The high withdrawal rate, one of the major limitations of our study, could have been possibly prevented if we had offered treatment at the fourth visit as an incentive to the subjects to return for this last visit. This issue should be taken into account for the design of future studies. Although the baseline characteristics of those who completed the study were similar to those who discontinued early, the former group may have been slightly more severe as suggested by higher CDIP-58 Head and Neck subscale score and higher total dose at treatment session 1, which may have compelled them to remain in the study.

Although the findings should be interpreted cautiously because of the open-label design and relatively high discontinuation rate, the strength of CD PROBE is that it is a large clinical registry of prospectively followed subjects that provides data on the clinical nuances of treatment that are not generally obtainable from randomizedcontrolled trials. The results confirm the robust efficacy and safety of onabotulinumtoxinA in the treatment of CD.

Table 4
Subject- and event-based adverse events.

Event, n (%)	Subjects N = 1041	Events
Overall AEs	273 (26.2)	515 (100.0)
Muscular weakness	73 (7.0)	87 (16.9)
Dysphagia	67 (6.4)	77 (15.0)
Neck pain	28 (2.7)	31 (6.0)
Headache	16 (1.5)	20 (3.9)
Injection site pain	13 (1.2)	13 (2.5)
Musculoskeletal pain	10 (1.0)	11 (2.1)
Treatment-related AEs	185 (17.8)	315 (61.2)
Muscular weakness	72 (6.9)	86 (16.7)
Dysphagia	65 (6.2)	75 (14.6)
Neck pain	24 (2.3)	26 (5.0)
Headache	11 (1.1)	14 (2.7)
Injection site pain	12 (1.2)	12 (2.3)
Serious AEs	33 (3.2)	46 (8.9)
Cardiac arrest	3 (0.3)	3 (0.6)
Chest pain	2 (0.2)	2 (0.4)
Convulsion	2 (0.2)	2 (0.4)
Dysphagia	2 (0.2)	2 (0.4)
Hip fracture	2 (0.2)	2 (0.4)
Loss of consciousness	2 (0.2)	2 (0.4)
Orthostatic hypotension	2 (0.2)	2 (0.4)
Pyrexia	2 (0.2)	2 (0.4)
Syncope	2 (0.2)	2 (0.4)
Urinary tract infection	2 (0.2)	2 (0.4)
Treatment-related SAEs	4 (0.4)	4 (0.8)
Dysphagia	2 (0.2)	2 (0.4)
Chest pain	1 (0.1)	1 (0.2)
Respiratory distress	1 (0.1)	1 (0.2)

Overall and treatment-related AEs in ≥1.0% of subjects, SAEs in >1 subject, and all treatment-related SAEs are presented.
Abbreviations: AE, adverse event; SAE, serious adverse event.

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