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Minimal clinically important change in patients with cervical dystonia: Results from the CD PROBE study

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ABSTRACT

Objective: To determine the minimal clinically important change (MCIC) on Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) scores using data from Cervical Dystonia Patient Registry for Observation of OnabotulinumtoxinA Efficacy (CD PROBE), which captured real-world practices and outcomes.

Methods: Changes in the baseline TWSTRS scores (point and percentage changes) were compared to changes in the Patient and Clinician Global Impression of Change (PGIC and CGIC) ratings. Using logistic regression, the discrimination of the model was determined.

Results: Among the 479 patients who completed all TWSTRS assessments, the mean TWSTRS Total score significantly decreased from baseline (39.2) to the final visit (27.1) ($P < .0001$). TWSTRS Total score point changes that compared with PGIC assessments "very much improved," "much improved" or better, and "minimally improved" or better were −11, −9, and −8, respectively, and were similar to previously published changes (ie, a decrease of ≥10 points). TWSTRS Total score data met indicators of good cutoffs for discrimination of the model including ≥70% percentage of outcomes correctly classified when compared with PGIC ratings. The TWSTRS Total score mapped to PGIC and CGIC ratings better than any TWSTRS subscale score.

Conclusions: The MCIC for improvement was ≥8 points based on mean TWSTRS Total scores in patients with cervical dystonia when compared against the patient-based evaluation of benefit (PGIC).

1. Introduction

Cervical dystonia (CD) is a chronic neurological disorder associated with involuntary contractions of neck and upper shoulder muscles resulting in abnormal movements and/or posturing of head, shoulders and neck [1]. CD is the most common focal dystonia and results in pain and decreased quality of life for most patients [2–5].

Intramuscular injection of botulinum toxin (BoNT) into affected muscles is generally considered first-line treatment for CD [6,7]. OnabotulinumtoxinA (BOTOX®, Allergan plc, Dublin, Ireland) is approved in several countries worldwide for the treatment of CD in adults to reduce the severity of abnormal head position and associated neck pain [8]. Several randomized controlled trials of onabotulinumtoxinA treatment of patients with CD showed significant decreases from

Abbreviations: CD, cervical dystonia; BoNT, botulinum toxin; MCIC, minimal clinically important change; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; CD PROBE, Cervical Dystonia Patient Registry of OnabotulinumtoxinA Efficacy; PGIC, Patient Global Impression of Change; CGIC, Clinician Global Impression of Change; ROC, receiver operating characteristic; AUC, area under curve

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baseline in TWSTRS scores [9–12]. However, as there is no validated minimal clinically important change (MCIC) for assessment of response to treatment in patients with CD [13], it is unclear whether these differences for onabotulinumtoxinA are clinically relevant.

MCIC has been defined as "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management" [14]. Determination of an MCIC is important for interpreting the clinical relevance to the patient of statistically significant changes observed in clinical trials [15–19]. Knowledge of the MCIC may aid physicians in tailoring treatments to individual patients and can be used to determine sample size calculations in clinical trials [15].

Some previous clinical trials of BoNT for treatment of CD have used a decrease from baseline in the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Total score of ≥10 points and/or ≥30% as a definition of response [20,21], but this definition has yet to be validated as clinically relevant. The Cervical Dystonia Patient Registry for Observation of OnaBotulinumtoxinA Efficacy (CD PROBE) was a prospective, observational, multicenter clinical registry that demonstrated safety and effectiveness of onabotulinumtoxinA following up to 3 treatment cycles in patients with CD [22,23]. In this secondary analysis, data from CD PROBE were used to determine an MCIC benchmark for change in TWSTRS Total score based on the Patient Global Impression of Change (PGIC) as an anchor measure. In addition, the change in TWSTRS Total score based on the Clinician Global Impression of Change (CGIC) was calculated.

2. Methods

2.1. Study design and patients

CD PROBE was an observational, multicenter, prospective clinical registry designed to capture real-world practices and outcomes for the use of onabotulinumtoxinA in treatment of CD in the United States (ClinicalTrials.gov identifier: NCT00836017). The study protocol was reviewed by institutional review boards, and informed consent was obtained for each subject prior to initiating the study. The methods of CD PROBE have been fully described in a previous publication [23] and are summarized briefly here.

A total of 1046 patients were recruited from 88 sites in the US, between January 12, 2009 and August 31, 2012, with 1041 patients attending the baseline visit and 502 patients completing the 3-treatment follow-up and final assessment. To be eligible for inclusion, patients diagnosed with CD and identified by their physician as being a suitable candidate for BoNT therapy had to meet at least one of the following criteria: be new to the principal physician's practice, be new to BoNT therapy, and/or if the patient had previously been exposed to a BoNT in a clinical trial, not have received BoNT for ≥16 weeks.

2.2. Treatments and follow-up visits

Patients received up to 3 onabotulinumtoxinA treatments: at baseline/visit 1, visit 2, and visit 3. Treatment was at full discretion of the physician, with drug dilution, dosing, and muscles injected all subject to real-world variability depending on patient response and the treating physician's standard care, thereby allowing individualization of doses by the third treatment cycle. Phone interviews were conducted 4 to 6 weeks post-injection, and the time to the next treatment was variable and determined by the physician. Visit 4 was a follow-up visit only and did not include any treatment with onabotulinumtoxinA (Fig. 1).

2.3. Outcomes

The objective of this secondary analysis was to use CD PROBE data to establish an MCIC based on TWSTRS assessments compared with PGIC and CGIC ratings. Changes from baseline TWSTRS score and subscores were compared with the anchor measures of the achievement of clinical improvement as assessed by the patient (PGIC) and clinician (CGIC). Results were then compared with the definition of response used in previously published trials (a decrease from baseline in TWSTRS Total score of ≥10 points and/or ≥30%) [20,21].

2.4. Assessments

A range of effectiveness assessments was used to verify an improvement in outcome. They included the TWSTRS Total and subscores, the PGIC and the CGIC.

TWSTRS Total (scored 0–85), composed of the Severity (0–35), Disability (0 − 30), and Pain (0 − 20) subscales, is a validated, disease-specific scale in which higher scores indicate greater impairment [24]. It is commonly used in clinical trials of BoNT for the treatment of CD [25,26].

The PGIC enables the patient to rate changes in their perception of their general health status over the duration of the assessment via a 7-point scale ranging from "very much improved" to "very much worse" [27]. Similarly, the CGIC is a 7-point scale ranging from "very much improved" to "very much worse" [28] based on the physician's perception of the patient's health status.

2.5. Statistical analyses

Statistical analysis of a subpopulation of patients with complete data for each TWSTRS assessment point was undertaken (n = 479). Analysis was also undertaken on a subset of patients that excluded those with the less common and more difficult to treat CD patterns of anterocollis and retrocollis.

To determine the MCIC for the TWSTRS scale, an anchor-based approach was utilized with the PGIC and CGIC as anchors. Receiver operating characteristic (ROC) analyses, based on the method of Farrar et al. [29], were undertaken with logistic regression model statistics at the optimal cutoff point. The optimal cutoff is the logistic regression model-based logit value that minimizes the difference between sensitivity and specificity for TWSTRS values and subscores. Once determined, the logit value is then transformed back to the appropriate score change scale (either a point change or percent change scale depending on the analysis being undertaken) and then compared with the PGIC or CGIC ratings.

Under the logistic regression model, if the percentage of TWSTRS scores or subscores that were classified correctly (Supplementary Table 1) based on the PGIC or CGIC ratings was ≥70%, it was considered to have a good level of discrimination. If the area under the curve (AUC) was ≥0.7 and < 0.8, the model was considered to have acceptable discrimination; if ≥0.8 to < 0.9, discrimination was excellent; and if the AUC was ≥0.9, the discrimination of the model was deemed outstanding [30].

3. Results

3.1. Patient disposition, demographics, and characteristics

The patient characteristics and primary results of CD PROBE have been previously published [22] and will be described briefly. Of the 1046 patients enrolled, 636 (60.8%) completed all treatment sessions and 502 completed all four visits (including the final assessment). Over the study, the most common reasons for withdrawal were loss to follow-up (243 patients, 23.2%), withdrawal of consent (95 patients, 9.1%) and lack of response (85 patients, 8.1%). Among those patients who completed the first treatment session and reported whether or not they had previously received BoNT therapy (n = 1041), the mean age was 58.0 years, and 74.4% of patients were women.

The majority of patients (63.5%) were BoNT-naïve at baseline, and

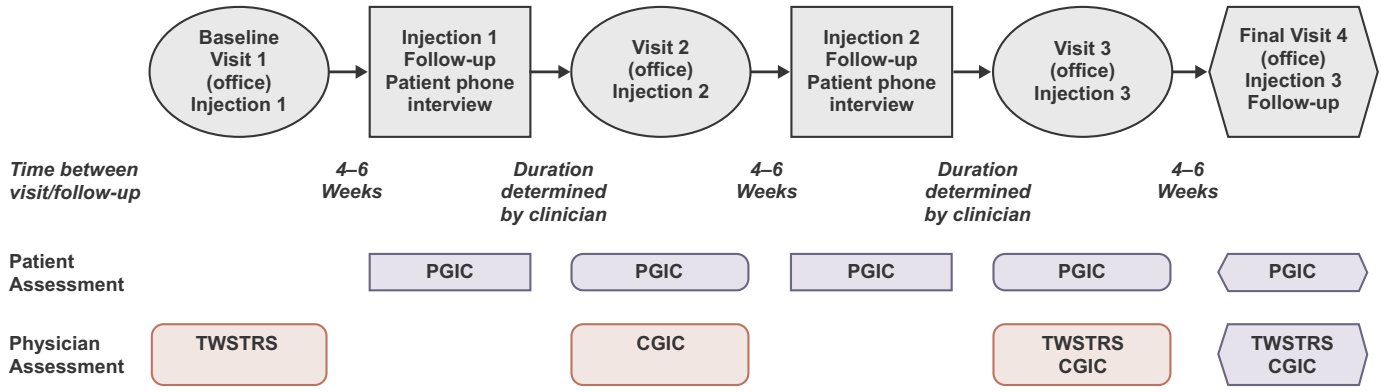

Fig. 1. CD PROBE study design and assessments. CGIC = Clinician Global Impression of Change; PGIC = Patient Global Impression of Change; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale. Adapted from Jankovic J, Adler CH, Charles PD, et al. Rationale and design of a prospective study: Cervical Dystonia Patient Registry for Observation of OnaBotulinumtoxinA Efficacy (CD PROBE). BMC Neurol 2011;11:140.

66.8% had moderately severe or severe disease. The predominant CD pattern was torticollis (47.5%), followed by laterocollis (38.9%), anterocollis (5.7%), and retrocollis (5.3%).

The mean (SD) number of injections given per patient over the 3 visits was 9.3 (5.7), with a total of 4.1 (1.4) muscles injected per treatment (most frequently in the splenius capitis, sternocleidomastoid, levator scapulae, and/or trapezius). Injection guidance was typically by electromyography (73.3%).

3.2. Outcomes

Across the 479 patients who completed all TWSTRS assessments, the mean TWSTRS Total score significantly decreased from 39.2 at baseline to 27.1 at the final visit ($P < .0001$). For both PGIC and CGIC, in the subset of patients that completed all TWSTRS assessments, there were significantly higher percentages of patients and physicians reporting improvement at the final visit compared to the first post-treatment assessment (PGIC: 91.7% vs. 83.0%; CGIC: 95.0% vs. 91.2%; both $P < .0001$).

3.3. MCIC in TWSTRS based on patient-reported outcomes

As the point change from baseline in TWSTRS scores improved (ie, larger decreases), the probability of achieving improvement in the PGIC rating increased (Fig. 2A, Supplementary Fig. 1A–C). Similarly, as the percentage change in TWSTRS scores improved, so, too, did the probability of achieving an improvement in the PGIC rating (Fig. 2A, Supplementary Fig. 1D–F).

3.3.1. Association using logistic regression

The association between the changes in TWSTRS (Total and subscales) and PGIC ratings from baseline to the final visit using logistic regression is presented in Fig. 3A and Table 1. The point changes in TWSTRS Total score that correlated with "very much improved" or "much improved" or better or "minimally improved" or better on the PGIC assessment were −11, −9 and −8, respectively, and were similar to the changes previously required (ie, a decrease of ≥10 points) by other investigators to demonstrate a meaningful clinical response [20,21]. The mean percentage changes in the TWSTRS Total score to achieve a "very much improved", "much improved" or better, or "minimally improved" or better were −27.12%, −21.21% and −19.1%, respectively.

The data for TWSTRS Total scores met indicators of good cutoffs for discrimination of the model including ≥70% percentage of outcomes correctly classified when compared with PGIC ratings. Using the point change in TWSTRS, 79.3% of outcomes were correctly classified based on "very much improved" and 72.3% outcomes were correctly classified based on "much improved" or better. Based on PGIC ratings of "minimally improved" or better, neither the point change nor the percentage change in TWSTRS Total score met the cutoff for discrimination of the model with respect to the percentage correctly classified (66.0% and 67.4%, respectively); however, both had acceptable discrimination based on AUC values of 0.723 and 0.746 (Table 1), respectively.

The TWSTRS subscales were, in general, less useful than the TWSTRS Total scale, with the Severity subscale being the least useful of the three subscales (Fig. 3A). Although the AUC values were in the acceptable range for all three subscales for the PGIC rating of "very much improved," the percentages correctly classified were ≥70% for only the Disability and Pain subscales.

3.3.2. Exploratory analyses

Exploratory analyses were undertaken to determine if the MCIC was skewed by any particular subgroup of patients. When analysis was undertaken excluding patients with the less common patterns of CD (ie, anterocollis and retrocollis) [$n = 397$], there was a slight decline in the percentage of patients that were correctly classified (Supplementary Table 2). Similarly, when PGIC ratings were limited to the mutually exclusive categories of "much improved" only ($n = 186$) and "minimally improved" only ($n = 129$), there was no improvement in the percentage of patients that were correctly classified nor was the potential definition of the MCIC improved (Supplementary Table 3).

MCIC analyses were not carried out to compare the patients who were BoNT-naïve and non-naïve at baseline since the data for the PGIC, CGIC, and TWSTRS are very similar in both groups as well as to those of the overall population (Supplementary Table 4). Thus, the MCIC in these subgroups would likely be similar to the one calculated for the overall population. In addition, baseline TWSTRS scores were similar in the overall, BoNT-naïve, and non-naïve population, suggesting that patients in all of these groups responded similarly to treatment.

3.4. Change in TWSTRS based on clinician-reported outcomes

As the point change or percentage change from baseline in TWSTRS scores improved, the probabilities of achieving improvement on the CGIC rating increased (Supplementary Fig. 2). The point changes in TWSTRS Total score that correlated with "very much improved" or "much improved" or better or "minimally improved" or better on the CGIC assessment were −10, −8, and −7, respectively (Table 2). Greater mean improvements from baseline on the TWSTRS scores were needed to achieve "very much improved" ($n = 139$; −19.5 points) on the CGIC ratings than to achieve "much improved" ($n = 217$; −12.0 points) or "minimally improved" ($n = 98$; −4.6 points).

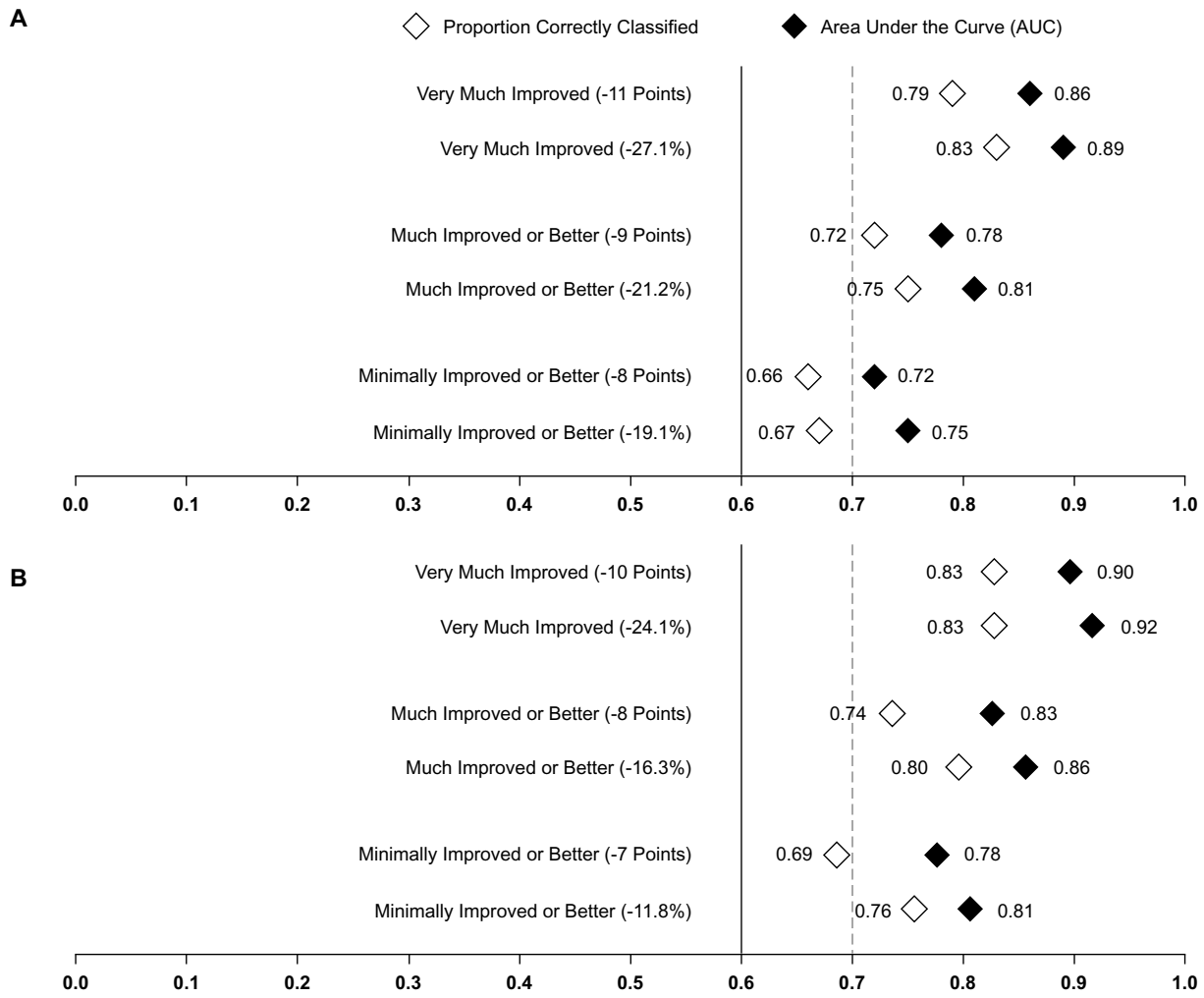

Fig. 2. The proportion of TWSTRS total scores correctly classified by A) PGIC* and B) CGIC† scales by point change and percentage change, and the discrimination of the model as measured by AUC of the logistic regression model (dashed line). AUC = area under the curve; CGIC = Clinician Global Impression of Change; PGIC = Patient Global Impression of Change; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale.
*PGIC: Very Much Improved, n = 121; Much Improved or Better, n = 307; Minimally Improved or Better, n = 436.
†CGIC: Very Much Improved, n = 139; Much Improved or Better, n = 356; Minimally Improved or Better, n = 454.

3.4.1. Association using logistic regression

The association between the changes in TWSTRS (Total and subscales) scores and CGIC ratings from baseline to final visit using logistic regression is presented in Fig. 2B and Table 2.

Across the TWSTRS Total and subscales, in general, the percentages correctly classified were greater and the AUC values larger for CGIC than those observed using the PGIC (see Fig. 3B). For all three subscale scores (Severity, Disability and Pain) the TWSTRS correlated well with a "very much improved" outcome rating on the CGIC, with key discriminators indicating a good model.

4. Discussion

The MCIC is an important concept as it captures both the magnitude of improvement and the value placed on the change by the patient [31]. This secondary analysis of CD PROBE data found that the improvement in TWSTRS Total score in patients with CD, as defined by mean change in patients rated "very much improved" on the PGIC and CGIC (−11 and −10 points, respectively), compared well with the previously published, unvalidated definition of clinical response (ie, a decrease of ≥10 points and/or ≥30% from baseline) [20,21]. The MCIC for improvement in TWSTRS Total score in patients with CD, as defined by mean change in patients rated "minimally improved" or better on the PGIC and CGIC was −8 and −7 points, respectively. The TWSTRS Pain and Disability subscales had a higher level of association with the PGIC and CGIC ratings than did the Severity subscale and could possibly have driven the association between the TWSTRS Total score and clinical improvements. This finding could suggest that indirect manifestations of disease may be relatively more important in the patients' and physicians' assessments of response to treatment than the direct motor manifestations of disease. The association between TWSTRS (a physician-assessed measure) and PGIC (a patient-based evaluation) is probably more clinically relevant than the association between TWSTRS and CGIC, since TWSTRS and CGIC are both clinician-based evaluations. Nevertheless, the values obtained using the PGIC or CGIC as anchors were similar.

One of the strengths of CD PROBE is that it is a large clinical registry of prospectively followed patients with CD in a real-world setting. The sample of patients in this cohort demonstrates the full clinical heterogeneity of patients with CD. Exploratory analyses that removed those patients with the less common and more difficult to treat patterns of CD (ie, anterocollis and retrocollis) showed similar associations between TWSTRS and PGIC as observed in the overall CD group, further suggesting that a decrease in TWSTRS score of ≥8 points after 3 onabotulinumtoxinA treatment cycles is a useful determinant of MCIC in clinical practice in patients with CD.

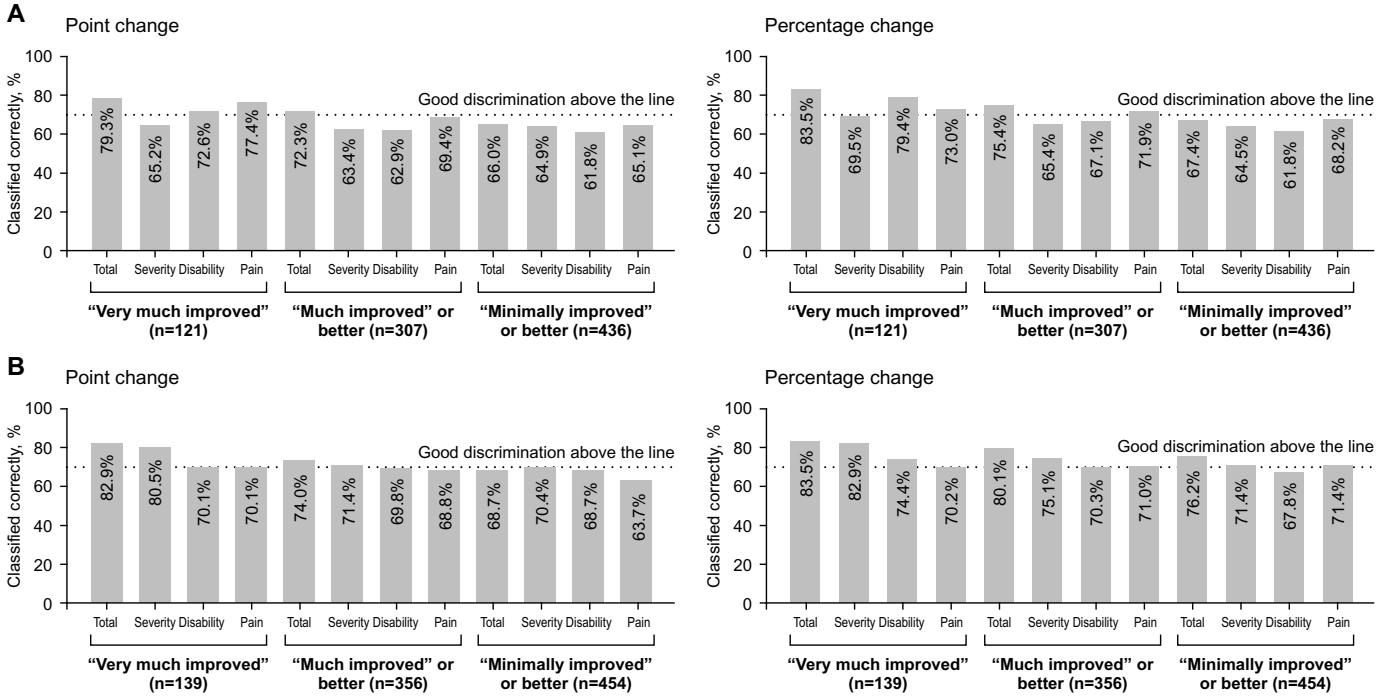

Fig. 3. Percentage of patients correctly classified by point and percentage change on TWSTRS Total and Subscale scores versus A) PGIC and B) CGIC. CGIC = Clinician Global Impression of Change; PGIC = Patient Global Impression of Change; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale.

There are limitations of this analysis. The observational study design led to variability in the timing of assessments following onabotulinumtoxinA treatment. This variability was due to a number of factors, including physician discretion and patient availability, and may have had an effect on response reported. Furthermore, 539 of the 1041 patients did not complete the final clinic visit and assessment for a

Table 1
Changes in TWSTRS (Total and Subscales) compared to each category of change in PGIC from baseline to final visit (N = 479)[a]

	Change output	Area under curve	Mean change in TWSTRS score	Sensitivity	Specificity	Correctly classified, %
Change in TWSTRS total						
"Very much improved"	Point change	**0.860**	−11.00	0.80	0.77	**79.3**
	% change	**0.893**	−27.12	0.83	0.84	**83.5**
"Much improved" or better	Point change	**0.783**	−9.00	0.72	0.72	**72.3**
	% change	**0.810**	−21.21	0.76	0.74	**75.4**
"Minimally improved" or better	Point change	**0.723**	−8.00	0.66	0.67	66.0
	% change	**0.746**	−19.05	0.67	0.67	67.4
Change in TWSTRS severity						
"Very much improved"	Point change	**0.714**	−6.00	0.64	0.67	65.2
	% change	**0.748**	−28.00	0.69	0.70	69.5
"Much improved" or better	Point change	0.677	−5.00	0.63	0.65	63.4
	% change	**0.714**	−25.00	0.65	0.65	65.4
"Minimally improved" or better	Point change	0.644	−4.00	0.65	0.60	64.9
	% change	0.678	−21.05	0.64	0.65	64.5
Change in TWSTRS disability						
"Very much improved"	Point change	**0.803**	−3.00	0.74	0.70	**72.6**
	% change	**0.846**	−26.92	0.80	0.79	**79.4**
"Much improved" or better	Point change	**0.723**	−3.00	0.62	0.70	62.9
	% change	**0.742**	−22.22	0.67	0.67	67.1
"Minimally improved" or better	Point change	0.666	−2.00	0.62	0.60	61.8
	% change	0.674	−15.38	0.62	0.62	61.8
Change in TWSTRS pain						
"Very much improved"	Point change	**0.811**	−3.00	0.77	0.79	**77.4**
	% change	**0.781**	−40.00	0.73	0.74	**73.0**
"Much improved" or better	Point change	**0.739**	−2.00	0.70	0.67	69.4
	% change	**0.710**	−25.00	0.72	0.71	69.4
"Minimally improved" or better	Point change	**0.705**	−2.00	0.65	0.67	71.9
	% change	0.674	−18.75	0.68	0.68	68.2

Abbreviations: PGIC = Patient Global Impression of Change; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale.
Values in bold met the indicators of good cutoffs for discrimination of the model: area under curve ≥0.7 or percentage correctly classified ≥70%.
[a] Of the 479 patients, 43 patients were assessed on the PGIC rating as no change or worse; 129 patients were "minimally improved"; 186 patients were "much improved"; 121 patients were "very much improved"; 436 patients were "minimally improved" or better; and 307 patients were "much improved" or better.

Table 2
Changes in TWSTRS compared with each category of change in CGIC from Baseline to Final Visit (N = 479)[a]

	Change output	Area under curve	Mean change in TWSTRS score	Sensitivity	Specificity	Correctly classified, %
Change in TWSTRS total						
"Very much improved"	Point change	**0.903**	−10.00	0.83	0.84	**82.9**
	% change	**0.924**	−24.14	0.83	0.84	**83.5**
"Much improved" or better	Point change	**0.835**	−8.00	0.74	0.76	**74.0**
	% change	**0.857**	−16.28	0.80	0.80	**80.1**
"Minimally improved" or better	Point change	**0.784**	−7.00	0.69	0.72	68.7
	% change	**0.806**	−11.76	0.76	0.76	**76.2**
Change in TWSTRS severity						
"Very much improved"	Point change	**0.845**	−4.00	0.81	0.76	**80.5**
	% change	**0.865**	−21.05	0.83	0.84	**82.9**
"Much improved" or better	Point change	**0.784**	−4.00	0.71	0.76	**71.4**
	% change	**0.798**	−16.67	0.75	0.72	**75.1**
"Minimally improved" or better	Point change	**0.741**	−3.00	0.71	0.64	**70.4**
	% change	**0.754**	−14.81	0.71	0.72	**71.4**
Change in TWSTRS disability						
"Very much improved"	Point change	**0.812**	−3.00	0.70	0.72	**70.1**
	% change	**0.829**	−25.00	0.74	0.76	**74.4**
"Much improved" or better	Point change	**0.762**	−2.00	0.70	0.72	69.8
	% change	**0.776**	−15.38	0.70	0.72	**70.3**
"Minimally improved" or better	Point change	**0.719**	−1.00	0.69	0.60	68.7
	% change	**0.726**	−10.00	0.68	0.68	67.8
Change in TWSTRS pain						
"Very much improved"	Point change	**0.766**	−3.00	0.70	0.72	**70.1**
	% change	**0.741**	−31.25	0.70	0.71	**70.2**
"Much improved" or better	Point change	**0.728**	−2.00	0.69	0.64	68.8
	% change	**0.712**	−25.00	0.71	0.71	**71.0**
"Minimally improved" or better	Point change	**0.701**	−2.00	0.64	0.64	63.7
	% change	0.684	−14.29	0.71	0.71	**71.4**

Abbreviations: CGIC = Clinician Global Impression of Change; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale.
Values in bold met the indicators of good cutoffs for discrimination of the model: area under curve ≥0.7 or percentage correctly classified ≥70%.
[a] Of the 479 patients, 25 patients were assessed on the CGIC rating as no change or worse; 98 patients were "minimally improved"; 217 patients were "much improved"; 139 patients were "very much improved"; 454 patients were "minimally improved" or better; and 356 patients were "much improved" or better.

range of reasons, including 117 patients (11.2%) who dropped out due to lack of clinical response or adverse events [22]. Therefore, those 502 patients remaining at the final visit are arguably those most likely to have had a positive response to therapy, potentially limiting the ability of the study to fully discriminate a meaningful MCIC. As a result, the size of the group assessed as "no change" or "worse" by the PGIC (n = 43) or CGIC (n = 25) was small, limiting our ability to compare the "minimally improved" and "much improved" groups and draw more robust conclusions. Due to limitations of the study design, with TWSTRS scores only being determined at baseline, at the time of the third onabotulinumtoxinA treatment and then at 4 to 6 weeks after treatment 3 (when doses may have been optimized for an individual patient to assess the "peak effect" of treatment), it is not possible to analyze the MCIC at an earlier time point before patients withdrew from the study. A larger study assessing the association between TWSTRS scores and PGIC and CGIC after each treatment may be helpful to more fully further discriminate the MCIC for patients with CD.

The subjective nature of PGIC/CGIC ratings could introduce bias that may affect the widespread applicability of the results of this study. Patients, especially, may have difficulty understanding the context of "improvement" [32]. Nonetheless, the use of the PGIC ratings introduces a real-world applicability that should not be overlooked. Recall bias may also influence the outcomes observed, particularly in terms of the PGIC ratings. For example, the current health status of the patient can have an impact upon their recollection of the past [31]. Further, the shorter average treatment intervals of 14.6 weeks between the first and second injection and 15.1 weeks between the second and third injection [22] may impact a patient's accurate recall. Nevertheless, improvements from baseline in the PGIC were observed at each timepoint [25].

It should also be noted that MCIC may vary depending on several factors, including the study population, effectiveness of the intervention, duration of evaluation period, presence or absence of a placebo control group, inclusion of an objective external anchor/criterion, and the analytical method employed [15]. While this manuscript was in review, another paper reported an MCIC of −11.9 for TWSTRS in patients with CD who rated as minimally improved on the PGIC [33]. In contrast, patients in CD PROBE achieved improvement in PGIC with a smaller change (−8) in the TWSTRS Total score. Although there were many similarities between the two studies (age at baseline, age at symptom onset, treatment patterns at the discretion of the physician, number of muscles injected, changes from baseline in TWSTRS scores), key differences between this and the present analysis include a somewhat higher baseline TWSTRS Total score (43.4 vs. 39.2 in CD PROBE), differences in the timing of treatments and assessments (4 weeks following the first treatment vs. 4–6 weeks following the third treatment), lower percentages of those who achieved minimally improved or better on the PGIC (77.8% vs. 83.0%), and exclusivity of the groups (minimally improved vs. minimally improved or better). Lower numbers of patients were analyzed in every PGIC category compared with CD PROBE, especially in the much or very much improved categories (very much improved, n = 35 vs. n = 121; much improved, n = 99 vs. n = 186; minimally improved, n = 103 vs. n = 129; and no change or worse, n = 32 vs. n = 43, respectively). It is also important to note that each study used a distinct BoNT formulation (abobotulinumtoxinA compared with onabotulinumtoxinA in CD PROBE) and that these are not interchangeable [34]. Different methodologies were used in each analysis, with the present analysis utilizing an anchor-based ROC analysis with logistic regression and the other an ordinary least squares regression analysis. However, despite these different methods, the calculated MCIC values for minimal improvement in PGIC were not radically different. Nevertheless, further study is required to fully validate the applicability of TWSTRS as an indicator of MCIC in patients with CD.

Finally, it should be noted that the outcome measures used do not capture whether perceived improvements during treatment are large enough to outweigh costs, potential adverse effects, and/or inconveniences of therapy to the patient [16]. These are important considerations that need further investigation.

5. Conclusions

Using the definition of MCIC as a decrease from baseline in TWSTRS Total score of ≥10 points and/or ≥30% as previously described in double-blind clinical trials of BoNT [20,21], 58% (280/479) of patients in CD PROBE achieved an MCIC during treatment with onabotulinumtoxinA. Based on at least a minimal improvement reported for the PGIC, a decrease from baseline in TWSTRS Total score of ≥8 points was identified as the MCIC using CD PROBE data, and more closely aligned with patient's or physician's impression of clinical outcome than a ≥30% decrease in TWSTRS from baseline. Using this definition, 62.8% (301/479) of patients in CD PROBE achieved an MCIC during treatment with onabotulinumtoxinA. However, it must be recognized that there was a high level of patient dropout during the CD PROBE study potentially causing selection bias favoring positive outcomes.

Although additional studies are needed for further validation, this information may be useful for interpreting TWSTRS scores, either for individual patients or for groups of patients in clinical trials, as well as for planning new trials in CD.

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Appendix A. Supplementary data

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