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Outcomes of Onabotulinum Toxin A Treatment for Adductor Spasmodic Dysphonia and Laryngeal Tremor

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[+] Supplemental content

IMPORTANCE The relative outcomes of onabotulinum toxin A injections for treatment of adductor spasmodic dysphonia (ADSD), ADSD with lateral laryngeal tremor (ADSD+LT), and lateral LT without ADSD are unclear.

OBJECTIVE To compare the outcomes of onabotulinum toxin A treatment on ADSD, ADSD+LT, and lateral LT without ADSD.

DESIGN, SETTING, AND PARTICIPANTS A retrospective cohort study was conducted from January 1, 1990, to September 30, 2016, at a tertiary referral voice center. Participants included 817 patients treated with onabotulinum toxin A injections for diagnosis of ADSD, ADSD+LT, and lateral LT without ADSD.

EXPOSURE Injection of onabotulinum toxin A into the thyroarytenoid/lateral cricoarytenoid muscle complex.

MAIN OUTCOMES AND MEASURES Data from patient diaries were used to evaluate patient-perceived effectiveness of onabotulinum toxin A injection. Primary outcomes were (1) patient-reported good voice days (voice breaks or tremor minimized to patient satisfaction) and (2) percentage of injections in which maximal voice quality was reached (significant or complete reduction in vocal tremor or spasms during a treatment cycle). Multivariate analysis of variance tests compared differences in outcomes between groups. Subanalysis was performed to compare outcomes in patients with isolated LT with those who had mixed tremor (lateral with concomitant anterior-posterior and/or vertical components).

RESULTS Of 817 patients treated with onabotulinum toxin A injections for laryngeal movement disorders, 548 patients (12 771 injection sessions) met inclusion criteria (ADSD: n = 328, ADSD+LT: n = 77, lateral LT without ADSD: n = 143). Of these, 408 (80.8%) were women; mean (SD) age was 57.2 (13.7) years. Among patients with tremor, those with isolated LT had better outcomes than those with mixed tremor. In adjusted analysis, good voice days in patients with ADSD, ADSD+LT, and lateral LT without ADSD were 81.1, 75.4, and 71.3 days, respectively (partial η^2, 0.05; 95% CI, 0.01-0.09). The percentage of maximally beneficial injections was 88.1% for ADSD, 83.4% for ADSD+LT, and 70.4% for LT without ADSD (partial η^2, 0.12; 95% CI, 0.06-0.17).

CONCLUSIONS AND RELEVANCE Onabotulinum toxin A injections into the thyroarytenoid/lateral cricoarytenoid muscle complex are an effective treatment for ADSD, ADSD+LT, and LT without ADSD; however, the greatest effectiveness was observed among patients with ADSD. Defining tremor directionality may help to prognosticate the effectiveness of onabotulinum toxin A injection among patients presenting with tremor components.

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aryngeal movement disorders consist of a broad spectrum of diagnoses, including spasmodic dysphonia (SD) and laryngeal tremor (LT).[1] Spasmodic dysphonia is a focal dystonia characterized by adductor (ADSD), abductor (ABSD), or mixed (ADSD+ABSD) spasms of the intrinsic laryngeal muscles during phonation.[2,3] Of these, ADSD is the most common variant (82%-92%) and has been extensively studied.[4-6] Laryngeal tremor is characterized by rhythmic hyperactivity of either the intrinsic or extrinsic laryngeal muscles, resulting in a periodic oscillation of the phonatory apparatus.[1,7-9] Tremor of the intrinsic laryngeal musculature occurs in 26% to 53% of patients with SD.[4,10-12]

Although the cause of these laryngeal movement disorders is unclear, imaging and neuropathologic evidence suggest that tremor originates from cerebellar dysfunction and SD involves basal ganglia–cortical abnormalities.[13,14] Neural dysfunction in both brain regions is present in patients who have combined SD and LT.[15] Studies also reveal differences in age and sex between patients with ADSD, ADSD with LT (ADSD+LT), and LT without ADSD.[3-5,7,12,16-25]

Despite these differences, onabotulinum toxin A is used for treating all of these conditions.[7,26,27] Onabotulinum toxin A has been shown to improve subjective patient outcomes, acoustic factors, perceptual variables, and quality of life in ADSD.[2,6,20,28-32] Although no comparative studies exist, small, noncomparative case series of patients with LT treated with onabotulinum toxin A have shown variable and generally inferior benefits compared with those observed in cases series of patients with ADSD.[7,8,21,22,33,34]

Poorer treatment success in tremor may arise from disease heterogeneity. Variable intralaryngeal and extralaryngeal muscles can be affected, resulting in periodic oscillations in the vertical, anterior-posterior, and/or lateral axes.[1,7-9,35] Although the thyroarytenoid/lateral cricoarytenoid (TA/LCA) muscle complex has been shown to be the most commonly affected muscle complex in LT, involuntary movement arising from beyond the muscles of the vocal fold proper have been suggested to contribute to inconsistent efficacy of onabotulinum toxin A treatment.[9,22,35] Based on its directionality and electromyographic findings, it is hypothesized that the LT variant is mediated by the same adductory muscles responsible for ADSD; therefore, onabotulinum toxin A may have comparable outcomes in both conditions.[8,35] The aim of the present study was to compare patient-reported onabotulinum toxin A treatment outcomes between those diagnosed with ADSD, ADSD+LT, and lateral LT without ADSD. In addition, outcomes of treatment between those with isolated lateral type and mixed tremor (MT) variants (lateral with concomitant anterior-posterior and/or vertical components) were compared. Patient-reported outcomes derived from patient diaries were selected because optimizing the patient experience by reducing or eliminating symptoms is the ultimate treatment goal.

Key Points

Question What are the comparative outcomes of onabotulinum toxin A treatment of adductor spasmodic dysphonia, adductor spasmodic dysphonia with lateral laryngeal tremor, and lateral laryngeal tremor without adductor spasmodic dysphonia?

Findings In an adjusted analysis of a cohort study, all 548 patients benefited from onabotulinum toxin A; the mean number of days with a good voice was higher for patients with adductor spasmodic dysphonia (81 days) than for patients with lateral laryngeal tremor with or without adductor spasmodic dysphonia (75 and 71 days, respectively).

Meaning Onabotulinum toxin A is an effective treatment for laryngeal dystonias included in this study. Careful selection of patients with tremor can result in comparable onabotulinum toxin A outcomes to similar patients with adductor spasmodic dysphonia.

dardized phonatory tasks combined with laryngoscopic examination aid in diagnosis. Laryngeal tremors are categorized as lateral, vertical, anterior-posterior, or mixed based on directionality of laryngeal movement (eAppendix 1 in the Supplement). All tremors identified in medical records review were confirmed by rereviewing each patient's laryngoscopy findings (P.N.P., J.C.S., C.G.G., and D.O.F.), and at least 2 investigators confirmed the tremor directionality. Isolated lateral LTs were recognized as repetitive rhythmic medial compression of the true and/or false vocal folds during phonation without evidence of anterior-posterior or vertical components. Injection of onabotulinum toxin A into the TA/LCA muscles for ADSD and LT is predicated on these movement disorders being actuated by these muscles.[8,22] Thus, only tremors with a lateral component that involve intrinsic adductory laryngeal muscles are considered candidates for onabotulinum toxin A treatment at our center.

This retrospective cohort study was performed in accordance with the Declaration of Helsinki,[36] Good Clinical Practice, and applicable regulatory requirements. The Vanderbilt University Medical Center Institutional Review Board approved this study with waiver of informed consent.

Inclusion and Exclusion Criteria

Patients diagnosed with and undergoing onabotulinum toxin A treatment for ADSD, ADSD+LT, LT without ADSD, and MT between January 1, 1990, and September 30, 2016, were included and followed up over time. Patients with ABSD and mixed SD (ADSD+ABSD) were excluded. Only patients with 3 or more treatment visits were included. Patients who failed to prospectively complete their treatment diaries were systematically queried during their intake by voice-specialized speech-language pathologists regarding voice quality over the previous injection period.

Treatment Approach

At treatment visits, patients undergo injection of reconstituted lyophilized onabotulinum toxin A into the unilateral or bilateral TA/LCA muscle complex with a hollow-bore, 27-gauge Teflon-coated electromyography needle (Allergan Pharmaceuticals). Electromyography guidance has been previously described.[6,20]

Methods

Diagnostic Approach

On initial evaluation, laryngologists and voice-specialized speech-language pathologists collaboratively examine each patient. Stan-

Injection dosing and laterality are adjusted based on diary-derived, patient-reported outcomes and preferences with the shared goal of optimizing time of good voice and minimizing the breathy period or swallowing adverse effects. Specifically, the diary asks patients to grade the severity of voice breaks (0, no symptoms to 5, voice spasms present 100% of the time) and tremor severity (0, no tremor to 4, can hardly talk) (eAppendix 2 in the Supplement). After each onabotulinum toxin A injection, patients maintain this diary of voice outcomes.

Outcomes

Patients have been consistently recording outcomes using the same diary system since 1990. Certified speech-language pathologists review patient-reported outcomes from the diary with each patient during preinjection interviews. These values are entered into the patient medical records at every onabotulinum toxin A visit. Two patient-reported voice outcomes were extracted for this study.

Good Voice Days

Three phases of voice changes occur after each onabotulinum toxin A injection (**Figure 1**). The first phase is characterized by a variable period of suboptimal voice (eg, breathy, rough) ranging from 0 days to several weeks. In the second phase, patients typically experience a plateau of good voice in which voice breaks and tremor are minimized. Good voice days are a patient-reported outcome derived directly from diaries and enumerate the number of days that a patient perceived his or her voice to be significantly improved. For tremor, we defined good voice days as days when there was no or mild tremor (ie, values 0 and 1) and bad voice days (ie, values 2, 3, and 4) on the 5-point tremor scale (eAppendix 2 in the Supplement). For ADSD, good voice days were considered those without any symptoms or symptoms less than 50% of the time involving voice spasms with complete understanding of speech by others (0 and 1 on a 6-point scale) (eAppendix 2 in the Supplement). For combined ADSD and tremor, good voice days required 0 and 1 on both scales. The third phase involves the declining quality and gradual return of voice breaks and tremor that become noticeable by the patient. Poor voice in phases 1 and 3 can represent significant proportions of each treatment cycle.[32] The patient-reported duration of phase 2 (good voice days) was used as a primary outcome.

Percentage of Injections With Maximal Voice Quality

Patients self-report in diaries whether they achieved optimal voice quality after each injection, defined as no discernable tremor or voice spasms for any duration of time (even if short) within phase 2: rating of 0 on either tremor or ADSD scale (eAppendix 2 in the Supplement). This outcome was extracted for each patient injection, and the percentage of injections with maximum voice quality was calculated (eg, 30 injection sessions with maximum obtained / 40 total sessions ×100 = 75%).

Variables Collected

Medical record data extraction was performed by an investigator and confirmed by a second independent investigator to ensure data accuracy. Extracted were the described outcomes, patient characteristics (ie, age, sex, race/ethnicity, and active tobacco

Figure 1. Phases of Onabotulinum Toxin A Treatment Cycle and Voice Quality
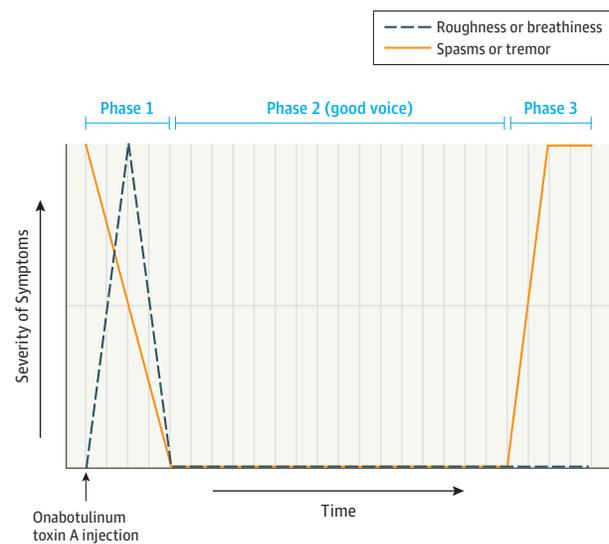
Phase 1, variable period of suboptimal voice (eg, breathy, rough) immediately after onabotulinum toxin A injection with decreasing or reduced tremor or spasms; phase 2, plateau of good voice in which voice breaks and tremor are reduced or eliminated (primary study outcome); and phase 3, gradual return of voice breaks and tremor.

and alcohol use at the start of treatment), and treatment variables (ie, dosing, laterality [right/left/bilateral], and number of injection sessions).

Statistical Analysis

Variables were checked for outliers and erroneous values, updated where necessary, and analyzed using SAS, version 9.4 (SAS Institute). We calculated descriptive statistics for patients with ADSD, ADSD+LT, and LT alone with regard to hypothesized potential confounders and clinical characteristics. We tested for the significance of differences across disease groups using analysis of variance for continuous variables and the χ^2 test for categorical variables. A similar comparison was made between patients with LT and those with MT.

Next we used analysis of variance to test whether the diagnosis at patient presentation is associated with differences in onabotulinum toxin A treatment outcomes (ie, the number of good voice days and the percentage of injections resulting in maximum voice benefit) and estimate the effect size for onabotulinum toxin A treatments. In these analyses, we sequentially adjusted for potential confounders. The first model adjusted for age at initiation of onabotulinum toxin A treatment, sex, and race/ethnicity. The second model additionally adjusted for the number of injections and injection interval, and the third model further adjusted for current smoking, alcohol use, and employment status. To control for multiple comparisons, the Tukey-Kramer test was used to adjust P values from between-group comparisons. We estimated partial η^2 and a corresponding 95% CI as a measure of effect size for onabotulinum toxin A treatment

Figure 2. Study Flow Diagram With Inclusions and Exclusions
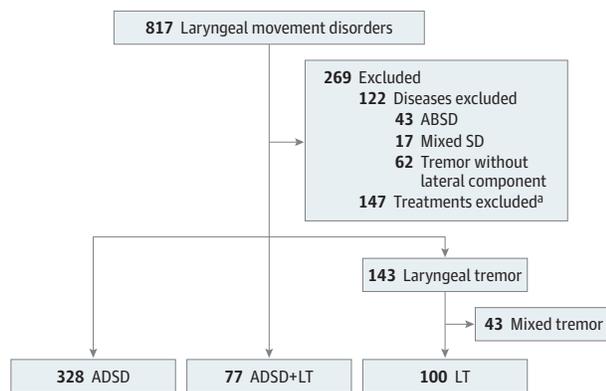
ABSD indicates abductor spasmodic dysphonia; ADSD, adductor spasmodic dysphonia; mixed SD, ADSD+ABSD; mixed tremor, combination of lateral and vertical and/or anteroposterior tremor; ADSD+LT, adductor spasmodic dysphonia with lateral laryngeal tremor.

[a] Patients with fewer than 3 injections and lack of follow-up. There is overlap between these factors (eg, patient may have received only 1 injection and did not return for follow-up).

and computed adjusted means and corresponding 95% CIs for patients with ADSD, ADSD+LT, and lateral LT. The effect size, as measured by η^2 value, is interpreted as small, approximately 0.02; medium, approximately 0.13; and large, approximately 0.26. Differences in means at a 2-tailed, unpaired P value ≤.05 were considered statistically significant. It was not possible to perform adjusted analysis for the comparison between LT and MT given insufficient statistical power.

Results

In all, 817 patients were treated for laryngeal movement disorders (16 512 injection sessions), of which 548 patients with ADSD (n = 328), ADSD+LT (n = 77), and LT without ADSD (n = 143) met the inclusion criteria (12 771 injection sessions) (Figure 2). Patients with lateral LT without ADSD were divided into LT (n = 100) and MT (eg, lateral and vertical directionality; n = 43) cohorts.

Directionality of Tremor

In preliminary analysis, the mean number of good voice days was greater in patients with lateral LT compared with those with MT. The mean difference in the number of good voice days was 11.3 (95% CI, −1.0 to 23.5), the mean being 72.7 (95% CI, 61.2 to 84.2) days for LT and 61.4 (95% CI, 46.9 to 75.9) days for the MT group. The mean percentage of injections in which maximal voice quality was achieved was higher for the lateral LT group (65.5%; 95% CI, 52.3% to 79.3%) than the MT group (57.7%; 95% CI, 40.6% to 74.8%), with the mean difference being 8.1% (95% CI, −6.3% to 22.5%). Further analyses included lateral LT and excluded MT.

Patient and Treatment Characteristics

Overall, patients had a mean (SD) age of 57.2 (13.7) years and received 15.7 (11.8) injections, with 121 (35) days between injections.

Most patients were women (408 [80.8%]), white (408 [80.8%]), and employed (55.4%). Patient characteristics varied significantly by the type of movement disorder (Table 1). Patients with ADSD were younger (52.3 years) compared with those with ADSD+LT (63.3 years) or LT (68.6 years). A total of 248 (75.6%) women were in the ADSD group compared with 67 (87.0%) and 93 (93.0%) of those with ADSD+LT and LT, respectively. Patients with lateral LT were treated with lower mean onabotulinum toxin A doses and had fewer injections. The mean number of injections was 19.7 (95% CI, 18.4-20.9) for ADSD, 14.6 (95% CI, 12.0-17.2) for ADSD+LT, and 8.2 (95% CI, 6.0-10.5) injections for LT (η^2 = 0.14; 95% CI, 0.08-0.19). The mean interval between injections did not differ significantly between groups.

Voice Outcomes

The number of good voice days was nonsignificantly higher in ADSD compared with ADSD+LT and LT patients in unadjusted analyses (ADSD, 78.0; ADSD+LT, 74.9; LT, 71.8 days; η^2 = 0.01; 95% CI, 0.0001-0.03) (Table 1). However, in multivariable analyses (Table 2) that adjusted for age, sex, and race/ethnicity differences, patients with ADSD had a higher number of days with a good voice compared with those with ADSD+LT or LT alone (η^2 = 0.02; 95% CI, 0.0004-0.04). These differences remained significant after further adjustment for number of injections, injection interval, smoking, alcohol use, and employment status (η^2 = 0.05; 95% CI, 0.01-0.09) (Table 2). Both unadjusted (Table 1) and adjusted (Table 3) analyses demonstrated that patients with ADSD had a higher percentage of injections in which they attained a maximum benefit (88.1%) compared with ADSD+LT (83.4%) and LT (70.4%; η^2 = 0.12; 95% CI, 0.06-0.17).

Discussion

To our knowledge, this is the first study to directly compare patient-reported outcomes of onabotulinum toxin A for treatment of ADSD, ADSD+LT, and LT. Currently, no standardized protocol exists to measure the effectiveness of onabotulinum toxin A injections in treating voice disorders; therefore, a variety of measures has been used.[37,38] Patient-reported outcomes were used in this study because a patient's self-perceived function is the ultimate measure of treatment success. The 2 patient-reported outcomes used to measure treatment benefit were duration of treatment effect (number of good voice days) and the percentage of injections with maximum voice benefit obtained.

Several differences in treatment characteristics between groups were identified. Patients with lateral LT had the fewest mean number of injections and lowest mean injection dosages. These findings are due to the expanding indications for onabotulinum toxin A during this time. Onabotulinum toxin A treatment of patients with ADSD has been well established at our center since 1990; however, the routine practice of injecting patients with lateral LT has been more recently implemented. Furthermore, refinement in technique over this period has resulted in lowering the starting dosage (eg, from 2.5 to 1.25 units). These 2 factors explain why patients with LT had fewer mean injections and lower mean onabotulinum toxin A dosages.

Table 1. Patient Characteristics at Baseline and Follow-up[a]

Variable	ADSD (n = 328)	ADSD + LT (n = 77)	LT (n = 100)
Age, mean (SD), y	52.3 (13.0)	63.3 (11.5)	68.6 (9.3)
Women, No. (%)	248 (75.6)	67 (87.0)	93 (93.0)
Race/ethnicity, No. (%)			
White	264 (80.5)	64 (83.1)	80 (80.0)
Black	11 (3.4)	4 (5.2)	5 (5.0)
Other	53 (16.2)	9 (11.7)	15 (15.0)
Current smoking, No. (%)	55 (16.9)	2 (3.0)	2 (2.1)
Current alcohol use, No. (%)	143 (43.6)	33 (42.7)	31 (33.7)
Employed, No. (%)	219 (66.8)	31 (39.7)	35 (36.5)
Dose of injection, mean (SD), units			
Left	2.20 (0.92)	2.06 (0.80)	1.72 (0.60)
Right	2.18 (0.87)	2.05 (0.81)	1.69 (0.59)
Injections, mean (SD), No.	19.7 (13.2)	14.6 (9.2)	8.2 (5.4)
Interval between injections, mean (SD), days	120.7 (32.5)	126.3 (38.0)	121.0 (33.4)
Injections reaching maximal quality, mean (SD), No.	90.7 (12.6)	80.9 (23.4)	71.5 (22.3)
Good voice days, mean (SD)	78.0 (25.9)	74.9 (35.9)	71.8 (24.3)

Abbreviations: ADSD, adductor spasmodic dysphonia; LT, lateral laryngeal tremor.

[a] Percentages are variable due to incomplete data resulting in differing denominators.

Table 2. Differences in Duration of Days With a Good Voice Following Treatment With Onabotulinum Toxin A

| Model | Adjusted Mean, % (95% CI)[a] | | | Partial η² (95% CI)[b] |
	ADSD	ADSD + LT	LT	
1[c]	82.6 (77.1-88.0)	76.9 (69.3-84.5)	72.7 (65.4-79.9)	0.02 (0.0004-0.04)
2[d]	80.3 (77.0-83.6)	72.7 (68.1-77.3)	72.3 (67.8-76.9)	0.04 (0.03-0.07)
3[e]	81.1 (77.0-85.3)	75.4 (70.1-80.7)	71.3 (66.2-76.5)	0.05 (0.01-0.09)

Abbreviations: ADSD, adductor spasmodic dysphonia; LT, lateral laryngeal tremor.

[a] Days with a good voice following onabotulinum toxin A treatment.

[b] The effect size, as measured by η² value, is interpreted as small, approximately 0.02; medium, approximately 0.13; and large, approximately 0.26.

[c] Adjusted for age at start of onabotulinum toxin A injections, sex, and race.

[d] Additionally adjusted for number of injections and injection interval.

[e] Further adjusted for smoking, current alcohol use, and employment status.

Table 3. Percentage of Onabotulinum Toxin A Injections That Reached Maximum Effect

| Model | Adjusted Mean, % (95% CI)[a] | | | Partial η² (95% CI)[b] |
	ADSD	ADSD+LT	LT	
1[c]	88.7 (85.3-92.1)	79.1 (74.4-83.8)	69.8 (65.3-74.3)	0.13 (0.08-0.18
2[d]	88.4 (85.1-91.8)	79.4 (74.7-84.1)	71.3 (66.7-75.9)	0.10 (0.06-0.15)
3[e]	88.1 (83.6-92.6)	83.4 (77.7-89.2)	70.4 (64.8-76.0)	0.12 (0.06-0.17)

Abbreviations: ADSD, adductor spasmodic dysphonia; LT, lateral laryngeal tremor.

[a] Onabotulinum toxin A injections with a maximum effect.

[b] The effect size, as measured by η² value, is interpreted as small, approximately 0.02; medium, approximately 0.13; and large, approximately 0.26.

[c] Adjusted for age at start of onabotulinum toxin A injections, sex, and race.

[d] Additionally adjusted for number of injections and injection interval.

[e] Further adjusted for smoking, current alcohol use, and employment status.

Directionality of Vocal Tremor

Prior small, noncomparative case series in which patients with LT were treated with onabotulinum toxin A showed beneficial treatment effects, but these outcomes have been inferior to results for ADSD.[5-7,21,22,30,33,35] Inferior effectiveness has been attributed to muscular involvement beyond the intrinsic adductory laryngeal muscles, which manifests in multiaxial laryngeal motion.[1,7-9,35] It has been suggested that patients with LT would benefit most from onabotulinum toxin A; however, to our knowledge, this hypothesis has yet to be evaluated systematically in a large cohort.

In this study, we found that patients with LT have greater benefit than those with the MT variant. They had a 10-day longer duration of treatment effect and 8% more injections that resulted in maximal voice quality. These findings support the use of a previously described vocal tremor scoring system in which a more favorable treatment outcome is seen in patients when the score given to the true vocal folds was equal or greater to the mean of the scores given to other anatomic laryngeal and pharyngeal sites.[35] In this scoring system, the anatomic localization of tremor to the vocal cords is synonymous with identifying tremor as being of lateral directionality in this study. Patients with MT benefit

from TA/LCA onabotulinum toxin A treatment likely by attenuating any intrinsic adductory muscle contribution. It is postulated that the greater the predominance of the lateral component in patients with MT, the better the treatment effectiveness of onabotulinum toxin A.

Treatment Outcomes

Onabotulinum toxin A proved to be an effective treatment for ADSD, ADSD+LT, and LT but was most effective for patients with ADSD who had a mean of 10 more good voice days than those with LT and 6 more good voice days than patients with ADSD+LT. Similarly, patients with ADSD had more injections after which they obtained maximal quality than patients with either ADSD+LT or LT. However, these findings must be considered from a clinical perspective, as statistical significance and clinical relevance are not equivalent.[39] These data should not be interpreted to mean that onabotulinum toxin A is not an effective treatment for ADSD+LT or LT. The clinical significance of these differences is relatively minor (a few days). Put another way, the mean proportion of time spent with good voice days in treatment cycles (phase 2/overall duration between injections) was similar between ADSD, ADSD+LT, and LT.

Nonetheless, a difference in effectiveness was observed. Although differential effectiveness is likely owing to greater intrinsic adductory muscle contribution to the laryngeal movement disorder, other possible explanations have been advanced. One difference may be divergent pathophysiology between ADSD, ADSD+LT, and LT. Imaging and neuropathologic evidence suggest that the cerebellum and basal ganglia-cortical network are the sites of dysfunction in LT and ADSD, respectively.[13,14] ADSD+LT shares abnormalities at both anatomic sites.[15] Prior data have suggested that, although afferent abnormalities contribute to dystonia and onabotulinum toxin A can alter the excitability of the cortical motor areas in SD, there may not be such an afferent component in the tremor cerebellar outflow pathways.[22,40-42] There may be a reduced therapeutic effect of onabotulinum toxin A in patients with LT and ADSD+LT. It is also possible that age-related changes are more likely to occur in the older tremor population and that preexisting vocal fold atrophy may necessitate lower onabotulinum toxin A doses to minimize adverse effects. If true, these lower doses may reduce treatment effectiveness. It remains unclear whether differential effectiveness can be overcome by the addition of systemic medications (ie, β-adrenergic antagonists, anticonvulsants, and benzodiazepines) that have previously been used alone for LT and ADSD+LT.[43-47]

Another finding is the intermediate voice outcomes of patients with ADSD+LT. Based on epidemiologic and neurophysiologic data, some suggest that this disease entity is a phenotype of dystonia and not tremor.[48] However, our findings of intermediate demographic variables and prior neuroimaging findings showing cerebellar contributions in ADSD+LT suggest that this disease may be a distinct process—in some studies referred to as dystonic tremor—that is on the spectrum of voice disorders that include ADSD and tremor.[15] This possibility is further supported by our findings in which patients with ADSD+LT responded to onabotulinum toxin A with outcomes intermediate to those with ADSD and LT.

Limitations

Several limitations deserve mention. Errors in manual data extraction are possible; however, these errors were minimized with dual and independent extraction. Patient perception of good voice and maximal or optimal voice can differ based on patient expectations and demands. However, standardized scales were used over the 27-year period of this study. Patients are the ultimate arbiters of successful treatment. The clinician obtains a sense of treatment success based on whether patients believed they had achieved optimal voice and a long duration of good voice. Different scales were used to assess SD and LT since the former has voice breaks and the latter has tremor. Although the 2 scales differ in symptoms, only scores of 0 (no symptoms on both scales) or 1 (minimal symptoms on both scales) were used to define maximal voice quality, which was one of the primary outcomes considered. Finally, although the evaluation of rare diseases is difficult and our sample size is relatively small, it is among the largest cohorts of patients with SD and, to our knowledge, is currently the largest sample of patients with vocal tremor reported in the literature.

Conclusions

Onabotulinum toxin A injections into the TA/LCA complex are an effective treatment for ADSD, ADSD+LT, and lateral LT without ADSD; however, the greatest effectiveness was observed among patients with tremor-free ADSD. Defining tremor directionality may help to prognosticate the outcomes of onabotulinum toxin A injection among patients presenting with tremor components.

REFERENCES

1. Merati AL, Heman-Ackah YD, Abaza M, Altman KW, Sulica L, Belamowicz S. Common movement disorders affecting the larynx. *Otolaryngol Head Neck Surg*. 2005;133(5):654-665.

2. Watts C, Nye C, Whurr R. Botulinum toxin for treating spasmodic dysphonia (laryngeal dystonia). *Clin Rehabil*. 2006;20(2):112-122.

3. Tanner K, Roy N, Merrill RM, Sauder C, Houtz DR, Smith ME. Spasmodic dysphonia: onset, course, socioemotional effects, and treatment response. *Ann Otol Rhinol Laryngol*. 2011;120(7):465-473.

4. Patel AB, Bansberg SF, Adler CH, Lott DG, Crujido L. The Mayo Clinic Arizona spasmodic dysphonia experience. *Ann Otol Rhinol Laryngol*. 2015;124(11):859-863.

5. Tisch SH, Brake HM, Law M, Cole IE, Darveniza P. Spasmodic dysphonia: clinical features and effects of botulinum toxin therapy in 169 patients. *J Clin Neurosci*. 2003;10(4):434-438.

6. Blitzer A. Spasmodic dysphonia and botulinum toxin: experience from the largest treatment series. *Eur J Neurol*. 2010;17(suppl 1):28-30.

7. Adler CH, Bansberg SF, Hentz JG, et al. Botulinum toxin type A for treating voice tremor. *Arch Neurol*. 2004;61(9):1416-1420.

8. Gurey LE, Sinclair CF, Blitzer A. A new paradigm for the management of essential vocal tremor with botulinum toxin. *Laryngoscope*. 2013;123(10): 2497-2501.

9. Koda J, Ludlow CL. An evaluation of laryngeal muscle activation in patients with voice tremor. *Otolaryngol Head Neck Surg*. 1992;107(5):684-696.

10. White LJ, Klein AM, Hapner ER, et al. Coprevalence of tremor with spasmodic dysphonia. *Laryngoscope*. 2011;121(8):1752-1755.

11. Kendall KA, Leonard RJ. Interarytenoid muscle Botox injection for treatment of adductor spasmodic dysphonia with vocal tremor. *J Voice*. 2011;25(1):114-119.

12. Blitzer A, Brin MF, Stewart CF. Botulinum toxin management of spasmodic dysphonia (laryngeal dystonia). *Laryngoscope*. 2015;125(8):1751-1757.

13. Louis ED. Linking essential tremor to the cerebellum. *Cerebellum*. 2016;15(3):235-242.

14. Vidailhet M, Grabli D, Roze E. Pathophysiology of dystonia. *Curr Opin Neurol*. 2009;22(4):406-413.

15. Kirke DN, Battistella G, Kumar V, et al. Neural correlates of dystonic tremor. *Brain Imaging Behav*. 2017;11(1):166-175.

16. Lundy DS, Lu FL, Casiano RR, Xue JW. The effect of patient factors on response outcomes to Botox treatment of spasmodic dysphonia. *J Voice*. 1998;12(4):460-466.

17. Payne S, Tisch S, Cole I, Brake H, Rough J, Darveniza P. The clinical spectrum of laryngeal dystonia includes dystonic cough. *Mov Disord*. 2014;29(6):729-735.

18. Schweinfurth JM, Billante M, Courey MS. Risk factors and demographics in patients with spasmodic dysphonia. *Laryngoscope*. 2002;112(2): 220-223.

19. Vasconcelos S, Birkent H, Sardesai MG, Merati AL, Hillel AD. Influence of age and gender on dose and effectiveness of botulinum toxin for laryngeal dystonia. *Laryngoscope*. 2009;119(10): 2004-2007.

20. Courey MS, Garrett CG, Billante CR, et al. Outcomes assessment following treatment of spasmodic dysphonia with botulinum toxin. *Ann Otol Rhinol Laryngol*. 2000;109(9):819-822.

21. Hertegård S, Granqvist S, Lindestad PA. Botulinum toxin injections for essential voice tremor. *Ann Otol Rhinol Laryngol*. 2000;109(2): 204-209.

22. Sulica L, Louis ED. Clinical characteristics of essential voice tremor. *Laryngoscope*. 2010;120(3): 516-528.

23. Orbelo DM, Duffy JR, Hughes Borst BJ, Ekbom D, Maragos NE. Differences in botulinum toxin dosing between patients with adductor spasmodic dysphonia and essential voice tremor. *J Voice*. 2014;28(1):123-127.

24. Patel A, Frucht SJ. Isolated vocal tremor as a focal phenotype of essential tremor. *J Clin Mov Disord*. 2015;2:4.

25. Wolraich D, Vasile Marchis-Crisan C, Redding N, Khella SL, Mirza N. Laryngeal tremor: co-occurrence with other movement disorders. *ORL J Otorhinolaryngol Relat Spec*. 2010;72(5):291-294.

26. Ludlow CL. Treatment for spasmodic dysphonia. *Curr Opin Otolaryngol Head Neck Surg*. 2009;17(3):160-165.

27. Benninger MS, Smith LJ. Noncosmetic uses of botulinum toxin in otolaryngology. *Cleve Clin J Med*. 2015;82(11):729-732.

28. Benninger MS, Gardner G, Grywalski C. Outcomes of botulinum toxin treatment for patients with spasmodic dysphonia. *Arch Otolaryngol Head Neck Surg*. 2001;127(9):1083-1085.

29. Mehta RP, Goldman SN, Orloff LA. Long-term therapy for spasmodic dysphonia: acoustic and aerodynamic outcomes. *Arch Otolaryngol Head Neck Surg*. 2001;127(4):393-399.

30. Novakovic D, Waters HH, D'Elia JB, Blitzer A. Botulinum toxin treatment of adductor spasmodic dysphonia. *Laryngoscope*. 2011;121(3):606-612.

31. Morzaria S, Damrose EJ. A comparison of the VHI, VHI-10, and V-RQOL for measuring the effect of Botox therapy in adductor spasmodic dysphonia. *J Voice*. 2012;26(3):378-380.

32. Paniello RC, Barlow J, Serna JS. Longitudinal follow-up of adductor spasmodic dysphonia patients after botulinum toxin injection. *Laryngoscope*. 2008;118(3):564-568.

33. Warrick P, Dromey C, Irish JC, Durkin L, Pakiam A, Lang A. Botulinum toxin for essential tremor of the voice with multiple anatomical sites of tremor. *Laryngoscope*. 2000;110(8):1366-1374.

34. Warrick P, Dromey C, Irish J, Durkin L. The treatment of essential voice tremor with botulinum toxin A. *J Voice*. 2000;14(3):410-421.

35. Bové M, Daamen N, Rosen C, Wang CC, Sulica L, Gartner-Schmidt J. Development and validation of the vocal tremor scoring system. *Laryngoscope*. 2006;116(9):1662-1667.

36. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194.

37. Braden MN, Johns MM III, Klein AM, Delgaudio JM, Gilman M, Hapner ER. Assessing the effectiveness of botulinum toxin injections for adductor spasmodic dysphonia. *J Voice*. 2010;24 (2):242-249.

38. Boutsen F, Cannito MP, Taylor M, Bender B. Botox treatment in adductor spasmodic dysphonia. *J Speech Lang Hear Res*. 2002;45(3):469-481.

39. Piccirillo JF. Improving the quality of the reporting of research results. *JAMA Otolaryngol Head Neck Surg*. 2016;142(10):937-939.

40. Hallett M. How does botulinum toxin work? *Ann Neurol*. 2000;48(1):7-8.

41. Gilio F, Currà A, Lorenzano C, Modugno N, Manfredi M, Berardelli A. Effects of botulinum toxin type A on intracortical inhibition in patients with dystonia. *Ann Neurol*. 2000;48(1):20-26.

42. Sulica L. Contemporary management of spasmodic dysphonia. *Curr Opin Otolaryngol Head Neck Surg*. 2004;12(6):543-548.

43. Justicz N, Hapner ER, Josephs JS, Boone BC, Jinnah HA, Johns MM III. Comparative effectiveness of propranolol and botulinum for the treatment of essential voice tremor. *Laryngoscope*. 2016;126(1):113-117.

44. Koller W, Graner D, Mlcoch A. Essential voice tremor. *Neurology*. 1985;35(1):106-108.

45. Massey EW, Paulson GW. Essential vocal tremor. *South Med J*. 1985;78(3):316-317.

46. Hartman DE, Vishwanat B. Spastic dysphonia and essential (voice) tremor treated with primidone. *Arch Otolaryngol*. 1984;110(6):394-397.

47. Fasano A, Bove F, Lang AE. The treatment of dystonic tremor. *J Neurol Neurosurg Psychiatry*. 2014;85(7):759-769.

48. Defazio G, Conte A, Gigante AF, Fabbrini G, Berardelli A. Is tremor in dystonia a phenotypic feature of dystonia? *Neurology*. 2015;84(10): 1053-1059.