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ORIGINAL RESEARCH

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Optimizing Botox regimens in patients with adductor spasmodic dysphonia and essential tremor of voice: A 31-year experience

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Abstract

Objective: The purpose of this study was to quantitatively compare the effectiveness of unilateral and bilateral botulinum toxin A (BTX-A) injections for mitigating undesirable weak/breathy voice quality and dysphagia for patients with adductor spasmodic dysphonia and/or essential tremor of voice (ETV).

Methods: Data were collected from the medical records of 319 patients, yielding three treatment cohorts: patients who received an equal dose bilateral injection regimen (BL=) throughout their course of treatment at VUMC, patients who switched to a unilateral injection regimen (UL), and patients who switched to an unequal dose bilateral injection regimen (BL≠). Changes in length of improvement, duration of weak/breathy voice, and dysphagia severity were compared.

Results: The BL = treatment group reported the longest duration of improved voice. Shorter periods of improved voice were reported at baseline by patients who later switched to UL or BL ≠ injection regimens. Patients receiving UL injections reported significantly reduced weak/breathy voice and dysphagia. Patients receiving BL ≠ injections reported increased length of improved voice; however, dysphagia symptoms increased. Ninety-two percent of patients with ETV switched to a UL regimen, with 61% of patients transitioning within the first three injections.

Conclusions: Patients with pronounced dysphagia and extended periods of weak/breathy voice may benefit from a UL injection approach to mitigate side effects from BTX-A without sacrificing improved voice outcomes. For patients seeking to extend their length of improved voice, a BL ≠ injection regimen may be effective provided the adverse side effects from BTX-A are minimal. Patients with ETV may benefit from a UL injection approach at the outset of their course of treatment with BTX-A.

Level of evidence: III.

Amy Stone and Maria E. Powell are the co-first authors

KEYWORDS
adductor spasmodic dysphonia, Botox treatment, essential tremor of the voice, voice disorders

1 | INTRODUCTION

Adductor spasmodic dysphonia (ADSD) and essential tremor of the voice (ETV) are neurological movement disorders affecting the larynx. Patients with these rare diseases experience over-closure of the vocal folds (as in ADSD) or rhythmic oscillations of intrinsic and/or extrinsic laryngeal, pharyngeal, or palatal muscles (as in ETV) during vocal tasks. Furthermore, a subset of patients presents with a combination of ADSD and ETV.

The gold standard treatment for these patients is recurrent injections of botulinum toxin A (BTX-A) into the affected muscles to reduce the effects this dystonic movement and/or rhythmic oscillation during speech tasks. Average length of vocal improvement has been reported previously as ranging between 8.0 and 15.1 weeks in patients with ADSD, 10.7 weeks in patients with lateral laryngeal tremor, and 10.1 weeks in patients with both lateral laryngeal tremor and ADSD.[1–3] Commonly reported side effects resulting from BTX-A injections include mild breathy voice (in 25%–35% of patients) and mild coughing or difficulty when swallowing liquids (10% of patients). Previous reports indicate that these side effects typically abate ~7–14 days following injection. Patient report of significant dysphagia or vocal breathiness/weakness of prolonged duration or substantial severity would warrant a change in dosing regimen. For patients who experience these side effects to an intolerable degree, a unilateral injection approach has been shown previously to reduce the duration of weak voice by an average of 12.7 days and also reduce the risk of dysphagia in patients with ADSD.[4]

Multiple studies have compared the benefit/side effect profile of bilateral and unilateral BTX-A injections of variable doses ranges for patients with ADSD with and without ETV.[3–13] However, ongoing management of these disorders is dynamic, and each injection is titrated based on the physician experience with injections and the patient's report of the previous injection's effectiveness in managing symptoms without causing excessive adverse side effects. The patient's unique communication needs over the course of the next dose cycle must also be considered, and to this end, multiple treatment regimens including bilateral injections, unilateral injections, and mini-doses may be used to optimize a patient's treatment outcomes.

The goal for this study was to quantitatively compare the effectiveness of unilateral and bilateral low dose (0.5–7.5 units per vocal fold) injections for mitigating undesirable patient-reported weak/breathy voice quality and dysphagia within these patient populations.

2 | METHODS

This study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice, and was approved by the Institutional Review Board at Vanderbilt University Medical Center (IRB#: 180641).

2.1 | Participants

Patient records were gathered and reviewed via the Spasmodic Dysphonia and Laryngeal Dystonia Clinical Outcomes Database. The retrospective database includes 31(sic) years of injection records for patients who received BTX-A treatment using electromyographic guidance at the Vanderbilt Voice Center dating back to 1990. Initially, 591 unique patients' treatment data were considered for this study. Inclusion criteria for this study included: (1) male and female treatment seeking patients; (2) age greater than or equal to 18 years; (3) diagnosis of ADSD, ETV, or ADSD+ETV; (4) having received consecutive BTX-A injections at VUMC. Patients were excluded from the study if they carried a primary or concomitant diagnosis of abductor spasmodic dysphonia. Application of these inclusion and exclusion criteria resulted in an initial sample size of 587 patients.

All patients included in this study initiated treatment of disease with bilateral TA injections. These records were then reviewed in greater detail to identify three subgroups of patients. **Bilateral injection regimen with equal doses (BL=):** The first cohort were patients who retained a bilateral injection treatment regimen for the duration of their course of treatment at VUMC. These patients were included in this group if they had received a minimum of four consecutive bilateral BTX-A injections. **Unilateral injection regimen (UL):** The second cohort were patients who switched from bilateral injections to alternating unilateral injections at some point during their course of treatment at VUMC. In order be included in this group, these patients must have received a minimum of one bilateral injection followed by two consecutive unilateral BTX-A injections. **Bilateral injection regimen with unequal doses (BL≠):** The third cohort were patients who received bilateral unequal doses of BTX-A. To be included in this cohort, patients had to have received a minimum of two consecutive injections of bilateral unequal doses preceded by either a bilateral injection of equal doses or a unilateral injection. Patients who did not meet the inclusion criteria for the subgroups as described above were excluded from this analysis. Detailed chart review yielded 45 patients in the BL = group, 223 patients in the UL group, and 51 in the BL ≠ group for a total sample size of 319 patients.

2.2 | Study procedures and data collection

The Spasmodic dysphonia and laryngeal dystonia clinical outcomes database was reviewed for demographic information (i.e., age, gender), diagnosis, and treatment information (i.e., injection approach

[BL=, UL, or BL≠], dosage of BTX-A, presence and duration of weak voice, presence and severity of dysphagia, length of improved voice).

For the UL and BL ≠ treatment regimen cohorts, all longitudinal injection data was reviewed, and the point at which the treatment regimen changed was identified. Data was collected from the injection immediately preceding the change in treatment approach (Baseline), the injection during which the treatment approach changed (Shift), and the injection immediately following the shift in treatment approach (Response). The injection timepoints analyzed represented the outcomes of the treatment regimen prior to the shift in approach and the stabilized outcomes following the change in treatment regimen. Since no change in regimen was documented for the BL = cohort, the data was systematically captured from the second, third, and fourth injections reported in the patient's chart. For continuity in comparing treatment regimens, the second injection was considered "Baseline," and the fourth injection was considered the "Response."

2.3 | Data analysis

Statistical analysis was performed using GraphPad Prism 9.3. Age comparisons between treatment regimen and diagnosis were compared using one-way ANOVA. Length of improvement (LoI) and length of weak/breathy voice are continuous variables. Therefore, correlation between age and these outcomes were calculated using Pearson's *r*. Between group comparisons (by diagnosis and injection approach) were calculated using Welch ANOVA, and within group comparisons (Baseline to Response) were calculated using paired *t*-test. Dysphagia severity is an ordinal variable. Therefore, correlation between age and dysphagia severity was performed using Spearman's ρ. Between group comparisons (by diagnosis and injection approach) were calculated using Wilcoxon test, and within group comparisons (Baseline to Response) were calculated using the Kruskill-Wallis test. Significance was established at $p < .05$ for all tests performed.

3 | RESULTS

Of the 319 participants, 45 patients were in the BL = group, 223 patients were in the UL group, and 51 patients were in the BL ≠ group. Two hundred fifty-two (79%) were female and 67 (21%) were male. Table 1 details the gender distribution by diagnosis. One-way ANOVA revealed age distribution between diagnoses was significant, where the mean age for ADSD patients (56.2 years) was significantly lower than ETV (70.0 years) and ADSD+ETV (65.7 years) patients ($p < .0001$). There was no significant difference between mean patient age across treatment groups (BL=: 57.2 years, UL: 59.9 years, BL≠: 63.1; $p = .0914$). Pearson Correlations of age by LoI and length of weak and breathy (LoWB) voice at Baseline were nonsignificant ($p = .9261$ and $p = .1017$, respectively). Spearman correlation of age by dysphagia severity ratings at Baseline was also nonsignificant ($p = .8341$).

TABLE 1 Age and gender distribution across diagnoses

Diagnosis	ADSD	ETV	ADSD+ETV
Sample size	201	25	93
Female	144	23	85
Male	57	2	8
Age****	56 (12.5)	70 (11.2)	66 (12.1)
Female	57 (12.5)	70 (11.4)	67 (11.7)
Male	54 (12.3)	71 (12.3)	56 (13.4)

Note: One-way ANOVOA revealed patients with ADSD were significantly younger than patients with either ETV or ADSD+ETV at the Baseline injection (****$p < .0001$).

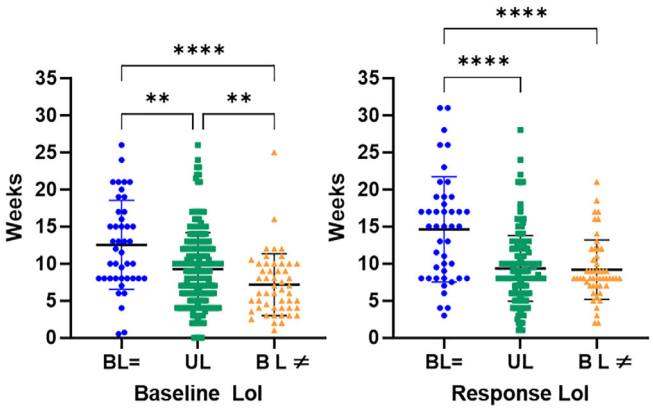

FIGURE 1 Results of Welch ANOVA comparing LoI between treatment groups at baseline (left) and response (right) injections. Paired comparisons using Dunnett's T3 multiple comparison test are significant at **$p < .01$ and ****$p < .0001$

Figure 1 shows the means and standard deviations of the LoI for each injection analyzed. Following the baseline injection, the BL = treatment regimen group reported longer periods of improved voice compared to the UL ($p = .0046$) or BL ≠ ($p < .0001$) groups. Following the third injection in the series (Response injection), patients in the BL = cohort maintained a longer LoI compared to the UL and BL ≠ cohorts ($p < .0001$). Figure 2A–C shows the distribution of reported durations of improved voice following the baseline and response injections for each treatment regimen. Within group comparisons showed that the LoI for the BL = and UL cohorts did not significantly change between the Baseline and Response injections ($p = .0575$ and $p = .8121$, respectively); however, the BL ≠ cohort reported a significant increase in LoI between the baseline and response injections ($p = .0080$). See Table 2 for details.

Figure 3 shows the means and standard deviations of the LoWB voice for each injection analyzed. Following the baseline injection, patients in the UL group reported longer periods of weak and breathy voice compared to the BL = and BL ≠ treatment regimen groups ($p < .0001$). Following the treatment shift, the UL treatment regimen cohort reported significantly shorter periods of weak and breathy voice compared to the BL = ($p = .0024$) and BL ≠ ($p < .0001$) groups.

Figure 4A–C shows the distribution of reported durations of weak and breathy voice following the baseline and response injections for each treatment regimen. Within group comparisons of LoWB data revealed that the outcomes following the Baseline and Response injections did not significantly change for the BL = and BL ≠ groups; however, the UL group reported a significant decrease in the duration of weak and breathy voice following the Response injection ($p < .0001$). See Table 2 for details.

Dysphagia incidence and severity were assessed based on patient report using the following scale: normal = no problems swallowing; mild = occasionally choking on thin liquids; moderate = choking on thin liquids and solids <50% of the time; and severe = choking on thin liquids and solids >50% of the time. Occasionally, patients self-reported intermediate levels of mild–moderate and moderate–severe swallowing difficulty. These intermediate levels were included for analysis. If patients reported more than one dysphagia severity level following injection, we used the highest severity reported for analysis. Because length of dysphagia was not systematically collected for the duration of the study period, these data were not included in analysis.

Analysis of dysphagia severity ratings indicate that there was no difference between dysphagia severity ratings between diagnoses at baseline, at which point all patients were receiving BL injections ($p > .9999$). Incidence of dysphagia in the BL = cohort remained stable over time, with 60% of patients reporting the presence of dysphagia following both injection time points. Within the BL ≠ cohort, 16% of patients reported the presence of dysphagia following the Baseline injection and 33% reported dysphagia following the Response injection. For the UL cohort, 51% of patients reported dysphagia following the Baseline injection, and 25% reported swallowing difficulty

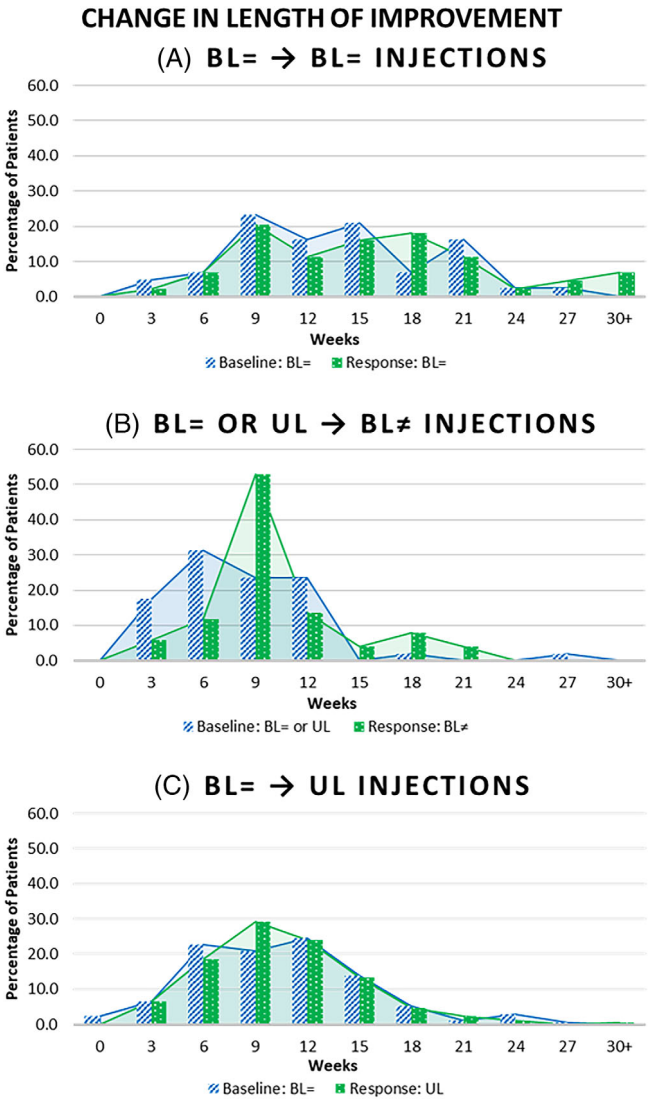

FIGURE 2 Distribution of reported lengths of improved voice between Baseline and Response injection timepoints. For the BL = cohort (A) and the UL cohort (C), length of improvement did not differ between injection timepoints. For the BL ≠ cohort (B), length of improvement increased significantly from a mean of 7.5–9.2 weeks ($p = .0080$)

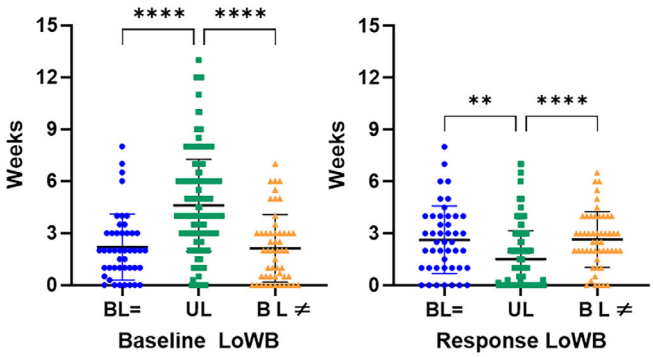

FIGURE 3 Results of Welch ANOVA comparing LoWB period between treatment groups at Baseline (left) and Response (right) injections. Paired comparisons using Dunnett's T3 multiple comparison test are significant at $^{**}p < .01$ and $^{****}p < .0001$

TABLE 2 Paired *t*-test of patient-reported LoI and LoWB period

Treatment group	BL = → BL=			BL = → UL			BL=/UL → BL≠		
Injection timepoint	Baseline	Response	*p* value	Baseline	Response	*p* value	Baseline	Response	*p* value
LoI m (stdv)	12.5 (6.0)	14.6 (7.1)	$p = .0575$	9.3 (4.9)	9.3 (4.4)	$p = .8121$	**7.2 (4.2)**	**9.2 (4.0)**	**$p = .0080$**
LoWB m (stdv)	2.2 (1.9)	2.6 (2.0)	$p = .2184$	**4.6 (2.7)**	**1.5 (1.6)**	**$p < .0001$**	2.1 (2.0)	2.7 (1.6)	$p = .0762$

Note: Mean (standard deviation) LoI and LoWB periods are reported before (Baseline) and after (Response) the shift in treatment regimen. Findings in bold are significant at $p < .05$.

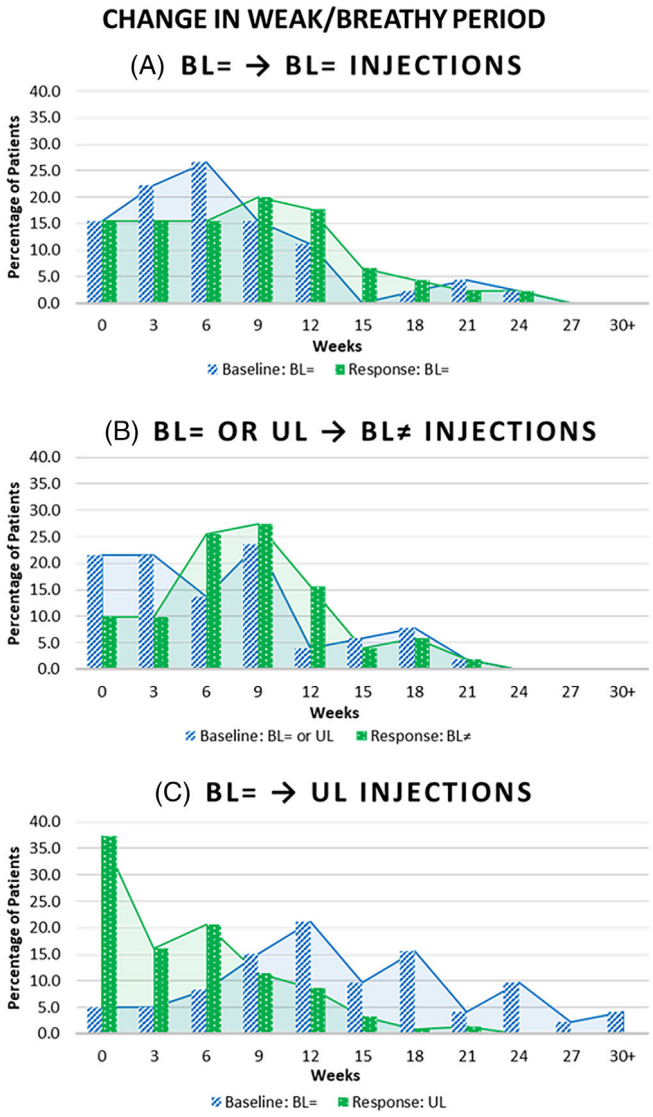

FIGURE 4 Distribution of reported lengths of weak and breathy voice between Baseline and Response injection timepoints. For the BL = cohort (A) and the BL ≠ cohort (B), LoWB voice did not differ between injection timepoints. For the UL cohort (C), LoWB voice decreased significantly from a mean of 4.6–1.5 weeks ($p < .0001$)

following the Response injection. Figure 5 shows the percentage of each cohort who reported dysphagia and its severity following the Baseline and Response injections. Dysphagia severity decreased significantly from Baseline to Response for patients in the UL cohort ($p < .0001$). For patients in the BL ≠ cohort, mean severity increased from Baseline to Response injections ($p = .0085$).

Within the ADSD cohort, 18% of patients remained on the BL = regimen, 68% of patients switched to a UL regimen, and 14% switched to a BL ≠ regimen. Within the ADSD+ETV cohort, 11% of patients remained on the BL = regimen, whereas 75% of patients switched to a UL regimen, and 14% switched to a BL ≠ regimen. For the ETV cohort, 92% of patients switched to a UL regimen, and 8% switched to a BL ≠ regimen. No ETV patients remained on the BL = regimen for the duration of their treatment.

The point at which patients switched their injection regimen to either UL or BL ≠ was variable. On average, patients made a switch by the 12th injection; however, patients most commonly switched injection approaches on the second or third injection. Analysis of the injection number at which patients shifted their treatment approach revealed that for patients diagnosed with ADSD, 43% of patients changed to either UL or BL ≠ approaches within the first five BTX-A injections, with 66% making a change by their 10th injection. For patients with ADSD+ETV, 40% made a change to either UL or BL ≠ injections within the first five BTX-A injections, and 59% made a change by the 10th injection. For patients with ETV, 74% of patients changed to UL injections within the first five injections, and 87% made a change within the first eight injections.

4 | DISCUSSION

Previous studies have compared acoustic and patient reported outcomes in patients receiving unilateral versus bilateral injections. Prospective studies using between group comparisons typically reported that patients receiving UL injections reported longer LoI and shorter durations of undesirable side effects such as weak and breathy voice or dysphagia compared to patients receiving BL = injections.[5–7,9–12] However, for these studies, patients maintained the same treatment regimen for the duration of the study. In the current study, we performed between and within group comparisons to investigate the effectiveness of altering injection approaches (i.e., BL=, UL, or BL ≠ injections) for mitigating undesirable patient-reported weak/breathy voice quality and dysphagia within these patient populations.

4.1 | Effect of treatment approach

In the current study, patients who maintained the standard starting injection approach of BL = injections reported the longest duration of vocal improvement of all three injection regimen types. The average length of improved voice for this cohort of patients was 12.5–14.6 weeks, with an average of 2.2–2.6 weeks of weak and breathy voice reported (Table 2). Transient dysphagia was reported in ~60% of these patients; however, the severity reported was generally mild (Figure 5).[3] Given that this group of patients continued to receive bilateral equal dose injections, the degree of these side effects experienced as reported above may be considered a baseline tolerable trade-off, given the average duration of vocal improvement achieved with this injection approach. These findings are consistent with other reports of patient satisfaction in bilateral injections despite reports of increased duration of negative side effects.[3,5,8]

The majority of patients in this study (69.9%) switched from a BL = to a UL injection approach. These patients were found to have an average length of vocal improvement of 9.3 weeks following both Baseline and Response injections, representing preservation of vocal of improvement despite the shift in treatment regimen (Table 2). The switch to UL injections did serve to significantly reduce the duration of weak and breathy voice from 4.6 to 1.5 weeks (Table 2, Figure 4C). UL injections also served to mitigate the incidence and severity of

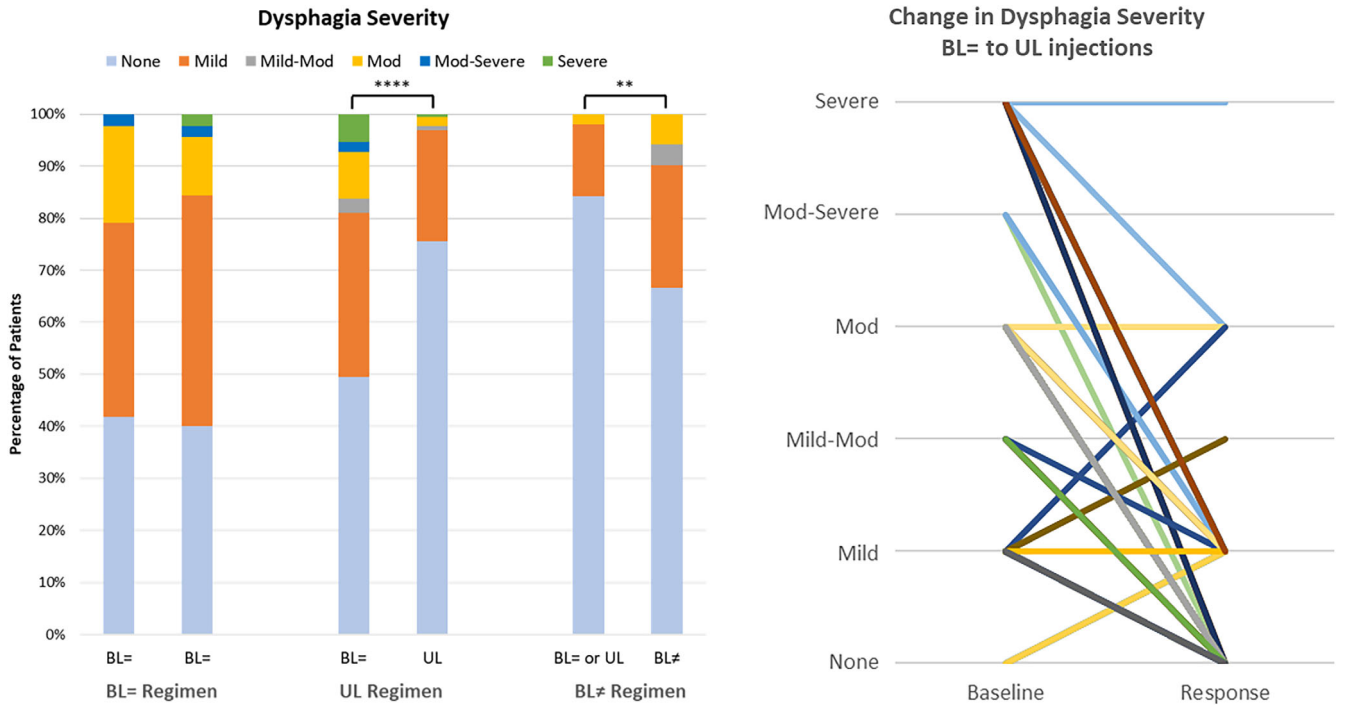

FIGURE 5 Distribution of dysphagia severity ratings between the first (left) and last (right) injections for each injection regimen. Prepost comparisons were performed using Wilcoxon matched pairs signed rank test. Following the switch from BL = to UL injections (UL Regimen), symptom severity decreased significantly ($p < .0001$). Following the switch from BL = or UL to BL ≠ injections (BL ≠ Regimen), symptom severity increased significantly ($p = .0085$)

dysphagia symptoms (Figure 5). Patients frequently reported either mild or no dysphagia symptoms following the shift to UL injections. These findings suggest that a UL injection regimen may be beneficial specifically for patients with suboptimal outcomes resulting from increased weak and breathy periods and/or swallowing complaints. Findings in the current study are consistent with previous retrospective[4,13] and crossover[3] studies which report UL injections provide a shorter length of improved voice compared to BL injections but effectively reduce extended durations of weak and breathy voice.

Administration of BL ≠ doses of BTX-A served to significantly increase the length of improved voice, by an average of ~2 weeks (Table 2). Weak and breathy side effects were not significantly affected with this changed treatment approach; however, patient reported dysphagia severity ratings were significantly *increased* on the BL ≠ treatment regimen (Figure 5). These findings suggest that unequal doses of BTX-A injected bilaterally may provide improved voicing outcomes but should be used with caution in patients who present at baseline with increased risk for swallowing difficulties.

4.2 | Effect of diagnosis

Patient diagnosis appears to be a significant factor in treatment outcomes, particularly for patients with pure ETV. Although ETV patients were found to be significantly older than the other cohorts, age was not found to be a significant factor for voice outcomes or undesirable side effects at baseline. No ETV patients analyzed in this study remained on a BL = treatment regimen: 92% of ETV patients (23/25) switched to UL injections, and the remaining two patients switched to a BL ≠ treatment regimen. Additionally, 74% of the ETV patients switched to a UL treatment regimen within the first five injections. These findings suggest that pure ETV patients may present with a unique response to BTX-A injections compared to patients who present with pure ADSD or ADSD+ETV phenotypes and that a UL approach may be the optimal starting regimen for ETV patients.

4.3 | Challenges and future directions

The current study is a retrospective study analyzing patient reported outcomes following BTX-A injections from 391 patients over the past 31 years. Although our sample size is robust, the records utilized in this were obtained through the previously designed Spasmodic Dysphonia and Laryngeal Dystonia Clinical Outcomes Database and are therefore not comprehensive of *all patients* seen at the Vanderbilt Voice Clinic since 1990. Further, the design of this study captured data across three injections. Many patients have received dozens of injections over their full course of treatment and may have made multiple regimen shifts based on changing responses and future needs. Although longitudinal analysis of these patients is warranted, it is outside the scope of the current study.

All outcomes were obtained by patient-report and are therefore subjective. Additionally, given the extended timeframe analyzed in this study, it is possible that general shifts in clinical practice over three

decades (e.g., changes in dosing practices) may have contributed to some of our reported findings. Furthermore, we cannot infer the clinical rationale for adjustments to treatment regimens. Future studies that systematically document the objective clinical data that informs the physician in their clinical decision making would help further refine clinical practice.

Length of dysphagia symptoms was not systematically recorded in the patient medical records. Therefore, a comprehensive analysis of the impact of dysphagia that includes both symptom severity and duration was not achievable. Although the results indicating a BL ≠ treatment regimen may increase the risk for dysphagia symptoms were statistically significant, further research should be performed on a larger sample size. Additionally, the BL ≠ group is comprised of patients switching from either BL = or UL approaches. Further investigation is needed to determine if there are systematic responses to a change in treatment when the Baseline injection is UL versus BL = .

In the current study, all ETV patients were considered together, regardless of the directionality of the tremor. Future studies should delineate between tremor subtypes (e.g., lateral laryngeal, vertical laryngeal, lateral pharyngeal, etc.).

5 | CONCLUSIONS

Clinical decision making for ongoing management of ADSD and/or ETV using BTX-A injections is highly driven by patient report of past response and future needs. This study describes patterns of patient-reported outcomes that may inform the need to change injection approach as well as anticipated clinical responses to those changes in treatment approach. All patients included in this study-initiated treatment with bilateral injections, an approach commonly administered at the outset of treatment to establish treatment efficacy of BTX-A for the patient and offer the greatest chance for a positive response to this treatment. For the entire group, 86% elected to change their dosing regimen to either UL or BL ≠ to reduce breathiness or increase length of improved voice. The clinical preference for unilateral injections in patients with vocal tremor suggests that this patient population may benefit from administration of this injection approach at the outset of their course of treatment with BTX-A. Additionally, patients with extended periods of weak and breathy voice and/or significant dysphagia may benefit from a UL injection approach to mitigate these symptoms without significantly impacting their length of improved voice. Patients seeking to extend their duration of improved voice may benefit from a BL ≠ dose unless they have significant dysphagia concerns, as the BL ≠ regimen appears to increase the risk for incidence and severity of dysphagia. For some patients, the BL = injection regimen affords the best outcome profile, with the longest duration of improved voice and relatively mild adverse side effects; however, most patients do not experience optimal outcomes on this regimen, necessitating a change in treatment regimen. Patient diagnosis may be a contributing factor to this phenomenon.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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