# Botulinum Toxin Dosing Trends in Spasmodic Dysphonia Over a 20-year Period

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**Summary: Objectives.** The study aims to (1) identify the botulinum toxin (BTX) dosing trend in a cohort of patients who received at least 20 injections for the treatment of adductor spasmodic dysphonia (ADSD), (2) describe two distinct BTX dosing trends in treating ADSD (a "classic" dosing trend that initially decreases before stabilizing, and a "fluctuating" dosing trend), and (3) determine if patients with the "classic" dosing trend differed in age or in dosing intervals from those with the "fluctuating" dosing trend.

**Study design.** This is a retrospective case series.

**Methods.** Of 149 patients who received a total of 2484 BTX injections for the treatment of spasmodic dysphonia in 1993–2013, 49 patients received at least 20 injections. The BTX dose and the interval between doses were recorded. The mean dose of injections 1–20 was determined. The age at initial injection, initial dose, and interval in days between treatments were compared for the "fluctuating" and "classic" groups.

**Results.** The cohort exhibits a significant decrease in dose during the first 10–15 injections. The "fluctuating" group had a significantly shorter interval between injections (mean interval = 97.09 days, SD = 29.41; mean interval = 136.90 days, SD = 43.76, $P = 0.002$). The mean age at initial dose was not significantly different between the "classic" and "fluctuating" groups.

**Conclusions.** The average BTX dose of patients with ADSD who receive long-term injections significantly decreases during the initial 10–15 injections before stabilizing. Patients who exhibit the "fluctuating" dosing pattern have a significantly shorter interval between injections than those with the "classic" dosing pattern.

**Key Words:** Spasmodic dysphonia–Botulinum toxin–Dosing intervals–Initial dose–Trend.

## INTRODUCTION

Spasmodic dysphonia is the third most common focal dystonia behind cervical dystonia and blepharospasm.[1] There are two main disease subtypes, adductor spasmodic dysphonia (ADSD) and abductor spasmodic dysphonia (ABSD). The general understanding of spasmodic dysphonia has made substantial strides since the 1960s, when it was believed to be a psychiatric disorder.[2] The first objective evidence supporting that spasmodic dysphonia was a neurological disorder came from symptom improvement in patients with spasmodic dysphonia after injecting the recurrent laryngeal nerve (RLN) with lidocaine. Patients with spasmodic dysphonia who underwent sectioning of the RLN also symptomatically improved.[3] Long-term follow-up found that patients treated with RLN sectioning had symptom recurrence as early as 6 months postoperatively secondary to re-innervation.[4,5] Many alternative surgical interventions have subsequently been developed; however, botulinum toxin (BTX) type A injections have remained the standard of care in treating spasmodic dysphonia during the past three decades.[6–10]

Despite the current lack of a definitive explanation for the etiology of spasmodic dysphonia, it is known that injecting BTX into the thyroarytenoid muscle improves the symptoms of ADSD.[1,11,12] BTX type A is a zinc-dependent metalloprotease that specifically cleaves the SNAP-25 target protein.[13] Blitzer et al gave the first BTX injection into the vocal cord in April 1984.[11,14] This first injection was a 2.5 U unilateral injection, which was followed by an additional 7.5 U unilateral injection because the first injection had little effect.[11] Following the 7.5 U injection, the patient experienced vocal cord paresis and breathy dysphonia; however, he eventually had 90% symptom improvement.[11] Since that first injection, Blitzer reports an average bilateral dose of 0.9 U, an average unilateral dose of 1.5 U, an average peak effect at 9 days, and an average duration for 15 weeks.[15]

Since the first injection of BTX for spasmodic dysphonia, there has been extreme variability in starting doses, use of unilateral versus bilateral injections, and delivery method when injecting BTX.[16,17] This variability is accounted for by differences in both physicians and patients. Certain patients may prefer small doses every month to avoid breathiness, whereas other patients may prefer one larger injection every 6 months and tolerate a significant period of breathiness and dysphagia.

Many patients with spasmodic dysphonia around the world have been receiving BTX injections for greater than 20 years.[18] Carefully analyzing treatment trends of patients over time and categorizing patient's dosage changes of BTX may allow physicians to gain more insight into patient's treatment responses. Prior studies have found that the BTX dose for ADSD tends to decrease with time.[19] A more recent study by Rosow et al has found that doses tend to stabilize over the course of long-term treatment.[20]

There were three objectives to this study:

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(1) Identify the BTX dosing trend in a cohort of patients who received at least 20 injections for the treatment of ADSD.
(2) Describe two distinct BTX dosing trends in the treatment of ADSD: a "classic" dosing trend that initially decreases before stabilizing, and a "fluctuating" dosing trend.
(3) Determine if patients with the "classic" dosing trend differed in age or dosing intervals from the patients who exhibited the "fluctuating" dosing trend.

## METHODS

The current study was approved by the Saint Louis University Institutional Review Board. This is a retrospective case series of all patients who received at least 20 BTX injections for the treatment of ADSD by the senior author between March 1993 and March 2013. The senior author offered a biweekly clinic where he performed BTX injections using electromyography guidance and a percutaneous technique. The Teflon-coated needle was routinely inserted through the cricothyroid membrane and turned laterally and superiorly into a targeted thyroarytenoid muscle. In patients who had experienced an unsuccessful injection (no response to BTX), the subsequent injection(s) was confirmed by simultaneous transnasal fiberoptic laryngoscopy to confirm proper needle placement. Overall, <5% of patents require this additional technique.

The initial patient search found that 149 patients received a total of 2484 BTX injections for the treatment of spasmodic dysphonia during the study period. A total of 49 patients met the inclusion criteria, having received at least 20 injections for the treatment of ADSD during the study period. The laterality, injection dose, injection number, and days since last injection were recorded for every injection that each patient received. The injection was categorically labeled as unilateral thyroarytenoid or bilateral thyroarytenoid. The average doses were determined per vocal cord injected. All doses in this study are reported per vocal cord. For example, an injection of 2.0 U bilaterally (and thus 4.0 U delivered to larynx) was recorded as a 2.0 U bilateral injection, and an injection of 2.0 U unilaterally (and thus 2.0 U delivered to larynx) was recorded as a 2.0 U unilateral injection.

The mean dose of injections 1–20 for the 49 patients with at least 20 injections were calculated and graphed to illustrate the dosing trend of the group as a whole. The 49 patients were divided into 2 groups. The patients whose doses decreased during an initial titration period and then stabilized were categorized as "classic." The patients who had at least four consecutive injections outside of a 0.4 U range after the titration period were defined as "fluctuating.". A range of 0.4 U was chosen because this represents an approximately 25% fluctuation outside of the patients typical dose range (given the initial dose in this study was approximately 1.6 U per vocal cord). Four consecutive injections outside of the 0.4 U range was chosen because most patients occasionally experiment with a different dose, but four consecutive doses would represent an entire year of treatment (given the average interval between treatments in this study was 3–4 months).

The mean dosing trends over the first 20 injections were then compared between the "fluctuating" and "classic" groups. The age at initial injection, initial dose, and interval in days between treatments were compared for the "fluctuating" and "classic" groups.

### Statistical analysis

All analyses were completed using *IBM SPSS Statistics version 21.0*.[21] When calculating the interval in days between injections, intervals greater than 200 days were excluded. The average initial dose, interval in days between injection, and age at initial dose were compared between patients with different dosing profiles who had received ≥20 injections using the independent samples *t* test. Repeated measures analysis of variance was used to evaluate the changes in dose and interval between injections from injections 1 through 20 for all patients in the groups who had received at least 20 injections. For these analyses, where the assumption of sphericity was violated, we used the Greenhouse-Geisser correction.

## RESULTS

A total of 49 patients with ADSD received at least 20 BTX injections during the study period. The dosing trend for the entire group during the first 20 injections illustrated a decreasing dose that then stabilized after the 11th dose. Doses 11 ($P = 0.03$), 12 ($P = 0.03$), 13 ($P = 0.03$), 15 ($P = 0.03$), 16 ($P = 0.03$), and 17 ($P = 0.03$) were all significantly less than dose 1 (Figure 1).

There were 15 patients (30.6%) who illustrated a "fluctuating" trend in dose over time, whereas 34 (69.4%) patients illustrated the "classical" dosing trend over the first 20 injections. The "fluctuating" group mean dose ranged from a low dose of 1.44 U (SD = 0.73) at visit 11 to a high dose of 1.75 U (SD = 1.08) at visit 20. The "classic" group decreased from a mean dose of 1.61 U (SD = 0.75) at injection number 1 to a mean dose of 1.24 U (SD = 0.48) at injection number 20 (Figure 2).

The "fluctuating" group had a significantly shorter interval between injections (mean interval = 97.09 days, SD = 29.41) compared with those in the "classic" group (mean interval = 136.90

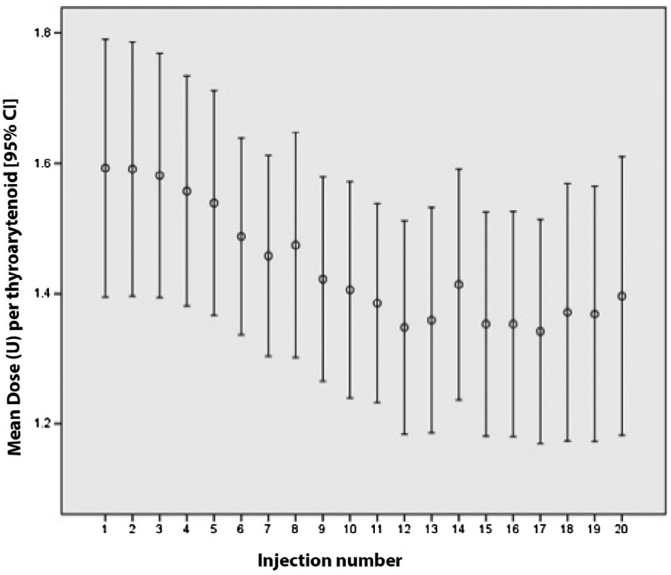


**FIGURE 1.** Average doses during initial 20 injections of the entire cohort. CI, confidence interval.