Botox Injections for Esophageal Motor Disorders

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KEYWORDS

• Botulinum toxin • Botox • Achalasia • Hypercontractile esophagus
• Esophageal spasm • Esophageal manometry

KEY POINTS

- Botulinum toxin (Botox, BTX) reduces muscle contraction by inhibiting acetylcholine (Ach) release at the neuromuscular junction by targeting synaptosomal-associated protein 25 kDa (SNAP-25).
- BTX injection therapy may be used to treat esophagogastric junction outflow obstruction, hypercontractile esophagus, and/or distal esophageal spasm as defined by Chicago Classification v4.0.
- For BTX injection, identify areas of puckered/hypertonic smooth muscle via direct visualization and inject the BTXunits slightly deeper than submucosal level.

INTRODUCTION

The esophagus is a tubular organ approximately 25 cm in length responsible for transporting food and liquid from the oral cavity to the stomach. It consists of a proximal skeletal muscle segment, a distal smooth muscle segment, and 2 functional/anatomic sphincters: the upper esophageal sphincter (UES) and lower esophageal sphincter (LES). These sphincters are tasked with preventing proximal migration of gastroesophageal contents whilst allowing timely passage of boluses. Activation of the esophageal smooth muscles occurs via vagal signaling initiated in the dorsal motor nucleus of the brainstem and modulated by the myenteric plexus. The distal smooth muscle, in particular, is heavily regulated by both inhibitory and excitatory signaling from the myenteric plexus.[1,2] Pathologies affecting smooth muscle function or neural signaling cause aberrant contraction and/or relaxation of the esophageal smooth muscle and generate symptoms such as dysphagia, chest pain, regurgitation etc. Advances in diagnostics, especially high-resolution manometry (HRM), have improved

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Gastrointest Endoscopy Clin N Am 35 (2025) 637–649
https://doi.org/10.1016/j.giec.2025.02.004 giendo.theclinics.com

Abbreviations	
Ach	acetylcholine
BTX	botulinum toxin
CC	Chicago Classification
CP	cricopharyngeus
DES	distal esophageal
EGJOO	esophagogastric junction outflow obstruction
EMDs	esophageal motor disorders
ESGE	European Society of Gastrointestinal Endoscopy
EUS	endoscopic ultrasound
FLIP	functional lumen imaging probe
GERD	gastroesophageal reflux disease
HE	hypercontractile esophagus
HRM	high-resolution manometry
IEM	ineffective esophageal motility
LES	lower esophageal sphincter
POEM	per-oral endoscopic myotomy
RCPD	retrograde cricopharyngeal dysfunction
SNAP-25	synaptosomal-associated protein 25 kDa
UES	upper esophageal sphincter

our understanding of the various patterns of esophageal motor disorders (EMDs) and have been translated into a formal scheme for characterizing EMDs. **Fig. 1** shows the prevalence estimates of the EMDs achalasia, esophagogastric junction outflow obstruction (EGJOO), hypercontractile esophagus (HE), distal esophageal (DES), and ineffective esophageal motility (IEM) in individuals with nonobstructive dysphagia according to Chicago Classification (CC) criteria.[3]

EGJOO and spastic and/or hypercontractile disorders are increasingly recognized causes of symptoms. However, unlikely achalasia, their pathogenesis, natural history,

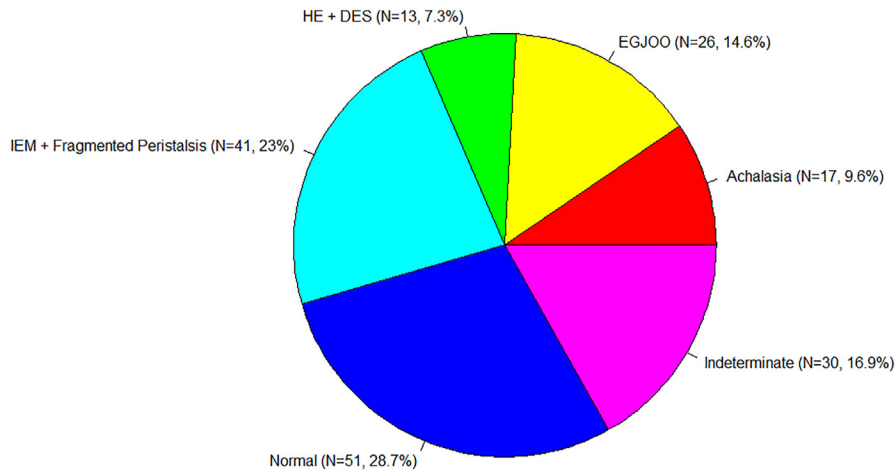

Fig. 1. Distribution of esophageal motility disorder diagnoses after conversion to CC version 3.0 (CC V3.0) criteria from 178 cases is shown. (*Adapted from* P. Laing, A. P. Bress, J. Fang, K. Peterson, D. G. Adler, A. J. Gawron, Trends in diagnoses after implementation of the Chicago classification for esophageal motility disorders (V3.0) for high-resolution manometry studies, Diseases of the Esophagus, 30 (12), December 2017, 1–6. https://doi.org/10.1093/dote/dox068.[3])

and optimal management strategies are poorly understood.[4–9] Botox, BTX is a well-known toxin that inhibits acetylcholine (Ach) release at the neuromuscular junction by targeting synaptosomal-associated protein 25 kDa (SNAP-25), thus reducing Ach-mediated muscle contraction. As a field, we have decades of experience injecting BTX endoscopically into the smooth muscle and sphincter regions in various part of the gastrointestinal tract. This article will describe the updated use profile of BTX in esophageal disorders. We will discuss the technique, clinical indications, and future directions of BTX therapy in the current landscape of EMDs.

CURRENT GUIDELINE RECOMMENDATIONS FOR ENDOSCOPIC BOTULINUM TOXIN THERAPY

There is a rich history of efficacy data for the use of BTX injection in EMDs in achalasia.[10–14] However, due to improvements in surgical and endoscopic myotomy techniques, particular per-oral endoscopic myotomy (POEM), the role of endoscopic BTX therapy in achalasia is largely reserved for patients who are not candidates for pneumatic dilation or myotomy. A summary of guidelines put forth by United States and international gastroenterological societies is below in **Table 1**.[15–19] These guidelines almost exclusively discuss the use of LES BTX in achalasia. The only society that discusses the role of BTX therapy in nonachalasia EMDs is the European Society of Gastrointestinal Endoscopy (ESGE), which recommended against routine use of BTX injection in patients with nonachalasia hypercontractile EMDs, which they defined as HE and DES.[18] This recommendation was due to the lack of high-quality evidence supporting efficacy of BTX in these disorders. Thus, there is a critical gap in our understanding of the BTX therapeutic effect in spastic and hypercontractile EMDs.

ENDOSCOPIC TECHNIQUES FOR BOTULINUM TOXIN INJECTION

LES: BTX is injected into the esophageal smooth muscle during a standard upper endoscopy procedure. Key considerations for this treatment include the *location* of injection and the *dose*. The majority of evidence supporting the efficacy and technique of BTX therapy in the esophagus pertains to injection into the LES. For LES injections, the typical dose is 100 units of Botox reconstituted in 4 to 5 mL of sterile water or 0.9% normal saline. The reconstituted volume is divided in 4 to 5 aliquots of 1 mL each (about 20 units/1 mL), which are then injected via a sclerotherapy needle.[20,21] The primary challenge lies in accurately identifying the most hypertonic areas of the LES. The general region of the LES should be localized 1 to 2 cm above the squamocolumnar junction. Then, the specific targets for the injection can be identified via one of 3 approaches: (i) direct endoscopic visualization to identify the most prominent and *puckered* areas of muscle, (ii) endoscopic ultrasound (EUS) guidance to target areas of increased muscle thickness, or (iii) random 4 quadrant-injections. We recommend the first technique, given its ease and the limited data supporting EUS-guided Botox therapy.[22,23] At the target areas, the injection needle should be inserted into the mucosa with a near-perpendicular angle to the esophageal wall. The needle should penetrate slightly deeper than the submucosal layer but should not be *jammed* into the esophageal wall such as to cause tenting or displacement. If the injectate disperses significantly into the submucosa during the injection, the needle can be advanced slightly deeper. This technique is repeated for 4 to 5 injections until the entire 100 units have been delivered. Any bleeding that occurs is usually minimal and on the order of that which occurs after esophageal biopsies. Antibiotics are generally not required after BTX injection and patients may be discharged following standard postprocedure

Table 1
Current society guidelines regarding the role of botulinum toxin therapy in esophageal motor disorders

Society	Year Published	Recommendation
American College of Gastroenterology[15]	2020	*BTX injection should be used as first-line therapy for patients with achalasia that are unfit for definitive therapies compared with other less effective pharmacologic therapies.* *Treatment with BTX injection does not significantly affect performance and outcomes of myotomy.*
American Society of Gastrointestinal Endoscopy 2020[16]	2020	*The use of BTX injection as definitive therapy for achalasia patients is not recommended. BTX injection may be reserved for patients who are not candidates for other definitive therapies.*
Seoul Consensus[17]	2019	*BTX injection is recommended for achalasia patients whose medical condition is unsuitable for endoscopic treatment or surgery.*
ESGE[18]	2020	*BTX therapy can be considered an effective and safe therapy for short-term symptom relief in esophageal achalasia.* *BTX should be reserved for patients who are unfit for more invasive treatments, or in whom a more definite treatment needs to be deferred.* *BTX injections should not be routinely used to treat patients with nonachalasia hypercontractile esophageal motility disorders (Jackhammer esophagus, distal esophageal spasm). However, if, in individual patients, endoscopic injection of BTX is chosen, ESGE recommends performing injections into 4 quadrants of the LES and the lower esophagus.*
International Society for Diseases of Esophagus[19]	2018	*The use of BTX injection in patients under 50 y of age, for control of symptoms is not recommended. BTX injection as an effective therapy (control of symptoms) for achalasia in patients fit for surgery is not recommended.* *BTX injection should be reserved for patients who are unfit for surgery or as a bridge to more effective therapies, such as surgery or endoscopic dilation.* *BTX injection can be safely repeated, but the clinician and the patients should be aware that their efficacy is lower than in initial treatment.* *BTX injection in the esophageal body is not recommended, even in the presence of type III achalasia.* *The use of increasing BTX dosage at retreatment is not recommended.*

recovery.[21] **Fig. 2** illustrates the injection technique and highlights the targeted area of the LES.

Esophageal Body: For BTX injection in esophageal body, a similar technique is used. Doses used in the esophageal body range from 50 to 200 units based on our anecdotal experience. However, the prior studies have used 100 units in the esophageal body delivered in 6 to 10 injections.[24,25] In the esophageal body, the target areas of muscle may be identified via manometric landmarks, direct endoscopic visualization, or EUS guidance of hypertrophied muscular areas.

UES: BTX injection into the cricopharyngeus (CP) for obstructive/hypertonic disorders of the UES (CP bar, retrograde CP dysfunction, poststroke or neurologic disorders) may be performed by otolaryngologists. A wide range of doses (15–100 units) has been used in clinical studies of these disorders.[26,27] The target areas of the CP can be identified via a transcutaneous approach using electromyographic guidance, or by direct pharyngoscopy or esophagoscopy. Typically, the posterior or posterolateral regions of the CP are targeted to avoid paralysis of laryngeal muscles.[28]

EFFICACY OF BOTULINUM TOXIN IN NONACHALASIA ESOPHAGEAL MOTOR DISORDERS

Pooled efficacy estimates of BTX from achalasia studies are 79% at 1 month, which drops to 41% at 12 months.[29] However, with the advent of POEM and improvements in surgical myotomy techniques, BTX is best used as salvage therapy in patients who are not candidates for myotomy or pneumatic dilation. Data regarding efficacy of BTX injection in EGJOO, spastic and/or hypercontractile disorders are thus more relevant. **Table 2** below summarizes original studies, which primarily assessed efficacy of endoscopic BTX in EGJOO, DES, and HE.[20,21,24,25,30–32]

The majority of these studies focused on outcome after LES directed BTX. Symptom improvement in these studies was measured by validated symptom scores [Eckardt score, Dysphagia Symptom Questionnaire (DSQ), or Brief Esophageal Dysphagia Questionnaire (BEDQ)] or modified versions of these. Short-term efficacy (1–2 months) of BTX therapy ranged from 46% to 87% across studies, while longer-term efficacy (4–12 months) varied from 30% to 57%. In studies performed before development of the CC, the term *nonspecific esophageal dysmotility* was

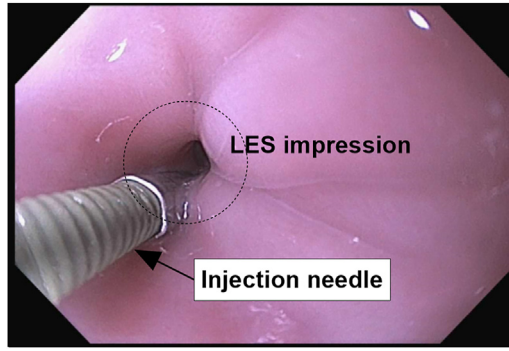

Fig. 2. Technique for endoscopic injection of BTX is shown. The area of the LES is identified as the puckered area 1 to 2 cm above the squamocolumnar junction and is marked by the circular dashed line. Appropriate depth of the sclerotherapy needle insertion is shown, which does not cause tenting of the esophageal wall.

Table 2
Studies assessing botulinum toxin efficacy in nonachalasia esophageal motor disorders

Author(s), Year	Included HRM Diagnoses	Study Design	N	Outcome	Efficacy (%)
Miller et al,[30] 1996	Diffuse esophageal spasm, nonspecific motility disorders, LES dysfunction	Prospective	15	Subjective improvement in dysphagia and chest pain	87% at 1 mo
Porter & Gyawali,[20] 2011	Incomplete LES relaxation with preserved peristalsis (EGJOO)	Retrospective	36	Composite esophageal symptom index	58% at >6 mo
Vanuytsel et al,[31] 2013	Diffuse esophageal spasm, nutcracker esophagus	Double-blind randomized sham-controlled trial	22	DSQ	73% at 1 mo
Marjoux et al,[25] 2015	Type 3 achalasia, jackhammer esophagus, DES, EGJOO	Retrospective	45	Eckardt Score	71% at 2 mo; 57% at 6 mo
Mion et al,[24] 2019	HE (type 3 achalasia, DES, jackhammer esophagus)	Double-blind randomized sham-controlled trial	23	Eckardt score	No benefit compared to sham
Biermann et al,[21] 2024	EGJOO	Prospective	69	BEDQ	61% at 2 mo
Reddy et al,[32] 2024	EGJOO	Retrospective	13	Graded response scale (poor, partial, or good)	46% at 1–6 mo

used to describe spastic and hypercontractile esophageal motor patterns. Notably, the sham-controlled studies performed by Mion showed no benefit, whereas the sham-controlled study conducted by Vanuytsel found a benefit of BTX over placebo.[24,31]

PREDICTORS OF BOTULINUM TOXIN RESPONSE IN ESOPHAGOGASTRIC JUNCTION OUTFLOW OBSTRUCTION, SPASTIC AND HYPERCONTRACTILE ESOPHAGEAL MOTOR DISORDERS

Several of the studies referenced in **Table 2** explored predictors of outcome following BTX therapy, with inconsistent findings. Porter and Gyawali found that less spastic features predicted longer-tern relief with BTX, whereas Marjoux and colleagues identified higher integrated relaxation pressure (IRP) and hypercontractile body motility as predictors of better response to BTX.[20,25] Biermann and colleagues demonstrated that functional lumen imaging probe (FLIP) contractile response patterns, particularly spastic-reactive patterns, were strongly predictive of favorable symptom improvement in patients with EGJOO.[21] Thus, at present, reliable physiologic or other clinical predictors of a BTX response remain uncertain.

LIMITATIONS OF BOTULINUM TOXIN AND SAFETY PROFILE

The primary limitation of BTX therapy for EMDs is its inability to provide durable therapy. After the peak effect of BTX within 1 week, mechanisms for Ach release will recover. There may also be some loss of effect due to antibody formation, particularly with retreatments.[33] Another limitation is the technical variance at the level of the operator in targeting the optimal muscular areas.

Safety data with BTX injection is present in the form of case reports, data reported from efficacy studies, and a large study, which specifically evaluated the safety of BTX in a multicenter retrospective design. In the latter study of 485 patients, the overall complication rate was 7.9%. These were predominantly mild and self-limited adverse events (chest pain or heartburn, abdominal pain/bloating, vertigo, nausea, vomiting, fatigue, and sore throat). One fatal case of acute mediastinitis was reported in this study.[34,35] One frequently raised question is the effect of BTX injection on the technical feasibility and therapeutic efficacy of future myotomy. There is limited and conflicting evidence regarding these questions.[36,37] Thus, a reasonable approach would be to limit BTX therapy to 1 or 2 injection in equivocal cases before committing to definitive therapy.

BOTULINUM TOXIN AND COMPARABLE THERAPIES FOR NONACHALASIA ESOPHAGEAL MOTOR DISORDERS

As discussed in this article thus far, the current role of endoscopic BTX injection therapy is primarily in the management of EGJOO, spastic, and/or hypercontractile disorders. Treatment considerations in these disease states as well as the novel entity of abelchia (retrograde cricopharyngeal dysfunction) are described below.

Esophagogastric Junction Outflow Obstruction

At present, EGJOO meeting CCv4.0 criteria is conceptualized as a mild or early achalasia variant, perhaps with more augmented cholinergic signaling rather than defective inhibition. Notably, myotomy is not recommended in EGJOO given the potential of Gastroesophageal reflux disease (GERD) as the causative entity and the high rates

of reflux afterward in this population.[38–40] Thus, in EGJOO, options to treat muscle hypertonicity include (i) pharmacologic agents that induce smooth muscle relaxation (calcium channel blockers, nitrates, phosphodiesterase inhibitors, and anticholinergics), and (ii) endoscopic BTX injection to the LES. The data supporting the use pharmacologic smooth muscle relaxants is low-quality and predominantly shows effects toward lowering LES pressures rather than clinical outcome.[8,41,42] However, clinical use of these agents is justified by anecdotal evidence and case reports of success included in larger retrospective cohorts in EGJOO. Use of these pharmacologic smooth muscle relaxants can be limited by hypotension or orthostatic symptoms, headache, and off-target GI effects. In contrast, LES BTX injection has efficacy of up to 87% short-term and up to 57% at 12 months as described earlier in **Table 2**. GERD continues to be an important confounder, even in CCv.40 defined conclusive EGJOO.

Spastic and/or Hypercontractile Disorders

Therapeutic options for spastic and/or hypercontractile disorders defined per CCv4.0 (HE, DES) are similar to EGJOO. Pharmacologic smooth muscle relaxants and BTX injection may be used. However, there are 2 unique considerations in this population—(i) there is a higher proportion of patients with non-cardiac chest pain related to esophageal hypersensitivity, and (ii) there is possibly a longer segment of smooth muscle, which is dysfunctional, akin to type 3 achalasia. The latter point is not substantiated, as the distal esophageal hypercontractile and/or spastic segment may be secondary to the outflow obstruction. However, this heterogeneity in patient profiles coupled with the low incidence of HE and DES has made these populations quite difficult to study.[43] The 2021 Pisa Symposium recommended medical therapy with smooth muscle relaxants and proton-pump inhibitors as first-line therapy in HE.[44] As presented earlier in **Table 2**, treatment data with BTX, myotomy or pneumatic dilation is sparse and uncontrolled in this population. Other reasonable considerations include adjunct use of neuromodulators or cognitive behavioral therapy in patients with chest pain predominant symptoms and HE or DES.[45] The data for BTX and other therapies is even less robust in DES, which is becoming an increasingly rarer entity with subsequent iterations of the CC.

In summary, for EGJOO, spastic and hypercontractile EMDs, endoscopic BTX injection and pharmacologic smooth muscle relaxants are both reasonable first-line therapeutic considerations to treat smooth muscle dysfunction. Due to the more controlled nature of BTX therapy trials, we advocate for BTX as first-line. GERD is an important, and perhaps causative, process toward the genesis of symptoms and smooth muscle changes in these disorders. Neuromodulators, cognitive behavioral therapy, and speech therapy can be additional considerations based on a given patient's specific symptoms.

Abelchia or Retrograde Cricopharyngeal Dysfunction

Retrograde cricopharyngeal dysfunction (RCPD) is a newly identified disorder characterized by impaired relaxation or spasm of the cricopharyngeus muscle (the key component of the UES) in response gas reflux such as that induced by a carbonated drink. The key symptoms are: inability to burp, excessive flatulence, chest pain, and/or bloating. The disorder is detected on HRM via a nonrelaxing UES following a carbonated drink challenge given in a sitting posture.[46,47] The mainstay of treatment of RCPD is BTX delivered to the cricopharyngeus.[28,48,49] BTX can be delivered via a transcricoid, EMG-guided approach, or via direct visualized during

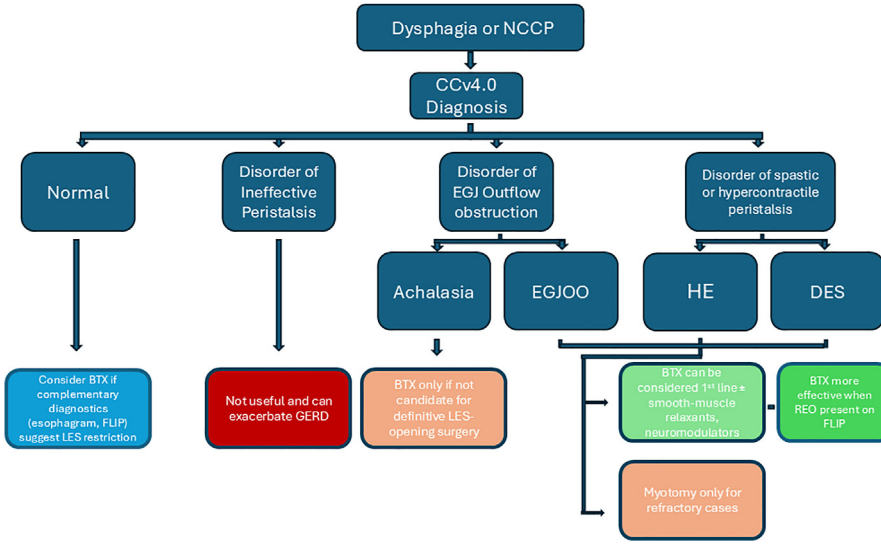

Fig. 3. Proposed algorithm for the use of BTX in the context of Chicago Classification V4.0. Diagnoses are specified in charcoal; and management considerations in other colors. BTX can be considered first-line in EGJOO, HE, and DES.

endoscopy under general anesthesia. Data suggest that injection under direct endoscopic visualized may be superior, with reported efficacy as high as 92%.[50,51] In this case, the technique is to inject 50 to 100 units of BTX into the posterior wall of the postcricoid region using a standard adult gastroscope with distal transparent cap attachment.[51]

SUMMARY OF CURRENT LANDSCAPE, AND FUTURE DIRECTIONS

Endoscopic injection of BTX continues to hold an important position in our current armamentarium of therapies for EMDs. As definitive therapy for achalasia has become less invasive with the advent of POEM, the role of BTX therapy is primarily in treatment of nonachalasia EGJOO and spastic/hypercontractile disorders, which are best understood within the framework of CCv4.0. For EGJOO, spastic and hypercontractile EMDs, BTX represents a safe, and minimally invasive, and practical intervention with modest short-term efficacy. These are conditions where myotomy is recommended only for refractory cases. In our opinion, BTX should be first-line therapy for these conditions along with pharmacologic smooth muscle relaxants. **Fig. 3** illustrates proposed uses of BTX in the context of CCv4.0. BTX should also be used in achalasia when patients are not candidates for definitive LES opening interventions.

An important area of investigation in the coming years will be phenotyping patients with dysphagia and normal esophageal motility per CCv4.0 (ie, functional dysphagia). In several small studies, this population has been shown to demonstrate a certain rate of abnormal FLIP findings (low distensibility, spastic-reactive contractility) as well as retention on esophagram.[52–54] Thus, given the favorable safety profile of BTX therapy, it is reasonable to trial LES BTX in the functional dysphagia population when appropriate symptoms are present and some form LES restriction or is identified on complementary modalities (FLIP, esophagram).

CLINICS CARE POINTS

- Patient Selection: Identify patients with esophagogastric junction outflow obstruction, hypercontractile esophagus, or distal esophageal spasm who may benefit from BTX therapy.
- Procedure Technique: During endoscopy, locate areas of puckered or hypertonic smooth muscle. Inject 100 units of reconstituted BTX in 4-5 mL (use similar dilutions for other dosages), targeting slightly deeper than the submucosal layer.
- Post-Procedure Monitoring: Evaluate for any signs of mediastinitis (rare) immediately after the procedure, and assess for symptom relief 1-2 weeks after BTX injection.

DECLARATION

During the preparation of this work the author(s) used ChatGPT in order to assist with literature review by compiling lists of relevant studies. After using this tool/service, the author(s) reviewed and edited the content as needed and take (s) full responsibility for the content of the publication.

FUNDING

This work was supported by grant NIH K23DK131317 awarded to Anand S Jain.

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