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Bilateral Thyroarytenoid Botulinum Toxin Type A Injection for the Treatment of Refractory Chronic Cough

Humberto C. Sasieta, MD; Vivek N. Iyer, MD, MPH; Diana M. Orbelo, PhD, CCC-SLP; Cynthia Patton, APRN, CNP, DNP; Rebecca Pittelko, MS, CCC-SLP; Karina Keogh, MD; Kaiser G. Lim, MD, PhD; Dale C. Ekbom, MD

IMPORTANCE Refractory chronic cough is a debilitating condition with limited therapeutic options. Laryngeal botulinum toxin type A (BtxA) has been anecdotally reported to benefit patients with chronic cough. We report on our experience with the use of BtxA for the treatment of patients with refractory chronic cough.

OBJECTIVE To describe the effects of electromyography (EMG)-guided thyroarytenoid (TA) BtxA injection for the treatment of refractory chronic cough.

DESIGN, SETTING, AND PARTICIPANTS For this single tertiary referral center retrospective case series, we included all patients with refractory chronic cough who received bilateral EMG-guided TA BtxA injections (n = 22) between July 1, 2013, and July 31, 2014, at the Mayo Clinic in Rochester, Minnesota.

INTERVENTION Bilateral TA BtxA injection.

MAIN OUTCOMES AND MEASURES The primary outcome is a self-reported improvement of 50% or more in cough severity and/or symptoms by a 2-month follow-up telephone call. Adverse events and patient-reported quality measures were also assessed.

RESULTS A total of 22 patients (median [interquartile range] age 61 [57.5-85] years; 19 of 22 women) underwent 31 distinct laryngeal BtxA treatment sessions. The primary outcome of self-reported improvement of 50% or more of cough severity and/or symptoms was achieved in 16 of 31 (52%) treatment sessions. Eleven patients (50%) reported greater than 50% improvement after the first BtxA injection. No major complications occurred. Postprocedural liquid dysphagia had a positive predictive value of 84% and negative predictive value of 100% for response to therapy.

CONCLUSIONS AND RELEVANCE In this case series, laryngeal BtxA injection was well tolerated in patients with refractory chronic cough with half of participants experiencing at least short-term improvement in their cough. The occurrence of liquid dysphagia after a BtxA injection appeared to be predictive of a beneficial response. The durability of response, patient selection criteria, and optimal BtxA dosage remains to be determined.

Invited Commentary
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Author Affiliations: Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota (Sasieta, Iyer, Patton, Keogh, Lim); Department of Otorhinolaryngology-Head and Neck Surgery, Mayo Clinic, Rochester, Minnesota (Orbelo, Pittelko, Ekbom).

Corresponding Author: Vivek N. Iyer, MD, Mayo Clinic, Division of Pulmonary and Critical Care, 200 First St SW, Rochester, MN 55905 (iyer.vivek@mayo.edu).

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Cough currently ranks as the fifth most common presenting complaint among ambulatory medical encounters in the United States. Cough persisting beyond 8 weeks is termed chronic cough and results in significant morbidity and impaired quality of life.[1] The diagnostic workup for chronic cough centers on the anatomy of the cough reflex.[2] Current American College of Chest Physicians (ACCP) chronic cough guidelines apply to nonsmoking patients and those with a normal chest radiography results. Common causes in this situation include upper airway cough syndrome (postnasal drip), asthma, nonasthmatic eosinophilic bronchitis, gastroesophageal reflux disease (GERD), and angiotensin-converting-enzyme (ACE) inhibitor use.[3] In spite of extensive evaluation and multiple empirical therapeutic trials, chronic cough persists in a subset of patients. These patients have been variously labeled as refractory chronic cough, neurogenic cough, idiopathic cough, habit cough, psychogenic cough, and the recently coined term cough hypersensitivity syndrome.[4-6] These patients often experience an urge to cough that results in a self-described sensation of a tickle, itch, soreness, globus, or scratchy sensation in the throat.[5] These patients frequently have symptoms of hypertussia (cough trigged by low intensity stimuli such as chemical odors, perfumes, dust, or changes in humidity or temperature) and/or allotussia (cough induced by nonirritating stimuli such as talking, laughing, singing, deep inspiration, or eating).[6] There is neither diagnostic consensus nor objective confirmatory testing available regarding refractory chronic cough, and it remains a diagnosis of exclusion.[5,7]

Mechanisms proposed for an increased urge to cough include central and/or peripheral sensitization occurring via increased and/or altered receptor expression on nerve endings and a lower threshold for activation.[4,8] A number of neuromodulatory agents including nebulized lidocaine,[9] tricyclic antidepressants,[10] baclofen, and gabapentin[11] have been used for refractory chronic cough with varying success.[12] Two small case series[13,14] reported favorable treatment of refractory chronic cough with laryngeal botulinum toxin type A (BtxA) injections. Chu et al[13] reported complete response in 4 adults while Sipp et al[14] described improvement in 3 children. Patient selection, response rate, number of treatments, and prior workup for chronic cough were not provided. We have used laryngeal BtxA to treat refractory chronic cough patients since July 2013. We present our initial experience with electromyography (EMG)-guided laryngeal BtxA for refractory chronic cough and discuss patient selection, diagnostic tests, and outcomes of this novel treatment approach.

Key Points

Question What is the efficacy of injected botulinum toxin type A (BtxA) in the treatment of refractory chronic cough?

Findings In this case series 22 refractory chronic cough patients treated with laryngeal BtxA, half the patients reported a 50% or greater improvement in their cough during follow up. The development of transient postinjection liquid dysphagia was a strong predictor of treatment success.

Meaning Laryngeal BtxA injection may have a role in the treatment of refractory chronic cough.

Methods

All patients who received laryngeal BtxA injection for refractory chronic cough at the Mayo Clinic Rochester between July 1, 2013, and July 31, 2014, were included in this retrospective study. Written informed consent was obtained from all patients before the procedures, and this study was reviewed and approved by the Mayo Clinic institutional review board.

All patients were evaluated at the Chronic Cough Clinic at our facility, a multidisciplinary clinic housed in the division of pulmonary medicine that collaborates closely with allergy, gastroenterology, otorhinolaryngology, speech pathology, and behavioral medicine specialties. Over 2500 unique chronic cough patients are evaluated annually in this clinic. All patients undergo a systematic evaluation (clinical and diagnostic) to exclude asthma, eosinophilic bronchitis, upper airway cough syndrome (postnasal drip), sinusitis, and GERD. A full complement of diagnostic tests including methacholine challenge, 24-hour pH-impedance, high-resolution esophageal manometry, 24-hour laryngopharyngeal reflux (Restech), sputum eosinophils, bronchoscopy, chest and/or sinus computed tomography, point-of-care rhinoscopy, and point-of-care exhaled nitric oxide are available.

Patients were classified as having refractory chronic cough (neurogenic cough) under the following circumstances: (1) unresolved chronic cough with no obvious underlying cause and (2) unresolved chronic cough even after adequate treatment for 1 or more qualifying conditions (upper airways cough syndrome [UACS], GERD, and/or eosinophilic airways disorders [asthma, cough variant asthma, and/or nonasthmatic eosinophilic bronchitis]). GERD was considered adequately treated if an oral dose equivalent of 20 mg or more daily omeprazole achieved symptomatic reflux control. This definition aligns with current ACCP guidelines.[3] Patients with refractory chronic cough are offered an urge to cough desensitization program with our behavioral medicine colleagues and/or a therapeutic trial of a neuromodulatory agent (amitriptyline, gabapentin, serotonin-norepinephrine reuptake inhibitor [duloxetine] and/or nebulized lidocaine) depending on patient preference, medication reconciliation, and response to prior treatments. If the patient failed to respond to an adequate trial of 1 or more of the above treatments for neurogenic cough, they were referred to our laryngologist (D.C.E.) and one of our board-certified speech language pathologists (R.P. and D.M.O.) for consideration of laryngeal BtxA. All patients then underwent a speech therapy consultation with a focus on education regarding the BtxA injection procedure. Information regarding the cough-injury-cough cycle, use of cough suppression, and substitution behaviors and relaxed diaphragmatic breathing were discussed with patients at various points during their consultation in the cough clinic. Speech quality was also assessed in a detailed fashion in all

patients along with a flexible laryngoscopy. A stroboscopic examination was also attempted or performed in all but 1 patient. The rating instrument used was the Stroboscopy Evaluation Rating Form (SERF).[15] A structured multisession speech therapy program was however not implemented because most patients traveled from a distance and were unable to return for follow up visits.

Patients found to have major laryngeal structural abnormalities such as malignancies, polyps, cysts, or other vocal cord lesions were treated accordingly and were excluded from further consideration for laryngeal BtxA. Patients with isolated arytenoid granulomas related to cough-related trauma were not excluded and did receive laryngeal BtxA. Eligible patients were counseled about BtxA and were required to watch an informational video of an actual laryngeal BtxA procedure being performed (https://www.youtube.com/watch?v=Gt41H5P4jmk).

Exclusion criteria included the following: (1) patient refusal, (2) inability to participate in postprocedure follow-up, and/or (3) anticoagulation that could not be withheld for medical reasons.

All laryngeal BtxA injections were performed by a single laryngologist (D.C.E.) using a percutaneous midline transcricothyroid membrane single point entry injection approach without local anesthesia. A monopolar teflon-coated hollow bore 27-gauge EMG needle attached to a tuberculin syringe was angled into the thyroarytenoid muscle on each side sequentially without complete needle withdrawal out of the skin between injections. The patient was instructed to phonate to increase EMG signal prior to injection. A neurophysiologist assigned to the EMG laboratory confirmed proper placement prior to injection. The initial treatment consisted of 2.5 U/0.1 mL (Botox, Allergan Pharmaceuticals) injected into each thyroarytenoid muscle. All the patients received bilateral injections. Postprocedurally, patients were monitored for aspiration, voice quality, and pain. A scheduled follow-up phone call occurred 1 month and 2 months after the procedure. Domains covered during the phone call included adverse effects (pain, dysphagia, loss of voice, aspiration), improvements in cough (perception and duration of cough relief, time to symptom return), and patient satisfaction (satisfaction with quality of education regarding the rationale and procedural aspects of BtxA, whether they would recommend the procedure to others). The primary outcome was treatment success as defined by a 50% or greater reduction in the patient's subjective perception or assessment of their cough severity.

Statistical analysis was performed using IBM SPSS Statistics, version 20 (IBM Corp). Continuous variables were presented as median and interquartile ranges (IQR) and qualitative variables as proportions. The χ^2 test was used to assess statistical significance for qualitative variables.

Results

A total of 26 patients received treatment with laryngeal BtxA during this time period. A total of 4 patients were excluded from further analysis (2 lost to follow-up after the first injection and 2 patients declined medical research authorization). Thus the final cohort included 22 patients who underwent 31 distinct laryngeal BtxA treatment sessions with available postprocedure follow up. This included 16 patients (73%) with 1 BtxA treatment; 4 patients (18%) with 2 treatments; 1 patient (5%) with 3 treatments; and 1 patient (5%) with 4 distinct BtxA treatments. Demographic characteristics, duration of chronic cough, smoking status, and prior treatments are shown in **Table 1**.

The median (IQR) age of patients was 61 (57.5-85) years with female predominance (n = 19 of 22 [86%]). The median (IQR) duration of cough was 13 (2-33) years. The median (IQR) body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) was 31 (27-41). None of the patients were taking ACE inhibitors, and only 1 (case 1) was a light smoker with 40 pack-year history. All patients had received 1 or more neuromodulatory agents either at our center or by the referring provider without significant improvement.

Details of evaluation for GERD, UACS, and eosinophilic airway diseases are shown in **Table 2**. GERD was excluded or treated in all patients. Eighteen patients (81%) were currently receiving or had received proton pump inhibitors (PPIs), and 1 patient had undergone a prior Nissen fundoplication. Fourteen patients (64%) underwent 24-hour esophageal pH monitoring and impedance testing, with 4 positive studies (mean DeMeester score of 30.8). No patient had a positive response to high dose PPI therapy. Evaluation for asthma and eosinophilic bronchitis showed 3 patients with a positive methacholine challenge (1 with obstruction, 2 with normal spirometry). Pulmonary function studies showed obstruction in 3 cases, restriction (obesity related) in 2 patients, and were normal in the rest of the cases (n = 17). Upper airways cough syndrome was evaluated in all cases by rhinoscopy and was abnormal in 10 patients (45%). These 10 patients received a trial of a triple combination nasal spray (azelastine, ipratropium, and flunisolide ormometasone) but did not have an improvement in their cough.

Treatment Outcomes After BtxA Injection

Treatment success (50% or greater subjective improvement in cough during the scripted phone call 2 months after a BtxA treatment session) occurred in 11 patients (50%) after the first BtxA injection. Three patients (14%) had a complete resolution of cough after the first treatment session. Four of 11 patients in the treatment success group underwent a second BtxA injection after a median (range) duration of 109 (93-316) days from the first BtxA treatment. Worsening cough was the primary reason for reinjection. Of these, only 1 experienced treatment success; 2 patients failed treatment, and 1 patient was lost to follow-up. One patient underwent 3 BtxA treatment sessions (day 0, 93, and 113) with treatment success recorded after each treatment. Another patient underwent 4 BtxA treatment sessions (day 0, 94, 187, and 289) and experienced success after the first, third, and fourth treatments. Symptom improvement occurred after a median (IQR) of 1 (0.65-2) week(s), and median (IQR) time to perceived decline in therapeutic effect was 3.5 (1-8) weeks. There was a strong and significant association between the development of liquid dysphagia and treatment success after BtxA treatment. The occurrence of liquid

Table 1. Demographics and Treatment Details

			Medical Therapy for Chronic Cough							
Patient No./Sex	BMI	Chronic Cough Duration, y	Azelastine, Ipatropium, and Nasal Steroid Combination	Nebulized Lidocaine	Gabapentin	Duloxetine	Venlafaxine	Proton Pump Inhibitor	Tricyclic Antidepressant	Baclofen
1/M[a]	36.7	"Many"	Yes	Yes	No	Yes	No	Yes	No	Yes
2/M	26.3	22	Yes	Yes	No	Yes	Yes	Yes	No	Yes
3/F	21.6	15	No	No	No	No	No	Yes	Yes	No
4/F	34.8	15	Yes	Yes	Yes	Yes	No	Yes	No	Yes
5/F	26.5	33	Yes	Yes	No	Yes	No	Yes	No	No
6/F	25.7	20	Yes	No	No	Yes	No	Yes	No	No
7/F	26.9	16	Yes	Yes	Yes	No	No	Yes	Yes	No
8/F	38.1	1	Yes	No	Yes	Yes	No	Yes	No	No
9/F	41.0	1.5	Yes	Yes	No	Yes	No	No	No	No
10/F	30.6	10	Yes	No	No	No	Yes	Yes	No	Yes
11/F	36.7	1	Yes	Yes	No	Yes	No	Yes	No	No
12/F	26.3	25	Yes	No	No	No	No	Yes	No	No
13/F	33.8	2	Yes	No	Yes	Yes	No	Yes	No	Yes
14/M	28.4	25	No	No	No	No	No	No	No	No
15/F	37.5	5	Yes	No	Yes	No	No	No	No	No
16/F	30.4	21	Yes	Yes	No	No	No	Yes	No	No
17/F	27.5	13	No	No	No	No	Yes	No	No	No
18/F	34.3	13	No	No	Yes	No	No	Yes	Yes	No
19/F	28.1	1	No	Yes	No	No	No	Yes	No	No
20/F	28.1	10	Yes	No	Yes	No	No	Yes	No	No
21/F	27.5	20	Yes	No	Yes	No	No	Yes	No	Yes
22/F	35.1	1	No	No	No	No	No	Yes	No	No

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] Patient 1 was the only patient who reported being a current smoker.

dysphagia after BtxA treatment had a sensitivity of 100%, specificity of 80%, positive predictive value of 84%, and negative predictive value of 100% for treatment success. The development of dysphonia had no significant correlation with treatment outcomes (**Table 3**). At the time of last study follow-up, no patient had reported a complete and permanent resolution of cough.

Eleven patients (50%) reported a less than 50% improvement in cough, of whom 4 underwent 1 additional treatment session after a median (range) of 110 (90-124) days. Of these, 1 reported improvement with the second BtxA injection, 2 reported no improvement, and 1 was lost to follow-up. Of these 11 patients with less than a 50% improvement in cough, only 6 reported absolutely no improvement in either the frequency or severity of the cough. Overall, 16 of 22 patients (73%) reported at least some improvement in cough after the first BtxA injection. The dose of BtxA was not associated with treatment outcome.

Stroboscopic Evaluation

Stroboscopy data were available for 18 of 22 patients from the initial speech-language pathology or ear, nose, throat evaluation (**Table 4**). These were subsequently rated by an experienced speech-language pathologist (R.P.) who was blinded to the results of BtxA (responder vs nonresponder status). Data was not available on 4 patients for the following reasons: patients 12 and 15 underwent stroboscopy, but video was unavailable for blinded review; patient 16 did not undergo stroboscopy due to scheduling issues; and patient 20 could not undergo satisfactory stroboscopy due to continuous coughing during the procedure (Table 4). No differences were found between the 2 groups using the 2-tailed Fisher exact test to compare amplitude of vibration and phase closure and the Pearson χ^2 test to compare the remaining variables. No differences were found in other SERF variables assessing vertical level difference, vocal fold roughness, and vocal fold motion (data not displayed).

Adverse Response to Laryngeal BtxA Injections

There were no immediate complications observed following the administration of BtxA. Transient dysphonia (n = 19 [86%]) and liquid dysphagia (n = 14 [64%]) occurred frequently after the first BtxA injection and was well tolerated (**Table 5**). Post-BtxA injection dysphonia occurred for a median (IQR) of 4 (3-5.25) weeks, and dysphagia occurred for a median (IQR) of 2 (1-3) weeks. These symptoms resolved completely in all patients on follow-up. The patients reported no instances of aspiration pneumonia or pneumonitis, requirement for antibiotics, or unexpected health care use at the time of follow-up.

Table 2. Details of Evaluation for GERD, UACS, and Eosinophilic Airways Disease

Patient No.	Pulmonary Function Test	Methacoline Test	Oral FeNO, ppb	Nasal FeNO, ppb	Esophageal 24-h pH	Esophageal Impedance	Esopageal Manometry	Rhinoscopy
1	Restriction	...	13.2	182	Normal	Positive	Normal	Abnormal
2	Normal	...	...	...	Normal	Normal	...	Abnormal
3	Normal	...	15	123	...	...	...	Normal
4	Normal	Negative	11.5	...	Positive	Positive	Abnormal	Abnormal
5	Obstruction	...	31.5	245	Normal	Normal	...	Abnormal
6	Normal	...	14.3	155	Positive	Positive	...	Normal
7	Normal	Negative	15.4	165	Normal	Normal	...	Normal
8	Restriction		23.4	116	...	...	...	Abnormal
9	Normal	Negative	31	...	...	...	...	Normal
10	Obstruction	Positive	9	...	Normal	Normal	...	Abnormal
11	Normal	...	10	...	Positive	Positive	Normal	Normal
12	Normal	Negative	10	197	Positive	Positive	...	Abnormal
13	Normal	Negative	9	201	Normal	Normal	...	Normal
14	Normal	...	30	...	...	...	...	Normal
15	Normal	Positive	19.7	180	Normal	Normal	...	Normal
16	Normal	Positive	7	...	Normal	Normal	Abnormal	Normal
17	Obstruction	...	6.8	220	....	...	...	Normal
18	Normal	Negative	...	...	Positive	...	Abnormal	Abnormal
19	Normal	...	20	...	Normal	...	...	Abnormal
20	Normal	...	18	...	Normal	Positive	Abnormal	Normal
21	Normal	Negative	18.1	396	Positive	Positive	Abnormal	Abnormal
22	Normal	Negative	23	...	Normal	...	...	Normal

Abbreviations: FeNO, fractional inhaled nitric oxide; GERD, gastroesophageal reflux disease; UACS, upper airways cough syndrome; ellipses, data not applicable and/or unavailable.

Patient Perception of Care

Laryngeal BtxA for chronic cough was well tolerated. Most patients (n = 14 [64%]) would either recommend (36%) or highly recommend (27%) this treatment to others with chronic cough. Most patients (n = 17 [77%]) were satisfied (27%) or highly satisfied (50%) with the care and follow-up after treatment, and most patients (n = 16 [73%]) were also satisfied (23%) or highly satisfied (50%) with the preintervention education.

Discussion

This is the first large series that we know of that reports on consecutive patients treated with laryngeal BtxA for refractory chronic cough. Overall 50% of patients reported treatment success (≥50% reduction in the subjective assessment of their cough severity) after the first injection of laryngeal BtxA. Only 3 of 22 patients had complete cough resolution, whereas 16 of 22 reported at least some improvement after BtxA. All patients in this study had undergone a comprehensive diagnostic evaluation and multiple therapeutic trials for asthma, GERD, and UACS where applicable. In addition, all patients had failed a trial of 1 or more neuromodulatory agents before receiving laryngeal BtxA. Patients also received counselling from 1 of 2 experienced speech therapists with a detailed laryngoscopy and stroboscopic exam. However, a structured multisession speech therapy program was not implemented owing to logistical reasons discussed in the Results.[7]

Table 3. Treatment Success and Occurrence of Dysphonia or Liquid Dysphagia

Occurrence	Success, No.			*P* Value
	Not Achieved	Achieved	Total Cases	
Dysphonia				
Not present	2	2	4	
Present	13	14	27	.68
Total	15	16	31	
Liquid dysphagia				
Not present	12	0	12	
Present	3	16	19	.001
Total	15	16	31	

Prior studies of laryngeal BtxA for chronic cough have been very small. Chu et al[13,16] reported complete response in 4 adults, and Sipp et al[14] described improvement in 3 children. These studies did not describe patient selection and did not report on prior workup of their patients. Ours is the largest series with follow-up on all patients who received BtxA therapy.

The exact mechanism(s) of action of laryngeal BtxA in chronic cough remain unclear. Botulinum toxin type A is a potent neurotoxin that is produced by *Clostridium botulinum* and inhibits the release of presynaptic acetylcholine via a complex series of steps involving binding, internalization, membrane translocation, and ultimately specific protease activity that inhibits acetylcholine release in an irreversible fashion.[8]

Table 4. Stroboscopy Evaluation Rating Form Scores by Botulinum Toxin Type A Injection Response

Patient No.	% Amplitude Vibration Right VF	% Amplitude Vibration Left VF	% Mucosal Wave Right VF	% Mucosal Wave Left VF	Supraglottic Activity	Phase Closure 0 = Normal 2 = Predominantly Open	Phase Symmetry 0-Normal Open/Close	Regularity	Glottal Closure Pattern
Responders									
1	40	40	40	40	2	0	100	100	Anterior gap
3	40	40	60	80	1	2	80	100	Anterior gap
7	40	40	60	60	1	0	100	100	Complete
8	40	20	60	20	1	2	60	80	Incomplete
9	40	40	40	40	1	2	60	80	Complete
11	40	40	20	20	3	2	80	80	Incomplete
12	...	...	...	...	...	...	...	...	...
13	40	40	40	40	1	0	100	100	Complete
14	40	40	40	40	2	0	100	100	Complete
18	40	40	40	40	1	0	80	100	Complete
20	...	...	...	...	...	...	...	...	...
22	20	40	40	60	1	0	80	100	Posterior gap
Nonresponders									
2	40	40	40	40	0	0	100	100	Anterior gap
4	40	40	40	40	2	2	80	80	Incomplete
5	20	40	40	60	2	2	20	20	Irregular
6	40	40	60	60	1	0	100	100	Complete
10	40	40	40	40	1	0	80	100	Complete
15	...	...	...	...	...	...	...	...	...
16	...	...	...	...	...	...	...	...	...
17	20	20	40	40	2	0	80	100	Complete
19	40	40	40	40	3	0	100	100	Anterior gap
21	40	40	60	60	2	2	100	100	Incomplete
P values	.56	>.99	.61	.39	.23	>.99	.40	.39	.80

Abbreviations: VF, ventricular fibrillation; ellipses, data not applicable and/or unavailable.

This occurs in a dose-dependent fashion with inhibition of neuronal transmission until the regeneration of new nerve terminals.[17] Direct analgesic effects of BtxA have also been recognized with attenuation of the release of neuropeptides (substance P, calcitonin gene-related peptide, and glutamate) from C-fiber receptors.[18] Cough has been found to be mediated by a number of nociceptive receptors found on free nerve endings infiltrating the epithelium of the pharynx, larynx, and the respiratory tract. Increased expression of the transient receptor potential vanilloid receptor type 1 (TRPV1) has been found in the airways of patients with chronic cough,[8]and capsaicin induces cough through its interaction with TRPV1. In the literature, the use of BtxA to reduce capsaicin-mediated nociception has been reported.[2,11,13,16] Using a skin model, BtxA reduced capsaicin-induced pain and neurogenic vasodilatation. The reduction in neurogenic vasodilatation by BtxA did not contribute to its analgesic action suggesting a direct action on capsaicin-mediated nociception. It is intriguing to speculate whether a similar mechanism of action is at play in chronic cough. Thus it is possible that laryngeal BtxA decreases the urge to cough by attenuating capsaicin and C-fiber–mediated nociception (cough receptors) thus desensitizing the urge-to-cough pathway. A neuropathic model and associated laryngeal hypersensitivity is increasingly recognized as a primary factor in a substantial number of patients with refractory chronic cough, and BtxA may have a role in modulating the peripheral afferent loop of this pathway.[4-6]

Another possible explanation is that laryngeal BtxA inhibits the cough-injury-cough cycle by temporarily weakening the vocal cords. It is well known that even a brief episode of coughing induces considerable laryngeal irritation and injury, thus setting up a self-perpetuating cough-injury-cough cycle. Weakening the vocal cords with laryngeal BtxA may allow for a time of rest and healing with reduced injury of both the larynx and the tracheobronchial tree, helping to interrupt this cough-injury-cough cycle. Blinded stroboscopic evaluation did not appear to predict BtxA responders from nonresponders.

An additional mechanism that merits consideration is the finding that a significant number of patients with chronic cough have laryngeal dysfunction manifesting as paradoxical vocal cord motion and/or laryngeal hypersensitivity.[19,20] It is not inconceivable that weakening the vocal cords using laryngeal BtxA can help attenuate and modulate sensory-motor circuits mediating repeated laryngeal adduction and/or spasms (coughing).

The placebo response also needs to be considered as a plausible explanation for the benefits of laryngeal BtxA.[11] It is also well recognized that active treatments may also have a

Table 5. Treatment Outcomes After Each BtxA Injection

Patient No.	First Treatment				Second Treatment			
	BtxA (IU)	Dysphagia	Dysphonia	Success	BtxA (IU)	Dysphagia	Dysphonia	Success
1	2.5	Y	Y	Y	2.75	N	Y	N
2	2.5	Y	Y	N	…	…	…	…
3	2.5	Y	Y	Y	…	…	…	…
4	2.5	N	N	N	…	…	…	…
5	2.5	Y	Y	N	…	…	…	…
6	2.5	N	Y	N	2.5	N	Y	N
7[a]	2.5	Y	Y	Y	3.75	N	Y	N
8	2.5	Y	Y	Y	…	…	…	…
9	2.5	Y	Y	Y	…	…	…	…
10	2.5	N	N	N	3	Lost to follow-up	Lost to follow-up	…
11	2.5	Y	Y	Y	…	…	…	…
12[b]	2.5	Y	Y	Y	3	Y	Y	Y
13	2.5	N	Y	N	3	Y	Y	Y
14	2.5	Y	Y	Y	3	Lost to follow-up	Lost to follow-up	…
15	2.5	N	Y	N	3	N	Y	N
16	2.5	N	Y	N	…	…	…	…
17	2.5	N	Y	N	…	…	…	…
18	2.5	Y	Y	Y	…	…	…	…
19	2.5	N	Y	N	…	…	…	…
20	2.5	Y	Y	Y	…	…	…	…
21	2.5	Y	Y	N	…	…	…	…
22	2.5	Y	Y	Y	…	…	…	…

Abbreviations: BtxA, botulinum toxin type A; ellipses, data not applicable and/or unavailable; IU, international unit.

[a] Patient 7 received a third treatment of 4 IU BtxA that successfully treated dysphagia and dysphonia and also received a fourth injection of 6 IU BtxA that successfully treated dysphagia and dysphonia.

[b] Patient 12 received a third treatment of 3.5 IU BtxA that successfully treated dysphagia and dysphonia.

substantial placebo-related effect hidden within the treatment response.[16] Several observations in our study diminish the possibility that the benefits were solely due to the placebo response. For instance, two patients with a positive response to the first BtxA treatment had no response to a subsequent injection (patients 1 and 7), (Table 5). Similarly, another patient (patient 13) (Table 5) with a negative response to the first BtxA injection responded positively to the second injection. These varying responses within an individual patient do not completely fit the placebo response. The only way to truly answer this question would be a double-blind, placebo-controlled, sham-controlled trial of laryngeal BtxA in chronic cough.[21]

Why did liquid phase dysphagia but not dysphonia seem to correlate with treatment success, and why was the treatment response so brief? The reasons remain unclear. Possible explanations include that loss of glottal closure may be reflective of proper needle placement and effective inhibition of sensory afferents. Additionally, dysphagia may have acted as a potent distraction that may have inhibited coughing. The larynx has the highest density of tussigenic nerve endings followed by the carina, trachea, and the proximal bronchi.[17,18] The diffusion of BtxA into the pharyngeal area and resultant dysphagia may be a factor to be considered in future studies. Behavioral response to the urge to cough is susceptible to suppression and modification by desensitization and distraction.[22] It is also unclear whether the use of a higher dose of BtxA or a longer-acting pegylated formulation of BtxA will result in improved treatment outcomes.

It is also unclear whether there is a synergistic response when laryngeal BtxA is used alongside other neuromodulatory agents such as amitriptyline, gabapentin, nebulized lidocaine, or cognitive behavioral therapy. These combined modality approaches are likely to better attenuate the urge to cough sensation by attacking various aspects of the cough reflex pathway. We also noted that in 7 of those who responded favorably to the treatment, no further injections were sought. Several factors may have played a part, including the cost of travel to our center, the short-term adverse effects, and the transient duration of benefits. We also cannot rule out that patients could have arranged to receive this treatment elsewhere.

The strengths of our study include the relatively large number of patients studied and the homogenous treatment approach of a limited number of treating physicians working in the chronic cough clinic.[20] A fairly extensive evaluation was undertaken for each patient before labeling them as refractory chronic cough. All BtxA injections were performed by a single provider with a structured follow-up phone call occurring after each BtxA injection.

Limitations of our study include the retrospective and single-center nature of this study. We could not report on data

from 4 patients, though it is unclear whether this may have positively or negatively affected our treatment results. Another shortcoming is the short duration of follow-up and the lack of long-term treatment outcomes. The use of self-reported subjective cough improvement is also easily influenced by patient subjectivity. This case series was not intended as a definitive study. It is offered as a relatively large observational study validating prior studies in different populations.[13,14]

Future studies should incorporate validated subjective cough-specific, health-related, quality-of-life instruments, as well as objective measures of cough severity, frequency, and response to preintervention and postintervention tussigenic challenges. In addition, optimal BtxA dose will require a dose ranging study and trials of long acting agents (ie, pegylated preparations).[23] The current BtxA dose was selected for its safety in spasmodic dysphonia.

Conclusions

We report on our initial treatment experience with laryngeal BtxA in refractory chronic cough and report a roughly 50% short-term treatment response. Several questions regarding mechanism of action, optimal dosing regimen, durability of response, and appropriate patient selection remain unanswered. Laryngeal BtxA may have a role in the management of patients with refractory chronic cough, and requires further study.

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Study concept and design: Sasieta, Iyer, Orbelo, Patton, Pittelko, Keogh, Lim, Ekbom.
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Drafting of the manuscript: Sasieta, Iyer, Orbelo, Patton, Lim, Ekbom.
Critical revision of the manuscript for important intellectual content: Sasieta, Iyer, Orbelo, Patton, Pittelko, Keogh, Lim, Ekbom.
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