Reference number(s)
2624-A

Standard Medicare Part B Management Botulinum Toxins

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Botox	onabotulinumtoxinA
Dysport	abobotulinumtoxinA
Xeomin	incobotulinumtoxinA
Myobloc	rimabotulinumtoxinB
Daxxify	daxibotulinumtoxinA-lanm

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

Botox

FDA-approved Indications[1]

- Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication
- Treatment of urinary incontinence due to detrusor muscle overactivity associated with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication
- Prophylaxis of headaches in adult patients with chronic migraine (>15 days per month with a headache lasting 4 hours a day or longer)

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- Treatment of spasticity in patients 2 years of age and older
- Treatment of cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain
- Treatment of severe primary axillary hyperhidrosis that is inadequately managed by topical agents in adult patients
- Treatment of blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and older
- Treatment of strabismus in patients 12 years of age and older
- Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients 5 years of age and older who have an inadequate response to or are intolerant of anticholinergic medication

Compendial Uses[2-3, 63]

- Achalasia
- Anal fissure, chronic
- Auriculotemporal syndrome
- Benign prostatic hyperplasia
- Cervicogenic headache
- Detrusor and sphincter dyssynergia
- Difficulty talking - total laryngectomy
- Disorder of nervous system – excessive salivation
- Dysphagia
- Epicondylitis
- Essential tremor
- Excessive salivation - Parkinson’s disease, advanced
- Excessive tear production
- Granuloma of vocal cords, refractory to conventional surgical and medical therapies
- Hemifacial spasm
- Idiopathic trigeminal neuralgia, refractory
- Infantile esotropia
- Injury to oculomotor nerve (acute)
- Isolated oromandibular dystonia
- Larynx closure, adjunct to surgical procedure
- Low back pain, chronic
- Myofascial pain syndrome
- Neuropathic pain - spinal cord injury
- Organic voice tremor

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- Palmar hyperhidrosis
- Pelvic floor dyssynergia
- Spasm, of pharyngoesophageal segment - total laryngectomy
- Spastic dysphonia
- Stuttering
- Tardive dyskinesia
- Temporomandibular joint disorder
- Tension-type headache
- Thoracic outlet syndrome
- Tourette syndrome or chronic tic disorders
- Whiplash injury to neck

Dysport

FDA-approved Indications[4]

- Treatment of adults with cervical dystonia
- Treatment of spasticity in patients 2 years of age and older

Compendial Uses[2-3]

- Achalasia, in patients who are surgical candidates
- Blepharospasm
- Hemifacial spasm

Xeomin

FDA-approved Indications[5]

- Treatment of chronic sialorrhea in patients 2 years of age and older
- Treatment of upper limb spasticity in adult patients
- Treatment of upper limb spasticity in pediatric patients 2 to 17 years of age, excluding spasticity caused by cerebral palsy
- Treatment of adults with cervical dystonia
- Treatment of adults with blepharospasm

Myobloc

FDA-approved Indications[6]

- Treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia

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- Treatment of chronic sialorrhea in adults

Compendial Uses[2-3]

- Axillary hyperhidrosis
- Bladder muscle dysfunction leading to overactive bladder
- Blepharospasm
- Hemifacial spasm
- Palmar hyperhidrosis
- Spastic dysphonia
- Upper limb spasticity

Daxxify

FDA-approved Indication[7]

- The treatment of cervical dystonia in adult patients.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Exclusions

Coverage will not be provided for cosmetic use.

Coverage Criteria

Botox

Overactive Bladder with Urinary Incontinence

Authorization of 12 months may be granted for the treatment of overactive bladder in adults, 18 years of age and older with urinary incontinence.

Urinary Incontinence Associated with a Neurologic Condition

Authorization of 12 months may be granted for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., spinal cord injury, multiple sclerosis) when members are 5 years of age and older.

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Chronic Migraine Prophylaxis

Authorization of 6 months (two injection cycles) may be granted for the treatment of chronic migraine headache when all of the following are met:

- Member has migraine headaches at least 15 days per month.
- Member is 18 years of age or older.

Limb Spasticity

Authorization of 12 months may be granted for the treatment of limb spasticity including hands and feet either as a primary diagnosis or as a symptom of a condition causing limb spasticity in members 2 years of age and older.

Cervical Dystonia

Authorization of 12 months may be granted for the treatment of adults with cervical dystonia (e.g., torticollis) when there is abnormal placement of the head with limited range of motion in the neck when members are 18 years of age or older.

Primary Axillary Hyperhidrosis

Authorization of 12 months may be granted for the treatment of primary axillary hyperhidrosis for members 18 years of age and older.

Blepharospasm

Authorization of 12 months may be granted for the treatment of blepharospasm, including blepharospasm associated with dystonia and benign essential blepharospasm or VII nerve disorders when the member is 12 years of age or older.

Strabismus

Authorization of 12 months may be granted for the treatment of strabismus when the member is 12 years of age or older.

Achalasia

Authorization of 12 months may be granted for the treatment of achalasia.

Anal Fissure, Chronic

Authorization of 12 months may be granted for the treatment chronic anal fissures.

Auriculotemporal Syndrome

Authorization of 12 months may be granted for the treatment of auriculotemporal syndrome.

Benign Prostatic Hyperplasia

Authorization of 12 months may be granted for the treatment of benign prostatic hyperplasia.

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Cervicogenic Headache

Authorization of 12 months may be granted for the treatment of cervicogenic headache.

Detrusor (Including Neurogenic Detrusor Overactivity (NDO)) and Sphincter Dyssynergia

Authorization of 12 months may be granted for the treatment of detrusor (NDO) and sphincter dyssynergia.

Difficulty Talking - Total Laryngectomy

Authorization of 12 months may be granted for the treatment of difficulty speaking following a total laryngectomy.

Dysphagia

Authorization of 12 months may be granted for the treatment of disorder of the esophagus (dysphagia).

Epicondylitis

Authorization of 12 months may be granted for the treatment of epicondylitis.

Essential Tremor

Authorization of 12 months may be granted for the treatment of disorder of essential tremor.

Excessive Salivation Secondary to a Disorder of the Nervous System or Advanced Parkinson's Disease

Authorization of 12 months may be granted for the treatment of excessive salivation secondary to a disorder of the nervous system or advanced Parkinson's disease.

Excessive Tear Production

Authorization of 12 months may be granted for the treatment of excessive tear production.

Granuloma of Vocal Cords, Refractory to Conventional Surgical and Medical Therapies

Authorization of 12 months may be granted for the treatment of granuloma of the vocal cords that is refractory to conventional surgical and medical therapies.

Hemifacial Spasm

Authorization of 12 months may be granted for the treatment of hemifacial spasm.

Idiopathic Trigeminal Neuralgia, Refractory

Authorization of 12 months may be granted for the treatment of refractory idiopathic trigeminal neuralgia.

Infantile Esotropia

Authorization of 12 months may be granted for the treatment of infantile esotropia.

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Injury to Oculomotor Nerve (Acute)

Authorization of 12 months may be granted for the treatment of oculomotor nerve injury.

Isolated Oromandibular Dystonia

Authorization of 12 months may be granted for the treatment of isolated oromandibular dystonia.

Larynx Closure, Adjunct to Surgical Procedure

Authorization of 12 months may be granted for the treatment of larynx closure as adjunct to surgical procedure.

Low Back Pain, Chronic

Authorization of 6 months may be granted for the treatment of chronic lower back pain.

Myofascial Pain Syndrome

Authorization of 12 months may be granted for the treatment of myofascial pain syndrome.

Neuropathic Pain - Spinal Cord Injury

Authorization of 12 months may be granted for the treatment of neuropathic pain secondary to spinal cord injury.

Organic Voice Tremor

Authorization of 12 months may be granted for the treatment of organic voice tremor.

Palmar Hyperhidrosis

Authorization of 12 months may be granted for the treatment of palmar hyperhidrosis.

Pelvic Floor Dyssynergia

Authorization of 12 months may be granted for the treatment of pelvic floor dyssynergia.

Spasm, of Pharyngoesophageal Segment -Total Laryngectomy

Authorization of 12 months may be granted for the treatment of pharyngoesophageal segment spasm following total laryngectomy.

Spastic Dysphonia

Authorization of 12 months may be granted for the treatment of spastic dysphonia.

Stuttering

Authorization of 12 months may be granted for the treatment of stuttering.

Tardive Dyskinesia

Authorization of 12 months may be granted for the treatment of tardive dyskinesia.

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Temporomandibular Joint Disorder

Authorization of 12 months may be granted for the treatment of temporomandibular joint disorder.

Tension-Type Headache

Authorization of 12 months may be granted for the treatment of tension-type headache.

Thoracic Outlet Syndrome

Authorization for 12 months may be granted for the treatment of thoracic outlet syndrome.

Tourette Syndrome or Chronic Tic Disorder

Authorization of 12 months may be granted for the treatment of Gilles de la Tourette's syndrome or chronic tic disorder.

Whiplash to the Neck

Authorization of 12 months may be granted for the treatment of whiplash to the neck.

Dysport

Cervical Dystonia

Authorization of 12 months may be granted for the treatment of adults 18 years of age and older with cervical dystonia (e.g., torticollis) when there is abnormal placement of the head with limited range of motion in the neck.

Limb Spasticity

Authorization of 12 months may be granted for the treatment of upper or lower limb spasticity either as a primary diagnosis or as a symptom of a condition causing limb spasticity in members 2 years of age or older.

Achalasia

Authorization of 12 months may be granted for the treatment of achalasia.

Blepharospasm

Authorization of 12 months may be granted for the treatment of blepharospasm, including blepharospasm associated with dystonia and benign essential blepharospasm.

Hemifacial Spasm

Authorization of 12 months may be granted for hemifacial spasm.

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Xeomin

Blepharospasm

Authorization of 12 months may be granted for the treatment of blepharospasm, including blepharospasm associated with dystonia and benign essential blepharospasm in members 18 years of age or older.

Cervical Dystonia

Authorization of 12 months may be granted for the treatment of adults, aged 18 years and older with cervical dystonia (e.g., torticollis) when there is abnormal placement of the head with limited range of motion in the neck.

Upper Limb Spasticity

Authorization of 12 months may be granted for the treatment of upper limb spasticity when all of the following are met:

- Member has a diagnosis of upper limb spasticity either as a primary diagnosis or as a symptom of a condition causing limb spasticity.
- Member meets one of the following criteria:
  - Member is 18 years of age or older
  - Member is 2 to 17 years of age and the spasticity is not caused by cerebral palsy.

Excessive Salivation

Authorization of 12 months may be granted for the treatment of excessive salivation (chronic sialorrhea) for members 2 years of age and older.

Myobloc

Cervical Dystonia

Authorization of 12 months may be granted for the treatment of adults, aged 18 years of age and older with cervical dystonia (e.g., torticollis) when there is abnormal placement of head and limited range of motion in the neck.

Axillary Hyperhidrosis

Authorization of 12 months may be granted for the treatment of primary axillary hyperhidrosis.

Overactive Bladder with Urinary Incontinence

Authorization of 12 months may be granted for the treatment of overactive bladder with urinary incontinence.

Blepharospasm

Authorization of 12 months may be granted for the treatment of blepharospasm.

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Excessive Salivation

Authorization of 12 months may be granted for the treatment of excessive salivation (chronic sialorrhea) in adults aged 18 years and older.

Hemifacial Spasm

Authorization of 12 months may be granted for hemifacial spasm.

Palmar Hyperhidrosis

Authorization of 12 months may be granted for the treatment of palmar hyperhidrosis.

Spastic Dysphonia

Authorization of 12 months may be granted for the treatment of spastic dysphonia.

Upper Limb Spasticity

Authorization of 12 months may be granted for the treatment of upper limb spasticity either as a primary diagnosis or as a symptom of a condition causing limb spasticity.

Daxxify

Cervical Dystonia

Authorization of 12 months may be granted for the treatment of adults, aged 18 years of age and older with cervical dystonia (e.g., torticollis) when there is abnormal placement of head and limited range of motion in the neck.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 24 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested botulinum toxin drug.
- The botulinum toxin drug requested is for a diagnosis or condition in the coverage criteria section.
- The botulinum toxin drug requested has been effective for treating the diagnosis or condition.

Summary of Evidence

The contents of this policy were created after examining the following resources:

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- The prescribing information for Botox, Daxxify, Dysport, Myobloc, and Xeomin.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- European Academy of Neurology guideline on trigeminal neuralgia

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Botox, Daxxify, Dysport, Myobloc and Xeomin are covered in addition to the following:

Botox

- Achalasia
- Anal fissure, chronic
- Auriculotemporal syndrome
- Benign prostatic hyperplasia
- Cervicogenic headache
- Detrusor and sphincter dyssynergia
- Difficulty talking - total laryngectomy
- Disorder of nervous system – excessive salivation
- Dysphagia
- Epicondylitis
- Essential tremor
- Excessive salivation - Parkinson’s disease, advanced
- Excessive tear production
- Granuloma of vocal cords, refractory to conventional surgical and medical therapies
- Hemifacial spasm
- Idiopathic trigeminal neuralgia, refractory
- Infantile esotropia
- Injury to oculomotor nerve (acute)
- Isolated oromandibular dystonia
- Larynx closure, adjunct to surgical procedure
- Low back pain, chronic
- Myofascial pain syndrome

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- Neuropathic pain - spinal cord injury
- Organic voice tremor
- Palmar hyperhidrosis
- Pelvic floor dyssynergia
- Spasm, of pharyngoesophageal segment - total laryngectomy
- Spastic dysphonia
- Stuttering
- Tardive dyskinesia
- Temporomandibular joint disorder
- Tension-type headache
- Thoracic outlet syndrome
- Tourette syndrome or chronic tic disorders
- Whiplash injury to neck

Dysport

- Achalasia, in patients who are surgical candidates
- Blepharospasm
- Hemifacial spasm

Myobloc

- Axillary hyperhidrosis
- Bladder muscle dysfunction leading to overactive bladder
- Blepharospasm
- Hemifacial spasm
- Palmar hyperhidrosis
- Spastic dysphonia
- Upper limb spasticity

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Botox to treat achalasia can be found in a trial by Annese and Bassotti. A double-blind, placebo-controlled trial verified the efficacy of botulinum toxin for previously untreated achalasia. Sixteen patients were randomized to placebo or botulinum toxin, endoscopically injected into multiple sites within the lower esophageal sphincter (total of 100 units as 0.5-mL aliquots of 12.5 units each). All patients in the

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botulinum group reported significantly improved mean symptom scores at the one-month visit. In contrast, all placebo-treated patients had unchanged symptom scores and required pneumatic dilation. When comparing pneumatic dilation to botulinum toxin, statistically similar reductions in symptom score, sphincter pressure and esophageal retention occurred. The beneficial effect of botulinum toxin lasted for a mean of 7.1 months and 10.8 months after the first and second injections, respectively.

Additionally, Kolbasnik and colleagues published one study of 30 consecutive patients. The authors reported an initial 77% response rate, with 30% of responders maintaining symptom relief after a single 80-unit injection for a mean of 21 months. Of the remaining 70% of responders who relapsed (at 11 months on average), 56% were successfully treated with additional injection(s). Those who failed the first botulinum toxin injection also failed subsequent injections. Reduction of lower esophageal sphincter pressure to less than 18 mmHg at one month post-injection was a significant predictor of symptomatic response.

Support for using Botox to treat auriculotemporal syndrome can be found in a study by Duluerov et al. Local infiltration of botulinum toxin was effective in reducing food-induced facial flushing and sweating in 15 patients with Frey syndrome. Patients received total doses of 15 to 75 units, given as 0.1-mL injections with a 1-cm inter-injection distance. An evaluation 2 weeks later demonstrated a significant reduction in sweat quantity as compared with baseline (p less than 0.05). Measurements of skin temperature and color (erythema) did not show a clear difference before and after treatment. Subjectively, symptoms were reported to disappear in all patients following treatment. No adverse effects were reported.

Support for using Botox to treat backache can be found in a study by Foster et al. Botulinum toxin type A administered paravertebrally was effective in relieving pain and improving function in patients with chronic lower back pain. Patients (n=31) were randomized to 200 units of Botox(R) (40 units per site at 5 lumbar paravertebral levels) on the side of maximum discomfort (n=15) or to placebo (n=16). At 3 weeks, 73.3% of patients receiving botulinum toxin had more than 50% pain relief compared with 25% in the placebo group (p equal to 0.012). At 8 weeks, 60% of the patients receiving botulinum toxin experienced relief compared with 12.5% in the placebo group (p equal to 0.009). A questionnaire on physical impairment and disability was given at 8 weeks and 66.7% patients in the botulinum toxin group showed improvement compared with 18.8% in the placebo group (p equal to 0.011). There were no side effects reported.

Support for using Botox to treat benign prostatic hyperplasia can be found in a study by Maria et al. A randomized, double-blind study demonstrated that botulinum toxin type A (Botox(R)) was significantly more effective than placebo for the treatment of benign prostatic hyperplasia (BPH). Patients with symptomatic BPH who no longer responded to medication and refused surgical treatment were randomized to receive botulinum toxin A injection (n=15) or placebo injection (n=15). Inclusion criteria were: moderate to severe symptoms of urinary obstruction based on the American Urological Association (AUA) index, mean peak urinary flow rate less than 15 mL/sec with voided volume of at least 150 mL, and an enlarged prostate gland. Primary study endpoints were the AUA symptom score and peak urinary flow rate. Each patient received an injection of 4 mL of solution into the prostate (2 mL into each lobe of the gland); the placebo group received saline solution only and the botulinum toxin A group received 200 Units of botulinum toxin type A. At both the 1 month and 2-month evaluations, patients in the botulinum toxin A group demonstrated significant improvement in all measures compared with baseline and to the

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placebo group. At 1 month, 11 of 15 patients in the botulinum toxin A group and 2 of 15 in the placebo group had symptomatic relief. In the botulinum toxin A group, the mean AUA score decreased from 23.2 at baseline to 10.6 posttreatment (54% decrease; p=0.00001) and mean peak urinary flow rate increased from 8.1 mL/sec to 14.9 mL/sec (p=0.00001). At the 2-month evaluation, 13 patients in the botulinum toxin A group and 3 in the placebo group had symptomatic relief; the botulinum toxin A group had a 65% decrease in mean AUA score (p=0.00001) and the mean peak urinary flow rate was 15.4 mL/sec (p=0.00001). At both evaluation time points, these post-injection measures did not change significantly from baseline in the placebo group and were significantly different from the botulinum toxin A group (p not stated). For the patients who received a botulinum toxin A injection, improvements in all outcome measures were maintained at 6 and 12-month evaluations. No adverse events were reported during the follow-up period (average duration 19.6 months).

Support for using Botox to treat cervicogenic headache can be found in a study by Freund and Schwartz. In a randomized, double blind, placebo-controlled pilot study, the efficacy of botulinum toxin A in reducing the pain associated with cervicogenic headache was tested in 30 otherwise healthy subjects ranging in age from 29 to 75 years. Patients were included if they suffered from chronic headache unrelieved by other therapies secondary to a cervical whiplash injury which occurred within 2 years of study entry and which restricted range of motion in the neck. Each patient was given an injection of botulinum toxin A (100 units diluted in 1 mL saline) or an equivalent volume of saline placebo dispersed in the five most tender cervical muscular trigger points. At 2 and 4 weeks later, the patients were evaluated for neck range of motion and for pain using a 10-point visual analog scale. At 2 weeks, the range of motion had increased for the treatment group (no p value reported). There was no significant change in the placebo group. At 4 weeks, both median pain scores and range of motion degree measurements improved significantly from pre-injection levels for the group treated with botulinum toxin A (p=0.01). No significant change from baseline was seen in the placebo group. A potential confounder in this study was the difference in pain scores between groups at baseline. The median headache pain score for the placebo group was 3 (on a scale from 0 to 10), while that of the treatment group was 6.5 (no statistics reported). Thus, the placebo group appeared to have less headache pain, and therefore less room to improve, at the start of the trial. No side effects attributable to botulinum toxin A were reported in this study.

Support for using Botox to treat chronic anal fissures can be found in several published studies. Mentes et al. found botulinum toxin type A had a lower, shorter-term healing rate but significantly better recovery and adverse effect profile than lateral internal sphincterotomy (LIS) for the treatment of chronic anal fissure. Patients with severe, chronic fissure with visible horizontal fibers in the base of the internal anal sphincter were randomly selected to receive botulinum toxin type A (Botox(R)) injection (n=61) or LIS (n=50). For the botulinum toxin group (BT), patients received 0.3 units per kg injected in equal volumes on either side of the anterior midline; treatment was repeated if there was non- or incomplete healing 2 months after the first injection. Healing rate, defined as complete healing of the fissure, was significantly higher for the LIS group at 28 days (62.3% BT group vs 82% LIS group; p=0.023), 2 months (73.8% BT group vs 98% LIS group; p less than 0.0001), and 12 months posttreatment (75.4% BT group vs 94% LIS group; p=0.008). At 6 months posttreatment, healing rate was comparable between the groups (86.9% BT group vs 94% LIS group; p=0.212). Sixteen patients with incomplete healing in the BT group were offered repeat treatment; 6 refused due to satisfaction with pain relief from the first treatment and were

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considered incomplete healers in healing rate determinations. The BT group recovered from treatment significantly faster than the LIS group; return to daily activities averaged 1 day for the BT group and 14.8 days for the LIS group (p less than 0.0001). Complication rate was significantly different between the groups, no adverse events were reported in the BT group compared with 16% of patients in the LIS group reporting transient flatus incontinence (p less than 0.001).

Minguez et al successfully treated chronic anal fissure in a nonrandomized, prospective, dose-ranging trial (n=69). Dosing consisted of 5 units of botulinum toxin A on each side of the fissure (low dose: total 10 units), 5 units on each side of the fissure plus 5 units below the fissure (middle dose: total 15 units) or 7 units on each side of the fissure plus 7 units below the fissure (high dose: total 21 units). At 6 months follow-up, the overall rates of healing (83%, 78%, 90%), reinjection (52%, 30%, 37%) and sphincterotomy requirement (17%, 19%, 5%) did not differ statistically between the low, middle and high dose groups, respectively. Adverse effects included puncture site infection (n=1), perianal hematoma (n=1) and transient flatus or fecal incontinence (n=7). All subjects were fully continent at the end of follow-up.

Support for using Botox to treat infantile esotropia can be found in a study by Campos, Schiavi and Bellusci. Botulinum toxin type A was effective in patients (n=60) with esotropia if treated by age 7 months. A minimum dose of 2.5 units of botulinum toxin type A per muscle was initially used in 10 patients but it was discovered that 3 units per muscle produced better results; therefore, the following 50 patients received the higher dose. The mean follow-up period was 5.2 years (2 to 9 years).

Support for using Botox to treat detrusor and sphincter dyssynergia can be found in a study by Gallien et al. Botulinum toxin A was not effective in treating detrusor sphincter dyssynergia (DSD) in patients with multiple sclerosis (MS) in a multicenter, double-blind, placebo-controlled clinical trial. Patients (n=86; mean age, 50 +/- 10 years) with DSD due to MS, who had post-voiding residual urine volumes between 100 and 500 mL were randomized to botulinum toxin A 100 units or placebo, administered as single transperineal injections using striated sphincter electromyography. Each patient was also started on an alpha-blocker (alfuzosin 5 mg slow-release twice daily) for 4 months. No significant differences were found in the primary endpoint, the post-voiding residual urine volume at day 30 (botulinum toxin A, 186 +/- 158 mL, n=43; placebo, 206 +/- 145 mL, n=40; p=0.45). Secondary endpoints that were assessed at day 30 included voiding variables (symptoms were assessed using 10 centimeter (cm) visual analogue scales) and urodynamic variables. Of the voiding variables, only the voiding volume was significantly improved (p=0.02) in the botulinum toxin A arm (197 +/- 143 mL; n=35) compared with the placebo arm (128 +/- 95 mL; n=34), while the other voiding variables (obstructive symptoms, pollakiuria, urgencies, incontinence, and International Prostatism Symptom Score) were no different between treatment groups. Urodynamic variables that were significantly improved in the botulinum toxin A arm compared with the placebo arm included pre-micturition detrusor pressure (botulinum toxin A, 24 +/- 11 cm of water, n=34; placebo, 34 +/- 18 cm of water, n=28; p=0.02) and maximal detrusor pressure (botulinum toxin A, 52 +/- 22 cm of water, n=35; placebo, 66 +/- 25 cm of water, n=32; p=0.02), while the other urodynamic variables (maximal and cloture urethral pressures, basal detrusor pressure, detrusor compliance, maximal bladder capacity, and maximal urinary flow) were no different between treatment groups. At time points between day 30 and day 120, few endpoints were significantly improved in the botulinum toxin A arm compared with the placebo arm; these included voiding volume (at days 30 and 60; p=0.05) and incontinence (between days 60 and 120; p=0.04). Adverse events were similar between treatment groups.

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Support for using Botox to treat difficulty speaking after total laryngectomy can be found in two studies published by Blitzer and colleagues and Terrell and colleagues. Preliminary reports indicate that botulinum A toxin injection of the upper esophageal sphincter appears to be effective in the management of voice failure after tracheoesophageal puncture (TEP) and prosthesis placement in most patients after total laryngectomy. Persistent focal constrictor hypertonicity/spasm appears to be responsible for the patients' poor speech production or inability to speak with the prosthesis. Botulinum A toxin injections of the cricopharyngeal muscle complex may be used successfully both diagnostically and therapeutically in patients who have voice production difficulties after TEP.

Support for using Botox to treat disorder of esophagus can be found in two studies. Alberty, Oelerich and Ludwig published a prospective study of patients with dysphagia. Botulinum toxin was effective in the treatment of dysphagia resulting from pure upper esophageal sphincter (UES) dysfunction. Ten patients (aged 39 to 77 years) with incomplete opening (n=8), delayed opening (n=1), or premature closure (n=1) of the UES received botulinum toxin 30 units injected into the UES under brief general anesthesia. One month following treatment, videofluoroscopic studies showed significant improvement in the opening of the pharyngoesophageal segment (from a mean of 47% at baseline to 71%, p less than 0.01). In addition, clinical symptoms scores improved in 9 of 10 patients (mean 4.9 at baseline to 2.0 post-injection).

Miller, Parkman, and Schiano published a study of fifteen patients with non-achalasia esophageal motility disorder, unresponsive to medical therapy, underwent endoscopic injection of botulinum toxin A at the level of the gastroesophageal junction. Twenty-unit injections were used in each of four quadrants above the squamocolumnar junction. There was significant improvement in chest pain (p less than 0.01), dysphagia (p less than 0.01), and regurgitation (p less than 0.01). After one month 73% of patients had a good or excellent response, while at the last patient interview (mean of 10.6 months) 33% continued to have a good to excellent response.

Support for using Botox to treat epicondylitis can be found in a study by Keizer et al. Botulinum toxin injection was as effective as surgical treatment for lateral humeral epicondylitis (tennis elbow) for patients who did not respond to conventional treatment. In this randomized pilot study, 40 patients received an injection of 30 to 40 units of botulinum toxin type A (Botox(R)) into the extensor carpi radius brevis (n=20) or a surgical wrist extensor release (Hohmann operation; n=20). Eight patients with insufficient paresis by the 6-week follow up received a second injection of botulinum toxin (50 units). Four of these patients still had insufficient paresis and had a Hohmann operation 6 to 18 months after initial treatment; only 1 of the 4 had a good result after surgery. During the 2-year follow up, the only significant difference between the groups was in the amount of sick leave at the 3-month follow-up, which was less in the operative group compared with the botulinum toxin group (p=0.01). The operative group experienced more extension problems of the elbow; 3 of 20 in the operative group and no patients in the botulinum toxin group had an extension deficit at the end of the 2-year follow-up. The overall results (modified Verhaar scoring system) showed no differences between the groups; 16 of 20 in the botulinum toxin group (15 of 16 for patients in botulinum toxin corrected group, with non-responders excluded) and 17 of 20 in the operative group had treatment ratings of good or excellent. Botulinum toxin type A injection may provide a less invasive alternative for the treatment of tennis elbow.

Support for using Botox to treat essential tremor disorder can be found in a study by Brin et al. Botulinum toxin type A resulted in limited functional efficacy for the treatment of essential hand tremor since it

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improved postural but not kinetic hand tremors. Patients (n=133) with essential hand tremor were randomized to low-dose (50 units) or high-dose (100 units) botulinum toxin type A (Botox(R)) or placebo. Injections were made into the wrist flexors and extensors. During a 16-week follow-up, both doses of botulinum toxin significantly reduced postural tremor after 6 to 16 weeks (p=0.0002 and 0.0001 for low-dose and high-dose, respectively, at 6 weeks). Kinetic tremor, however, significantly reduced only at the 6-week examination (p=0.03 and 0.005 for low-dose and high-dose, respectively, at 6 weeks). Measures of motor tasks and functional disability were not consistently improved with treatment. In addition, grip strength was reduced for both doses of botulinum toxin type A compared with placebo. Dose-dependent hand weakness was the major adverse reaction reported.

Support for using Botox to treat excessive salivation secondary to advanced Parkinson's disease can be found in two studies. Lagalla et al conducted a double-blind, randomized, placebo-controlled study (n=32), botulinum toxin type A was safe and led to subjective and objective improvement in drooling in outpatients with Parkinson disease. Nobrega et al conducted a open-label, prospective study. Ultrasound-guided, intraparotid injections of botulinum toxin type A decreased the severity, and to a limited extent, the frequency of diurnal drooling in outpatients with advanced Parkinson disease (PD) in an open-label, prospective study. Patients with PD characterized by presence of bradykinesia associated with muscular rigidity, 4 to 6 Hertz rest tremor, or postural instability were evaluated for sialorrhea. The drooling score was based on the sum of the scores for severity (1 to 5 scale; 1=dry: never drools; 5=profuse: clothing, hands, and tray moist wet) and frequency (1 to 4 scale; 1=never drools; 4=constant drooling). Patients (n=21; 18 males; mean age, 70 years; range, 55 to 84 years) with a diurnal sialorrhea of grade 5 or higher were included. Patients with dementia, severe depression, who had received treatment with neuroleptics within 1 years prior to onset of symptoms, or who had previously received treatment for drooling or anticholinergic drugs were among those excluded. Study patients were injected with botulinum toxin type A 125 units (500 units diluted in 2.5 mL saline) in two points of the parotid gland using ultrasonography. Drooling was evaluated by a speech therapist at 15 and 30 days following the injection. All patients were on levodopa therapy with entacapone and/or pramipexole during the study. At 15 days posttreatment, 19 of 21 patients reported a decrease in drooling; of the remaining 2 patients, one had no substantial change while the other's condition worsened. The total drooling score decreased from a mean baseline score of 6.85 to 5.14 at 1 month following the injection (p less than 0.001). The mean pre- and 1-month posttreatment drooling severity scores were 3.42 and 2.14, respectively (p less than 0.001), and drooling frequency scores were 3.42 and 3, respectively (p=0.021). Overall, the severity of drooling decreased in 18 (86%) patients and the frequency of drooling decreased in 8 (38%) patients. The frequency of drooling remained unchanged in 11 (52%) patients. Among treatment-emergent adverse events, two patients experienced mild dry mouth lasting 1 month. One patient developed bilateral local edema, which was mild, self-limited, and resolved after 4 days.

Support for using Botox to treat excessive salivation secondary to a disorder of the nervous system can be found in two published studies. Porta and colleagues found that ultrasound guided botulinum toxin type A was safe and effective in the treatment of sialorrhea in patients with neurological disorders. Botulinum toxin type A (Botox(R)) was injected bilaterally into the parotid and submandibular glands at doses which were calculated based on patient weight and rate of salivation. The mean parotid dose was 27.7 units/gland and the mean submandibular dose was 11.9 units/gland (mean total dose was 76.6 units).

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After treatment, there was a subjective reduction in salivation reported for 9 patients and no improvement in 1 patient. Visual analogue scale scores showed a 55% decrease in mean rate of salivation for all patients and a 61% decrease for the responder group. No serious adverse events occurred.

Additionally, Giess et al found that injections of botulinum toxin into the salivary glands successfully ameliorated sialorrhea and improved quality of life without significant adverse effects in patients with bulbar amyotrophic lateral sclerosis. Five patients (mean age 64 years) received 6 to 20 mouse units of botulinum toxin A injected into each parotid gland in 3 divided doses. This was repeated 2 weeks later if, as judged by the patient, the clinical response was inadequate. Additional injections (5 units) into each submandibular gland were required in 2 patients. In 4 of 5 patients, botulinum toxin injections markedly reduced sialorrhea as measured by paper handkerchiefs used before and at 4 weeks after treatment (11 vs 3, p=0.068) and by a reduced radiotracer uptake in both parotid glands noted on salivary gland scintigraphy. At up to 3 months of follow-up, a slight increase of sialorrhea was noted in 1 patient. Quality of life was markedly improved in 3 patients, moderately improved in 1 patient, and not enhanced in the last.

Support for using Botox to treat excessive tear production can be found in a study by Whittaker et al. A small pilot study demonstrated the effectiveness of botulinum toxin type A in the treatment of functional epiphora. Patients (n=14) with symptoms of epiphora and a patent lacrimal system received a single injection of 2.5 to 5 units of botulinum toxin A (Botox(R)) into the palpebral lobe of the lacrimal gland on the worst affected side. Four patients received 5 units of botulinum toxin A, but 2 of the 4 patients experienced side effects, so the remaining 10 patients received 2.5 units of botulinum toxin A. Evaluation of efficacy was based on a 5-minute Schirmer test and subjective reports from the patients at week 1, week 4, and week 13. A reduction in epiphora was reported by 71.4%, 85.7%, and 72.7% of patients at week 1, week 4, and week 13, respectively. Based on Schirmer test results, a reduction in tearing occurred in 78.6%, 71.4%, and 54.5% at week 1, week 4 and week 13, respectively. Adverse effects were reported in 2 patients who received a 5-unit botulinum toxin A dose; 1 patient had a ptosis that resolved within 4 weeks and another patient had vertical diplopia for 3 weeks after the injection. Additional studies to determine the optimal dosage as well as the safety and effectiveness of multiple injections over a longer term are recommended.

Support for using Botox to treat myofascial pain syndrome can be found in a systematic review of four randomized controlled trials by Soares (2014). Botulinum A toxin demonstrated a nonsignificant difference in spontaneous and evoked pain intensity, spontaneous and evoked pain relief, pressure pain detection threshold, and pressure pain tolerance. A significant difference in the duration of pain in hours and pain intensity scores was observed.

Support for using Botox to treat Gilles de la Tourette's syndrome can be found in a study by Kwak, Hanna and Jankovic. Botulinum toxin injections were effectively used to treat tics and associated premonitory symptoms in an open study of patients with Tourette syndrome. Thirty-five patients aged 8 to 69 years, who had a mean tic duration of 15 years, received an average of 120 units during each of 3 visits. The most common muscles injected were cervical, and those in the upper face, particularly the eyelids. During a mean follow-up period of 21 months (range 1.5 to 84 months), 29 patients experienced an improvement, with 23 of these patients demonstrating a marked improvement, based on a peak effect score of 3 or greater (0 to 4 scale). In addition, 21 (84%) of 25 patients with premonitory symptoms (described as discomfort, tingling, or tension preceding the tic) experienced significant relief from these symptoms. The

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duration of therapeutic benefits averaged 14 weeks. Adverse effects included neck weakness (n=4), ptosis (n=2), generalized weakness (n=1), dysphagia (n=2), fatigue (n=1), and nausea and vomiting (n=1).

Support for using Botox to treat granuloma of vocal cords which is refractory to conventional surgical and medical therapies can be found in a study by Orloff and Goldman. In a case series (n=8), botulinum A toxin (Botox(R)) was 100% effective in eradicating vocal fold granulomas that were refractory to conventional surgical and medical therapies. The toxin was injected under electromyographic guidance transcutaneously or during laryngoscopy into one or both thyroarytenoid muscles at an average dose of 10 units per site. All granulomas disappeared within 2 months. Four patients required early reinjection due to inadequate paresis. All patients remained free of recurrence throughout the follow-up period (11 to 41 months). Adverse effects included mild-to-moderate breathiness and reduced Valsalva effect in 7 and 1 patients, respectively. Depending on the etiology of vocal fold granuloma, treatment may also include voice therapy, behavioral modification and medication for contributory conditions (i.e., gastroesophageal reflux).

Support for using Botox to treat hemifacial spasm can be found in a retrospective chart review and open-label trial. In a retrospective chart review of 51 patients with benign essential blepharospasm (BEB, n=17), hemifacial spasm (HFS, n=17), or aberrant facial nerve regeneration synkinesis (AFR, n=17), and a minimum treatment period of 10 years, mean blepharospasm disability score (BDS) significantly improved from 6 to 3 at last review across all 3 groups, and improvement was significantly greater in patients receiving flexible-interval injections compared to fixed-interval injections (Bladen et al, 2019). Mean BDS improved significantly in the BEB group with a trend to improvement in the HFS and AFR group, and BDS improvement mainly occurred in the first year with smaller fluctuations in following years. Mean duration of maximal effect was 10.5 weeks across the 3 groups but increased progressively only in the flexible-interval group. Patients (mean age, 63 years) received injections at a fixed, 12-week interval (n=14; mean annual injections, 4) or at flexible intervals (n=37; mean annual injections, 3.4). The cumulative complication rate was the same in the flexible- and fixed-interval groups and included ptosis, dry eye, and lagophthalmos.

In an open-label, time series in adults with hemifacial spasm (n=137), serial treatment with onabotulinumtoxinA led to an overall response rate of 88%. Patients with right- or left-sided hemifacial spasm refractory to other forms of therapy received treatment (mean age, 56.3 +/- 13 years; 55% female; mean disease duration, 5.6 +/- 6.4 years) (Chen, 1996). Patients with a history of previous peripheral facial palsy were excluded. Most patients received a total of 12 to 15 units of onabotulinumtoxinA per injection, which was injected as follows: 2.5 units each into the central and lateral orbicularis oculi of the lower eyelid, 2.5 to 5 units into the lateral orbicularis oculi of the upper eyelid, and 5 units divided into the buccolabial and/or platysma muscles. However, 20 patients received a total dose of 25 units. Efficacy was assessed both objectively and subjectively prior to each injection and at each follow-up (2 weeks after the initial injection, then monthly until the subsequent injection). Objective assessment involved grading of clinical severity of spasm, by 2 assessors, using a 5-point scale (0=no abnormality/normal blinking to 4=severe prolonged disfigurement/incapacitating social activities) and videotape recording. Subjective assessment involved patient-report degree of spasm relief using a 5-point scale (0=baseline, 1=25% improvement, 2=50%, 3=75%, 4=more than 90% improvement). A total of 228 treatments were administered, with an average of 1.7 treatments per patient. Based on both objective and subjective

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measures, the overall response rate was 88% (57% substantial improvement and 31% improvement), and the overall mean duration of spasm relief was 20 weeks (range, 2 to 52 weeks). Only 4 patients achieved complete remission after the first injection, with most patients requiring subsequent treatments on average every 3 to 4 months. No significant difference in response rate was observed among those who received doses less than 15 units and those who received 15 units or more. Additionally, analysis of the first 5 treatments did not reveal a significant difference in the duration of spasm relief based on severity of pretreatment spasm. Among 216 treatments, the most common adverse events included facial weakness in 95% of patients, which led to dynamic or static facial asymmetry in 37% of these patients, ptosis (29%), and diplopia (5%). Diplopia and ptosis resolved within 8 and 10 weeks, respectively, and the incidence decreased with consecutive treatments.

Support for using Botox to treat isolated oromandibular dystonia can be found in a several small open-label clinical trials. Jankovic and Hallett enrolled patients (n=96) who were diagnosed with jaw-closing OMD (n=51; 74.5% female), jaw-opening OMD (n=40; 67.5% female), or jaw-deviation OMD (n=5; 100% female) with over 70% of all cases considered idiopathic. Patients received botulinum toxin A (Botox(R)/Oculinum(R); Allergan Pharmaceuticals) into 3 to 5 sites of each involved muscle. Median doses for each muscle were 24.5 +/- 17.7 units (masseter; range, 2 to 100 units), 18.5 +/- 11.9 units (temporalis; range, 2 to 75 units), 16.3 +/- 8.1 units (medial pterygoid; range, 5 to 40 units), 15.9 +/- 8.7 (lateral pterygoid; range, 2.5 to 60 units), and 9.8 +/- 4.6 (anterior digastric; range, 3.75 to 30 units). Initial treatments were typically inadequate, and patients received an additional treatment of botulinum toxin A administered 2 to 4 weeks after the first dose. Patients rated their current condition using a linear, global clinical rating scale, with 0% defined as fully disabled/no useful function and 100% defined as normal. Patients with all 3 types of OMD reported statistically significant improvements, with improvements from 29.6% +/- 2.7% to 72% +/- 4.4% (p=0.0001) in the jaw-closing group, 30.8% +/- 4% to 73.8% +/- 4.2% (p=0.0001) in the jaw-opening group, and 38.8% +/- 9.2% to 75.8% +/- 12.2% (p=0.014) in the jaw-deviation group. Duration of benefit was 14.6 +/- 2.1 weeks, 11.8 +/- 2.1 weeks, and 10.8 +/- 5 weeks for the jaw-closing, jaw-opening, and jaw-deviation groups, respectively. Adverse effects occurred in 11.8% of patients in the jaw-closing group, 17.5% of patients in the jaw-opening group, and no patients in the jaw-deviation group. The most common adverse effect was dysphagia (n=14). One patient developed antibodies to botulinum toxin A.

Additionally, Jankovic, Schwartz, and Donovan studied patients (n=62; mean age, 57.2 years; range, 14 to 78 years) with idiopathic OMD, who despite optimal pharmacological therapy, surgery, or both, were treated with botulinum toxin A every 3 to 6 months, injected into masseters, submental, temporalis, and pterygoids muscles. Doses were initiated at 25 units per muscle and increased to 50 units each into the masseters and temporalis muscles. Assessments consisted of severity of dystonia (0 to 4 scale with 0 as no spasm and 4 as severe, incapacitating spasm) rated in a patient diary, latency (interval between the injection and first sign of improvement), peak effect (maximum benefit obtained; determined from patient diary, interview of family or friends, and patient's perception rated as no effect (0), mild improvement (1), moderate improvement but no change in function (2), moderate improvement in severity and function (3), or marked improvement in severity and function (4)), and global rating (peak effect score minus one point for mild or moderate complications or minus 2 points for severe or disabling complications). Patients received a total of 407 injections during 186 visits. Favorable response (global rating of 2 or more)

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occurred in 73% of evaluable patients (n=45) with OMD. Mean global rating was 2.2 +/- 1.5, while peak effect was 2.4 +/- 1.6, latency to response was 4.6 +/- 5.6 days (range, 0 to 30 days), and total duration of response was 10.3 +/- 8.7 weeks (range, 0 to 54 weeks). Over half (55.6%) of patients failed (global rating of 1 or less) one or more visits. Overall, adverse events were observed on 37% of visits (n=115) with the most common adverse event of dysphagia occurring in 12% of patients.

Support for using Botox to treat neuropathic pain secondary to spinal cord injury can be found in a randomized, double blind, placebo-controlled, parallel group study by Han et al (2016). A 1-time, 200-unit, subcutaneous botulinum toxin type A dose was administered to the painful area in 40 patients with spinal cord injury-associated neuropathic pain. Patients in this study had spinal cord injury of any level, with daily neuropathic pain for at least 3 months, and a visual analog scale (VAS; 0-100mm) score of ≥ 40 at baseline. A total of 3 visits were scheduled over 8 weeks (baseline, 4 weeks, and 8 weeks after injection). The single administration of subcutaneous botulinum toxin A significantly reduced the VAS scale pain scores compared with placebo at both 4 weeks (18.6 +/- 16.8 vs 2.6 +/- 14.6) and 8 weeks (21.3 +/- 26.8 vs 0.3 +/- 19.5). Adverse effects included reports of pain during injection or triggering of spasticity, though there was no difference between the botulinum toxin treatment and placebo groups reported by the authors.

Support for using Botox to treat larynx closure as adjunct to surgical procedure can be found in a small study by Pototschnig et al (1996). In a small number of patients (n=6) requiring larynx closure, botulinum toxin A injections into the laryngeal musculature was effective at completely paralyzing the larynx and allowing for wound healing. Patients in this study all suffered from severe chronic aspiration caused by previous injury (e.g., stroke, tumor removal, and hypoxic trauma). Two weeks prior to surgery, patients were injected with 1 to 1.4 mL (200 to 280 units) of botulinum toxin A into the intrinsic laryngeal musculature (i.e., bilateral injections of posterior cricoarytenoid, aryepiglottic, medial thyroarytenoid, and lateral thyroarytenoid). Five of 6 patients had complete closure and the other patient had a thin fistula of the posterior commissure. This procedure reportedly preserves the ability of speech rehabilitation and can be performed in high-risk patients. Additional study is needed to further investigate the use of botulinum toxin A as adjunctive therapy to surgical procedures of the larynx.

Support for using Botox to treat oculomotor nerve injury can be found in a study by Talebnejad, Sharifi, and Nowroozzadeh. Botulinum toxin A injection was effective for treatment of trauma-induced, acute-phase, third nerve palsy (n=9). Additionally, Saad and Lee conducted a retrospective review of botulinum toxin A for the treatment of exotropia of third nerve palsy provides evidence that long-term efficacy may rely on pretreatment markers and that treatment is not a reliable predictor of surgical outcomes.

Support for using Botox to treat organic voice tremor can be found in a study Hertegard et al. Botulinum A toxin successfully ameliorated essential voice tremor in the majority of a case series (n=15, mean age 73 years). After injection into the bilateral thyroarytenoid muscles (dose range 0.6 to 5 units of Botox(R), typically at 3-month intervals), 67% of patients reported positive subjective results. Depending on the method of evaluation, the treatment was effective in 50% to 60% of patients. Adverse effects included transient breathiness, hoarseness and mild dysphagia.

Support for using Botox to treat palmar hyperhidrosis can be found in a study by Naver, Swartling and Aquilonius. Twenty-eight patients with palmar (n = 19) and/or axillary (n = 13) hyperhidrosis were treated with intracutaneous injections of botulinum toxin (Botox(R)) 2 U/4 cm2. Sweat function was studied

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clinically and by objective measurements after treatment of one side. Treated and untreated sides, and pre- and post-treatment skin areas were compared. Subjective evaluation was performed after treatment of one side and 2-5 months after treatment of both sides. Duration of effect was controlled by a one-year follow-up. Sweating disappeared in eight out of 13 patients with axillary and in five out of 19 with palmar hyperhidrosis, and was reduced markedly in another five out of 13 and 10 out of 19 patients. Two-thirds of those treated for hand sweat noticed a slight and transient reduction of power of finger grip. No side-effects were noticed after treatment of axillary hyperhidrosis.

Support for using Botox to treat pelvic floor dyssynergia can be found in a study by Hallan et al. The group conducted an uncontrolled study involving 7 patients with constipation has suggested benefits of botulinum A toxin in the treatment of anismus in intractable constipation. Botulinum A toxin was injected into the puborectalis muscle (bilaterally), at a dose of 3 nanograms (ng) (1.5 ng on each side of the muscle). At 4 weeks following treatment, total symptoms scores improved significantly, and were correlated with a reduction in the maximum voluntary squeeze anal canal pressure and an increase in the anorectal angle upon straining. Clinical response was considered excellent in 4 of the patients, with repeat injections being given at 8 to 10 weeks. There was one complete failure and 2 partial failures. More studies are required under controlled conditions to evaluate the efficacy of botulinum A toxin in anismus, and to evaluate the efficacy and safety of administering the toxin over prolonged periods.

Support for using Botox to treat pharyngoesophageal segment spasm following total laryngectomy can be found in a study by Bartolomei et al. Treatment with botulinum A toxin plus participation in a voice therapy program led to improved phonation in a published case series of 34 patients with pharyngoesophageal segment spasm after laryngectomy. After the first patient failed to demonstrate a response with a dose of 20 units (who then received a repeat injection of 100 units), 26 patients received 100 units of botulinum A toxin, 3 patients with minor spasm received 50 units, 3 patients received 30 units, and 1 patient received 60 units. Doses were administered in 1 injection unilaterally (n=29) or bilaterally (n=1), or unilaterally in 6 to 7 divided injections (n=4). Electromyography was used to guide the injections in the pharyngeal constrictor muscles. Benefit was seen in all but 2 patients at 72 hours postinjection, and patients were able to count to 9, say their name, and speak short sentences. Rapid decline occurred in 8 patients, requiring botulinum A toxin injection every 3 months, while the other patients demonstrated long-lasting benefit. No adverse effects were reported except for mild dysphagia in 1 patient.

Support for using Botox to treat refractory idiopathic trigeminal neuralgia can be found in the European Academy of Neurology (Bendtsen, 2019). A weak recommendation for the addition of botulinum toxin type A to other medications for medium-term treatment of trigeminal neuralgia is based on very low-quality evidence.

Liu et al published a study where botulinum toxin A significantly reduced visual analogue scale (VAS) pain scores from 8.5 to 4.5 in patients aged 80 years and older (n=14; mean age 82.6), and from 8 to 5 in patients less than 60-years-old (n=29; mean age 49.5). Patients were examined at baseline and at 1 month after treatment; median VAS scores were significantly lower at 1 month compared to baseline but did not differ significantly between groups. Drug administration was guided by pain and trigger zones, and delivered transdermally and/or submucosally. Botulinum toxin A dosages were 45 to 150 units in the older group (mean, 91.3 units) and 30 to 200 units (mean, 71.8 units) in the younger group. Transient mild side effects occurred in 2 patients in each group and resolved spontaneously within 3 weeks.

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Support for using Botox to treat spastic dysphonia can be found in a study published by Blitzer, Brin and Stewart. Based on 12 years of experience treating spasmodic dysphonia (6300 injections in 901 patients), botulinum A toxin is considered to be the treatment of choice. The types of dysphonia included adductor (82%), abductor (17%), and adductor breathing or paradoxical vocal fold motion (1%). Dosing of Botox(R) was individualized. For adductor dystonia, the average onset and duration were 2.4 days and 15 weeks, respectively, with patients achieving 90% of normal function. Corresponding values for abductor dystonia were 4 days, 10.5 weeks and 67%, respectively. Patients with adductor breathing dystonia returned to 82% of normal functioning for a mean of 14 weeks. Botulinum A toxin was generally well-tolerated with a few patients developing mild and transient adverse effects such as breathiness, exertional wheezing/stridor and dysphagia.

Support for using Botox to treat stuttering can be found in a study by Brin, Stewart, and Blitzer. Botulinum A toxin 1.25 units (Botox(R)/Oculinum(R)) into each thyroarytenoid muscle has been shown to be effective in the treatment of stuttering with glottal block, resulting in a moderate improvement in fluency.

Support for using Botox to treat tardive dyskinesia can be found in an open-label study conducted by Rappaport et al. In an open-label study, the administration of botulinum toxin was effective and safe in the treatment of oro-facial-lingual-masticatory tardive dyskinesia due to dopamine receptor blocking agents. In this study, 12 psychiatric patients (mean age 74 years), who had received long-term treatment with phenothiazines or butyrophenones and were resistant to at least 1 prior treatment for dyskinesias, received 80 units of botulinum toxin injected subcutaneous into 4 facial sites (Lateral to the buccal commissures, midpoint of the upper lip, and the mid-central area of the chin). As assessed by the Tardive Dyskinesia Rating Scale, a significant improvement in dyskinesias was noted at 1, 5, and 8 weeks following treatment. A significant response was observed for pouting, grimacing, and dysarthria, while a trend for improvement was noted for puckering and choreoathetoid movements of the tongue. No adverse effects were observed.

Support for using Botox to treat temporomandibular joint disorder can be found in a study conducted by Freund, Schwartz, and Symington. A small, uncontrolled trial (n=15) provides preliminary evidence suggesting efficacy and safety of botulinum A toxin (Botox(R)) for chronic temporomandibular joint disorders. Subjects received a total of 150 units administered with electromyographic guidance to the masseter and temporalis muscles. When assessed every 2 weeks through week 8, average scores for pain, functional disability index, mouth opening, and tenderness improved from pretreatment values (p=0.05). Mean bite force did not change appreciably. Botulinum toxin therapy did not induce adverse effects or complications.

Support for using Botox to treat tension-type headache can be found in a several small trials. Porta (1999) reported headache pain scores were decreased by botulinum toxin to a greater extent than with methylprednisolone in a randomized, single-blind, comparative trial conducted in 20 patients ranging in age from 18 to 70 years. The subjects were recruited if they presented with a history of 2 or more tension-headache episodes per month for at least the past 3 months. They were then randomized to receive an IM injection of either 40 mg of methylprednisolone or multiple IM injections of 5 to 15 units per site of botulinum toxin A (Botox(R)) into various tender points on the head identified using algometry. The amount of botulinum toxin A varied with each patient. Visual analog pain scores were assessed at baseline and 30 and 60 days posttreatment for all patients. Quantitative algometry was performed in 5 patients at

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these same time points. At baseline and 30 days there was no difference in pain severity scores between the 2 groups (p=0.94 and p=0.67, respectively). However, at 60 days posttreatment there was a statistically significant difference in the median visual analog pain scores between the two groups, with the botulinum toxin A group experiencing less pain (p=0.0003). No adverse events were reported.

A study by Smuts et al addressed the use of botulinum toxin A for the prophylaxis of chronic tension-type headache (TTH). Investigators recruited 41 patients meeting the International Headache Society criteria for chronic TTH who had failed prior prophylactic drug therapy. Using a double-blind, placebo-controlled design, patients were randomized to receive either IM injections of 100 units botulinum toxin A (Botox(R)) or an equivalent volume of normal saline. The injections were given in 2 sites in the temporal muscles and 4 sites in the cervical muscles bilaterally. Patients kept a headache diary for 4 weeks prior to treatment, and for 3 months afterwards. Headache pain was recorded using a 6-point scale, and a chronic pain index was used as an indirect quality-of-life measurement. The authors noted a statistically significant improvement in headache pain and headache-free days in the botulinum toxin A group compared with baseline values after 3 months. The botulinum toxin A group also experienced a statistically significant improvement in chronic pain index scores from baseline by month 3 (p=0.001). No between-group differences were noted with respect to adverse effects.

Support for using Botox to treat thoracic outlet syndrome can be found in a study by Jordan et al. Chemodenervation of the scalene muscles using botulinum toxin injections has been associated with substantial relief of symptoms related to thoracic outlet syndrome. In a study of 22 patients unresponsive to physical therapy and suboptimally managed with anesthetic and steroid injections, botulinum toxin 100 units was administered, under electrophysiologic and fluoroscopic guidance (12 units each into the anterior and middle scalene muscles, 76 units into the ipsilateral trapezius muscle). During a 6-month follow-up period, 14 of 22 (64%) patients reported greater than 50% relief of pain, numbness, and fatigue of the treated upper extremity. This improvement lasted for an average of 88 days (range 30 to 180 days). In contrast, only 4 of 22 patients responded similarly following lidocaine and steroid injections (p=0.0051). The positive, long-lasting response associated with botulinum toxin is useful for patients awaiting surgical decompression for this disorder.

Support for using Botox to treat whiplash injury to neck can be found in a study by Freund and Schwartz. Botulinum A toxin (Botox(R)) as a total of 100 units injected into five tender cervical muscle trigger points decreased subjective neck pain with resultant increase in range of motion, but had only equivocal effects on functioning in a randomized, double-blind, placebo-controlled trial (n=26). Subjects had chronic whiplash-associated neck pain following a motor vehicle accident that occurred an average of 3 years prior to baseline. At 4 weeks post-injection, the composite visual analogue scale (VAS) score for neck pain, headache and shoulder pain was significantly lower and total range of neck motion was significantly greater in the botulinum group as compared with the saline group (p less than 0.01). However, the Vernon-Mior score revealed no statistical difference in subjective functioning. Botulinum A toxin did not induce adverse effects.

Support for using Dysport to treat achalasia in a patient who is not a surgical candidate can be found in a study by Mikaeli et al. There was no significant difference between adjunctive treatment with abobotulinumtoxinA before pneumatic dilatation compared with pneumatic dilatation alone for the treatment of newly diagnosed achalasia in a prospective, randomized, controlled trial (n=52). Adults (18

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years (yr) or older) with symptomatic, treatment-naïve achalasia were eligible and enrolled consecutively. Patients with functional class 3 or 4 cardiovascular disability and coagulopathy were excluded. Patients were randomly assigned to receive two 50-unit aliquots (0.5 milliliters) of abobotulinumtoxinA (400 units total dose) injections to each quadrant of the lower esophageal sphincter 1 month before pneumatic dilatation (PD) (n=26; median age 38 yr; interquartile range (IQR), 26 to 49 yr; 62% male) or PD-alone (n=26; median age 30 yr; IQR, 24 to 45 yr; 46% male). PD was performed with a 30 millimeter (mm) balloon, gradually inflated up to 10 pounds per square inch in 30 seconds (sec) and maintained for another 60 sec for all patients. Clinical evaluation was performed at baseline, 1-month after treatment, and every 6 months thereafter for 1 year. Clinical response was defined as a symptomatic total score less than 4 and relapse was defined as a symptomatic total score of 4 or greater. The symptomatic total score was based on 5 symptoms: dysphagia with solids, dysphagia with liquids, and active regurgitation, ranked as 0=none, 1=weekly, 2=daily and 3=with each meal, and passive regurgitation and chest pain, ranked as 0=none, 1=monthly, 2=weekly, and 3=daily. Despite significant reductions in total symptom scores within treatment groups at 1 month, which were sustained at 12 months (p less than 0.001), the cumulative remission (response) rate at 12 months was not significantly different between treatment groups. At 12 months, after a single treatment with abobotulinumtoxinA before PD, the cumulative remission rate was 77% (95% CI, 68% to 86%) compared with 62% (95% CI, 52% to 72%; p log rank=0.1) with PD-alone. Relapse occurred in 23% (6/26) of evaluable patients in the abobotulinumtoxinA before PD group and 38% (10/26) of evaluable patients in the PD-alone group. Relapse patients received a second treatment of PD-alone with a 35 mm balloon. After retreatment, 100% of patients in the abobotulinumtoxinA before PD group and 85% of patients in the PD-alone group had symptomatic remission at 12 months from initial treatment. The cumulative remission rate was significantly higher in the abobotulinumtoxinA before PD group compared with PD-alone group after retreatment (p less than 0.05). No significant bleeding, perforation or aspiration occurred in either group and no confounding factor was found to be a predictor of treatment response.

Additionally, Kroupa et al (2010) found adjuvant therapy with abobotulinumtoxinA prior to pneumatic dilatation did not offer additional benefit compared with pneumatic dilatation alone for the treatment of esophageal achalasia in a prospective, historical-controlled study (n=91). Treatment-experienced and -naive adults with achalasia who underwent combined treatment (n=51; mean age 49.7 years (yr); range 24 to 83 yr; 39% male) were compared with historical controls who received PD-alone using the same procedural method and time protocol for evaluation (n=40; age range 26 to 80 yr; 40% male). Prior interventions among treatment-experienced patients included pharmacological treatment with nitrates or nifedipine (46/51), surgical myotomy (3/51), and at least 1 pneumatic dilatation (6/51) Eight days prior to pneumatic dilatation (PD), the adjuvant-therapy group received abobotulinumtoxinA 200 international units (IU) total dose injected in 0.5 milliliter aliquots in the z-line area of each quadrant of the lower esophageal sphincter (LES). PD was performed with a 30 millimeter (mm) balloon for dilatation 1, and a 35 mm balloon for subsequent dilatations. Repeat dilatations were indicated for patients with insufficient cardia relaxation after dilatation 1 as evident upon X-ray verification. Follow-up was conducted every 3 months (mo) for the first year, then annually thereafter; with a mean follow-up duration of 48 mo (range, 12 to 96 mo) and 42 mo (range, 12 to 96 mo) in the adjuvant therapy and control groups, respectively. Efficacy was assessed by application of a grading scale (1=excellent to 5=failure/complete relapse) for symptoms of dysphagia with liquids and solids, heartburn, regurgitation, chest pain or pressure, and weight change. Remission was defined as no or mild dysphagia, and acceptable individual symptoms as

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compared with baseline levels. About 3 to 4 days following the initial PD, 13 patients required 2 dilatations and 4 patients required 3 dilatations. For the adjuvant-therapy group, baseline measurements were 4.6 points (95% CI, 3.8 to 5.4 points) and 29 mmHg (range, 10 to 80 mmHg) for mean symptom score and median LES pressure, respectively. The initial treatment effect was observed in 91% (43/47) of patients (4 patients were lost to follow-up). After 3 months, the mean symptom score improved to 2.1 points (95% CI, 0.8 to 3.4 points) and the median LES pressure significantly improved to 14 mmHg (range, 5 to 26 mmHg; p less than 0.001). However, LES pressure slightly increased to 17 mmHg (range 8 to 40 mmHg) and 19 mmHg (9 to 38 mmHg) after 2 and 5 yr since initial treatment, respectively. Treatment durability was sustained in 75% (31/41) of patients with greater than 2-yr follow-up, and 70% (12/17) of patients with greater than 5 yr follow-up. The cumulative remission rate at the end of 5 yr was not significantly different between the adjuvant-therapy group (69%; 95% CI, 61% to 77%) and the historical control groups 50% (95% CI, 41% to 59%; p=0.07). Of 17% (8/47) of patients with relapse dysphagia, laparoscopic Heller myotomy was performed without complications. The most common adverse event was heartburn (36%), which was treated with proton pump inhibitors.

Support for using Dysport to treat blepharospasm can be found in a study by Truong et al. In a multicenter, phase 2, randomized, double-blind, placebo-controlled, parallel-group trial (n=120), a single injection of abobotulinumtoxinA 40 units, 80 units, or 120 units per eye was superior to placebo for the treatment of benign essential blepharospasm (BEB). Adults (age range, 33 to 91 years (yr)) with bilateral BEB for at least 6 months and who scored at least 8 points on the Blepharospasm Disability Scale (BDS; range, 0 to 26 points; higher score indicates greater disability) were eligible. Receipt of botulinum toxin prior to study entry was allowed provided a minimum of 12 weeks had elapsed since the last injection. Use of concomitant medications (e.g., benzodiazepines) that could potentially compromise evaluation of study outcomes was not permitted; however, concomitant use of antispasmodics, muscle relaxants, or other medications affecting the neuromuscular junction was allowed provided doses were stable during the study period. Patients were randomized to receive a total dose per eye of either abobotulinumtoxinA 40 units (n=30; median age, 66 yr; 68% female), 80 units (n=31; median age, 67 yr; 77% female), 120 units (n=31; median age, 62 yr; 81% female) or placebo (n=28; median age 62 yr; 68% female) injected subcutaneously in 0.1 milliliter (mL) aliquots into 6 areas of the orbicularis oculi muscle (0.6 mL total volume/eye). The primary outcome was improvement in functional disability, measured as the difference in the median percentage of normal activity on the BDS between active treatment and placebo at week 4. Notably, 50% of patients in placebo group dropped out of the study citing lack of efficacy compared with 20%, 16%, and 10% of patients in the abobotulinumtoxinA 40-, 80-, and 120-unit dose groups, respectively. An intent-to-treat analysis at week 4 showed significant improvement in functional disability with all abobotulinumtoxinA doses compared with placebo (p less than 0.01); improvement was dose-related and was sustained through week 12. Among secondary outcomes, the frequency of involuntary movements (FIM; measured using a modified FIM scale; range, 0 (no involuntary movements) to 5 (movements present greater than 75% of the time)) and the severity of oculofacial spasm (measured using the Severity Rating Scale) significantly improved at weeks 4, 8, and 12 with all doses of abobotulinumtoxinA compared with placebo. Median differences over placebo in FIM scores at week 4 were -2 (95% confidence interval (CI), -3 to -1), -3 (95% CI, -4 to -2), and -3 (95% CI, -4 to -1) for the 40-unit, 80-unit, and 120-unit dose groups, respectively (p less than 0.001 for all); correspondingly, median differences over placebo in the severity of oculofacial spasm scores were -1 (95% CI, -2 to -1), -2 (95% CI, -

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2 to -1) and -2 (95% CI, -2 to -1), respectively (p less than 0.001 for all). Improvements in the primary and secondary outcomes were maintained through week 16 only in the 80- and 120-unit groups (p less than 0.05). AbobotulinumtoxinA was well tolerated, with dose-related treatment events that were mild to moderate in severity and resolved without sequelae. Common events included eyelid ptosis, blurred vision, lagophthalmos, diplopia, increased lacrimation, and aggravated dry eyes.

Support for using Dysport to treat hemifacial spasm can be found in a study by Jitpimolmard, Tiamkao, and Laopaiboon. The authors conducted a long-term, prospective, descriptive study (n=158), serial abobotulinumtoxinA injections were effective and led to sustained improvement of hemifacial spasm in adults. Over a 7-year period, 175 consecutive patients with idiopathic hemifacial spasm received abobotulinumtoxinA subcutaneous injections, with the dose ranging from 28 to 220 units per treatment session based on sites and severity of the spasm. The primary injection sites were the medial and lateral lower eyelid; and the lateral junction area of the orbital and preseptal orbicularis oculi, below the lateral eyebrow and orbital area of the upper eyelid. The upper eyelid injection site was later shifted to the lateral orbital orbicularis oculi above the lateral eyebrow to reduce the incidence of ptosis. Subsequent injections were administered upon recurrence of spasm and if patient perception of the spasm was severe enough to request additional treatment. Efficacy assessments, which included peak improvement (measured using a visual analog scale; range, 0% to 100%) and duration of improvement, were conducted for 855 treatments administered to 158 patients (mean age, 49.1 +/- 11.39 years; 75% female). The median number of treatments was 4 (range, 1 to 19) and the mean follow-up period was 2.39 years (range, 3 to 80 months). The median duration of hemifacial spasm prior to receiving treatment was 4 years (range, 0.25 to 25 years). Among the 855 treatments, the response rate was 97%, with an adjusted mean peak improvement of 77.2% (95% confidence interval (CI), 74.7% to 79.4%); 70% of the treatments were rated as 75% to 100% improved. The adjusted duration of improvement was 3.4 months (95% CI, 3.2 to 3.6 months). Analysis of serial injections from treatment 1 up to treatment 12 revealed sustained effects for mean peak improvement (range, 72.07% to 80.17%) and duration of improvement (range, 2.93 to 3.71 months), but there was no additional benefit in either parameter over the series of treatments (p=0.4 and p=0.87, respectively). Of 26 treatment failures (peak improvement of less than 20%) occurring in 23 patients, subsequent treatments at the same dose (n=12) or higher dose (n=6) resulted in satisfactory improvements. Over 855 treatments, the most common adverse events were ptosis (22.1%) and drooping of the mouth (8.38%). Ptosis resolved in a mean of 2.64 weeks (range, 1 to 4 weeks). Following the change in site of upper eyelid administration, the incidence of ptosis significantly reduced from 27.17% (138 treatments) to 9.67% (21 treatments; p less than 0.001), with no significant difference in mean peak improvement or duration of improvement.

Support for using Myobloc to treat axillary hyperhidrosis can be found in a study by Hecht, Birklein, and Winterholler. Botulinum toxin type B effectively treated axillary hyperhidrosis in 4 patients. Patients received 250 mouse units (diluted in 2.5 milliliters saline) of botulinum toxin type B injected subcutaneously into 10 to 15 sites in each axilla. Using gravimetry, the mean pretreatment axillary sweating was 212.5 milligrams (mg) and 161.3 mg on the right and left sides, respectively. Three weeks after the botulinum toxin type B injections, 3 of 4 patients had axillary anhidrosis. In the other patient axillary sweating had decreased from 585 mg on the right side and 408 mg on the left side to 27 mg and 10 mg on

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the right and left sides, respectively. The effect duration ranged from 1 to 3 months. No adverse effects were reported.

Support for using Myobloc to treat bladder muscle dysfunction leading to overactive bladder can be found in a study by Dykstra, Enriquez, and Valley. The results of a prospective, open-label, dose-escalation study suggest that botulinum toxin type B (Myobloc(R)) is effective for overactive bladder and the effect duration may be dose related. All patients (n=15) were female, had symptoms of overactive bladder for at least 6 months, and urinary frequency of 8 or more micturitions per 24 hours with or without incontinence. Botulinum toxin type B was injected into the bladder wall at 10 different sites (trigone was avoided) at doses of 2500 Units (n=5), 3750 Units (n=4), 5000 Units (n=2), 10,000 Units (n=2), or 15,000 Units (n=3). Fourteen of 15 patients responded to treatment with decreased frequency, urgency, and no incontinence; the average decrease in the number of frequency episodes per day was 5.27 (p less than 0.001). There was a correlation between the dosage and the response duration (correlation coefficient=0.96, p less than 0.001). The shortest response duration (approximately 3 weeks) occurred at the 2500 Unit dose while the longest response duration (approximately 3 months) occurred in the patients who received 10,000 Unit and 15,000 Unit doses. Five patients experienced mild, transient injection site discomfort and 2 patients in the 15,000 Unit group reported mild general malaise and dry mouth.

Support for using Myobloc to treat blepharospasm and hemifacial spasm can be found in the American Hospital Formulary System- Drug Information resource. Myobloc has been used in the management of blepharospasm. The available published studies are in patients who have responded previously to onabotulinumtoxinA. The American Academy of Neurology (AAN) states that onabotulinumtoxinA and incobotulinumtoxinA should be considered as treatment options, and abobotulinumtoxinA may be considered for the treatment, of blepharospasm; AAN does not make a recommendation regarding rimabotulinumtoxinB for this use due to lack of data (Simpson, 2016).

Support for using Myobloc to treat palmar hyperhidrosis can be found in a study by Baumann et al. Twenty participants (10 men, 10 women) diagnosed with palmar hyperhidrosis were injected with either Myobloc (5,000 U per palm) or a 1.0 mL vehicle (100 mM NaCl, 10 mM succinate, and 0.5 mg/mL human albumin) into bilateral palms (15 Myobloc, 5 placebo). The participants were followed until sweating returned to baseline levels. The main outcome measures were safety, efficacy versus placebo, and duration of effect. A significant difference was found in treatment response at day 30, as determined by participant assessments, between 15 participants injected with Myobloc and 3 participants injected with placebo. The duration of action, calculated in the 17 participants who received Myobloc injections and completed the study, ranged from 2.3 to 4.9 months, with a mean duration of 3.8 months. The single most reported adverse event was dry mouth or throat, which was reported by 18 of 20 participants. The adverse event profile also included indigestion or heartburn (60%), excessively dry hands (60%), muscle weakness (60%), and decreased grip strength (50%). Myobloc proved to be efficacious for the treatment of palmar hyperhidrosis. Myobloc had a rapid onset, with most participants responding within 1 week. The duration of action ranged from 2.3 to 4.9 months, with a mean of 3.8 months. The adverse event profile included dry mouth, indigestion or heartburn, excessively dry hands, muscle weakness, and decreased grip strength.

Support for using Myobloc to treat spastic dysphonia can be found in a case report by Sataloff et al. Botulinum toxin type B was an effective treatment for spasmodic dysphonia for a patient who had

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developed resistance to botulinum toxin type A. The 49-year old patient received an injection of 750 mouse units of botulinum toxin type B in the left thyroarytenoid muscle and 500 mouse units of botulinum toxin type B in the right thyroarytenoid muscle. Improvement was reported 8 days after the injection; the response lasted approximately 14 weeks.

Support for using Myobloc to treat upper limb spasticity can be found in a study by Brashear et al. The authors conducted a double-blind, placebo-controlled, randomized trial. 10,000 units of botulinum toxin type B was administered over a 16-week treatment period was not found to be beneficial in lowering muscle tone in the elbow, wrist, or finger flexors when compared to placebo of post-stroke patients. However, in the open-label portion of the trial, Botulinum toxin type B at four weeks showed statistically significant improvements in muscle tone in the elbow (p=0.039), wrist (p=0.002), finger (p=0.001), and thumb flexors (p=0.002). Fifteen patients (8 male) were enrolled into the double-blinded trial with ten patients randomized to the botulinum toxin type B arm. Following 16 weeks of therapy, thirteen patients continued into the open-label trial. Efficacy was measured with the 5-point Ashworth Scale, which is designed to measure the degree of spasticity in the muscle. While global assessment of change (GAC) did not reach significance in the double-blind trial, GAC did show statistically significant improvement with botulinum toxin type B in the open-label trial as reported on the physician, patient, and occupational therapist GAC scales. No improvements were seen with regards to function and pain (via a Jebsen test, 9-hole peg test, or pain assessment) in either trial. Overall, botulinum toxin type B produced mild side effects; vital signs were not shown to have changed significantly with treatment. The most commonly reported adverse effect was dry mouth, which occurred in 89% of the treatment group versus 20% of the placebo group. The researchers noted that the high prevalence of dry mouth with botulinum toxin type B treatment could have led to possible unblinding. Ten subjects also experienced dry mouth in the open label trial, but all subjects had complete resolution of dryness by week 12 of the trial. One patient with a history of stroke and atrial fibrillation in the double-blind trial died of a large stroke following his week 4 follow-up visit; this serious adverse effect did not appear to be related to botulinum toxin type B. The authors conclude small sample size may have accounted for why the primary endpoint was not found to be statistically significant in the double-blinded trial, and that the disparity in results between the double-blind and open-label study may have resulted from rater bias.

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