



Louisiana

Botulinum Toxins

Policy # 00012

Original Effective Date: 01/28/2003

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Treatment of Hyperhidrosis is addressed separately in medical policy 00172.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Botulinum Toxin Type A

Based on review of available data, the Company may consider the use of botulinum toxin Type A products (Botox[®]†, Dysport[®]†, or Xeomin[®]†) to be **eligible for coverage** for **any** of the following conditions:

- Strabismus[∞]
- Blepharospasm or facial nerve (VII) disorders (including hemifacial spasm) [∞]
- Cervical dystonia (spasmodic torticollis; applicable whether congenital, due to child birth injury, or traumatic injury). For this use, cervical dystonia must be associated with sustained head tilt or abnormal posturing with limited range of motion in the neck AND a history of recurrent involuntary contraction of one or more of the muscles of the neck, e.g., sternocleidomastoid, splenius, trapezius, or posterior cervical muscles[∞]
- Upper limb spasticity[∞]
- Lower limb spasticity[∞]
- Axillary hyperhidrosis that is inadequately managed with topical agents[∞]
- Urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., Spinal Cord Injury, Multiple Sclerosis) in patients who have an inadequate response to or are intolerant of an anticholinergic medication[∞]
- Overactive bladder (OAB) in adults unresponsive to or intolerant of an anticholinergic medication[∞]
- Chronic migraine headaches[∞]:
 - Prophylaxis of chronic migraine headaches in adult patients (≥ 15 days per month with headaches lasting 4 hours a day or longer); **and**
 - There is documented failure of, contraindication to, or intolerance of at least two different migraine prophylaxis medications (e.g. beta-blockers, calcium channel blockers, tricyclic antidepressants or anticonvulsant medications) from two different therapeutic drug classes. (*Note: This specific patient criterion is a company requirement for coverage eligibility and will be denied as not medically necessary** if not met.*)
- Dystonia/spasticity resulting in functional impairment (interference with joint function, mobility, communication, nutritional intake) and/or pain in patients with **any** of the following:
 - Focal dystonias:
 - Focal upper limb dystonia (e.g., organic writer's cramp)
 - Oromandibular dystonia (orofacial dyskinesia, Meige syndrome)

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- Laryngeal dystonia (adductor spasmodic dysphonia)
- Idiopathic (primary or genetic) torsion dystonia
- Symptomatic (acquired) torsion dystonia
- o Spastic conditions
 - Cerebral palsy
 - Spasticity related to stroke
 - Acquired spinal cord or brain injury
 - Hereditary spastic paraparesis
 - Spastic hemiplegia
 - Neuromyelitis optica
 - Multiple sclerosis or Schilder's disease
- Esophageal achalasia in patients who have not responded to dilation therapy or who are considered poor surgical candidates
- Chronic sialorrhea (drooling) associated with Parkinson disease, atypical parkinsonism, stroke, or traumatic brain injury[∞]
- Chronic anal fissure
- Palmar hyperhidrosis that is inadequately managed with topical agents
- Hirschprung's disease with obstructive symptoms caused by internal sphincter achalasia following a pull-through surgery

[∞]FDA-approved indication for at least one of the agents

Botulinum Toxin Type B

Based on review of available data, the Company may consider the use of botulinum toxin Type B products (Myobloc[®])[‡] to be **eligible for coverage** for **any** of the following conditions:

- Cervical dystonia (spasmodic torticollis; applicable whether congenital, due to child birth injury, or traumatic injury). For this use, cervical dystonia must be associated with sustained head tilt or abnormal posturing with limited range of motion in the neck AND a history of recurrent involuntary contraction of one or more of the muscles of the neck, e.g., sternocleidomastoid, splenius, trapezius, or posterior cervical muscles. [∞]
- Sialorrhea (drooling) associated with Parkinson disease
- Incontinence due to detrusor overreactivity (urge incontinence), either idiopathic or due to neurogenic causes (e.g., spinal cord injury, multiple sclerosis), that is inadequately controlled with anticholinergic therapy

[∞]FDA-approved indication

****Note that for re-authorizations of either botulinum toxin type A or B, documentation of a positive response to the botulinum toxin therapy must be provided, otherwise it will be denied as not medically necessary****

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of botulinum toxin Type A products (Botox, Xeomin, or Dysport) in the treatment of chronic migraines in the absence of failure, contraindication, or intolerance to

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at least two different migraine prophylaxis medications from two different therapeutic drug classes to be **not medically necessary**.**

Based on review of available data, the Company considers the re-authorization of botulinum toxin Type A or B products (Botox, Xeomin, Dysport, or Myobloc) in the absence of a positive response to treatment to be **not medically necessary**.**

Based on review of available data, the Company considers the use of incobotulinumtoxinA (Xeomin) in chronic sialorrhea (drooling) associated with any conditions OTHER than Parkinson disease, atypical parkinsonism, stroke, or traumatic brain injury to be **not medically necessary**.**

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers, with the exception of cosmetic indications, the use of all botulinum toxin formulations to be **investigational*** for all other indications (not specifically mentioned above for the requested drug), including but not limited to the following:

- Non-migraine headaches (e.g. cluster headaches, tension-type headaches, etc.)
- Chronic low back pain
- Joint pain
- Mechanical neck disorders
- Neuropathic pain after neck dissection
- Myofascial pain syndrome
- Temporomandibular joint disorders
- Trigeminal neuralgia
- Pain after hemorrhoidectomy or lumpectomy
- Tremors such as benign essential tremor
- Tinnitus
- Chronic motor tic disorder, and tics associated with Tourette's syndrome (motor tics)
- Lateral epicondylitis
- Benign prostatic hyperplasia
- Interstitial cystitis
- Detrusor sphincteric dyssynergia (after spinal cord injury)
- Prevention of pain associated with breast reconstruction after mastectomy
- Hirschsprung's disease (EXCEPT those with obstructive symptoms caused by internal sphincter achalasia following a pull-through surgery)
- Gastroparesis
- Facial wound healing
- Internal anal sphincter (IAS) achalasia
- Depression

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Based on review of available data, the Company considers the use of onabotulinumtoxinA (Botox) or abobotulinumtoxinA (Dysport) in chronic sialorrhea (drooling) associated with any conditions OTHER than Parkinson disease, atypical parkinsonism, stroke, or traumatic brain injury to be **investigational**.*

When Services Are Not Covered

The use of all botulinum toxin formulations as treatment of wrinkles or other cosmetic indications is a contract exclusion and is therefore **not covered**.

Background/Overview

Botulinum is a family of toxins produced by the anaerobic organism *Clostridia botulinum*. Four formulations of botulinum toxin have been approved by the U.S. Food and Drug Administration (FDA). Labeled indications of these agents differ; however, all are FDA-approved for treating cervical dystonia in adults. Botulinum toxin products are also used for a range of off-label indications.

There are seven distinct serotypes designated as type A, B, C-1, D, E, F, and G. In the United States, four preparations of botulinum are commercially available; three using type A serotype and one using type B serotype. The drug names of the botulinum toxin products were changed in 2009; trade names and product formulations did not change. The three formulations of botulinum toxin type A are currently called onabotulinumtoxinA (Botox), abobotulinumtoxinA (Dysport) and incobotulinumtoxinA (Xeomin). Xeomin, the newest product marketed in the U.S., consists of the pure neurotoxin without complexing proteins and is the only product that is stable at room temperature for up to four years. Myobloc contains botulinum toxin type B; the current name of this drug is rimabotulinumtoxinB.

All four products are approved by the FDA for the treatment of cervical dystonia in adults; this is the only FDA-approved indication for Myobloc. Dystonia is a general term describing a state of abnormal or disordered tonicity of muscle. As an example, esophageal achalasia is a dystonia of the lower esophageal sphincter, while cervical dystonia is also known as torticollis. Spasticity is a subset of dystonia, describing a velocity-dependent increase in tonic-stretch reflexes with exaggerated tendon jerks. Spasticity typically is associated with injuries to the central nervous system. Spasticity is a common feature of cerebral palsy.

Cervical dystonia is a movement disorder (nervous system disease) characterized by sustained muscle contractions. This results in involuntary, abnormal, squeezing and twisting muscle contractions in the head and neck region. These muscle contractions result in sustained abnormal positions or posturing. Sideways or lateral rotation of the head and twisting of the neck is the most common finding in cervical dystonia. Muscle hypertrophy occurs in most patients. When using botulinum toxin to treat cervical dystonia, the postural disturbance and pain must be of a severity to interfere with activities of daily living; and the symptoms must have been unresponsive to a trial of standard conservative therapy. In addition, before using botulinum toxin, alternative causes of symptoms such as cervicogenic headaches must have been considered and excluded.

FDA or Other Governmental Regulatory Approval **U.S. Food and Drug Administration (FDA)**

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There are four botulinum toxin products currently approved by the FDA. These include onabotulinumtoxinA (Botox), abobotulinumtoxinA (Dysport), incobotulinumtoxinA (Xeomin), and rimabotulinumtoxin B (Myobloc).

Among the botulinum toxin products, onabotulinumtoxinA (Botox) is FDA-approved for the largest number of indications. It is approved for the treatment of overactive bladder, treatment of urinary incontinence, prophylaxis of migraine headaches, treatment of spasticity (upper and lower), treatment of cervical dystonia, treatment of severe axillary hyperhidrosis, treatment of blepharospasm, and the treatment of strabismus

IncobotulinumtoxinA (Xeomin) is indicated for the treatment of chronic sialorrhea, upper limb spasticity, cervical dystonia, and blepharospasm with prior treatment with onabotulinumtoxinA (Botox). AbobotulinumtoxinA (Dysport) is indicated for the treatment of cervical dystonia, the treatment of spasticity in adults, and the treatment of lower limb spasticity in pediatric patients. RimabotulinumtoxinB (Myobloc) is indicated for the treatment of cervical dystonia.

Rationale/Source

This evidence review was originally created in 1997 and has been updated regularly with searches of the MEDLINE database. Most recently, the literature was reviewed through August 23, 2017. For studies published before 2000, it is assumed that botulinum toxin (Botox), the only FDA-approved agent at that time, was used.

Dystonia/Spasticity

This evidence review section is based on a 1996 TEC Assessment (updated in 2004) that focused on the use of botulinum toxin for the treatment of focal dystonia or spasticity, the American Academy of Neurology (AAN) 2008 assessment of movement disorders and spasticity, and additional controlled trials and systematic reviews identified by MEDLINE literature searches.

The AAN assessment concluded that the evidence was AAN level A (established as effective, should be done) for equinus varus deformity in children with cerebral palsy and level B (probably effective, should be considered) for upper-extremity, for adductor spasticity, and for pain control in conjunction with adductor-lengthening surgery in children with cerebral palsy. The evidence was rated level B for treatment of adult spasticity in the upper and lower limb for reducing muscle tone and improving passive function, but insufficient evidence to recommend an optimum technique for muscle localization at the time of injection. The evidence was rated level B for upper-limb focal dystonia but insufficient for lower-limb focal dystonia, and was rated level B for adductor laryngeal dystonia but insufficient for abductor laryngeal dystonia.

In a 2013 meta-analysis, Foley et al identified 16 randomized controlled trials (RCTs) comparing injection of botulinum toxin to placebo injections or a nonpharmacologic treatment of moderate-to-severe upper-extremity spasticity following stroke. Studies evaluated the impact of treatment on activity limitations. Ten trials (total N=1000 patients) had data suitable for pooling. In a pooled analysis of effect size, botulinum toxin was associated with a moderate treatment effect compared with other interventions (standardized mean difference [SMD], 0.54; 95% confidence interval [CI], 0.35 to 0.71; $p < 0.001$). In another systematic review published in 2013, Baker et al pooled RCT data and found a statistically significant benefit of botulinum toxin type A for treating limb spasticity. Evidence was limited on botulinum toxin for spasticity-related pain.

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A 2014 systematic review and meta-analysis by Marsh et al identified 18 studies evaluating botulinum toxin type A for treatment of cervical dystonia; five were RCTs, and the remainder were observational studies. A pooled analysis found the mean duration of effect of botulinum toxin to be 93.2 days (95% CI, 91.8 to 94.6 days) using the fixed-effects model, and 95.2 days (95% CI, 88.9 to 101.4 days) using the random-effects model. Most studies included did not have control groups. A 2016 Cochrane systematic review and meta-analysis of 3 RCTs by Duarte compared botulinum toxin type A with botulinum toxin type B in cervical dystonia. The primary efficacy outcome was improvement on any validated symptomatic rating scale, and the primary safety outcome was the proportion of participants with adverse events. All trials evaluated the effect of a single treatment session using multiple dosing regimens. Reviewers reported no difference between the 2 types of botulinum toxin in terms of overall efficacy or safety. A 2016 Cochrane systematic review and meta-analysis of 4 RCTs (total N=441 participants) by Marques et al compared botulinum toxin type B with placebo in cervical dystonia. The primary efficacy outcome was overall improvement on any validated symptomatic rating scale. All trials evaluated the effect of a single treatment session using doses between 2500 U and 10,000 U. Compared with placebo, botulinum toxin type B was associated with an improvement of 14.7% (95% CI, 9.8% to 19.5%) in the patients' baseline clinical status with a placebo-corrected reduction of 2.2 points (95% CI, 1.25 to 3.15 points) in the Toronto Western Spasmodic Torticollis Rating Scale at week 4 after injection.

A 2015 systematic review by Dashtipour et al identified 16 RCTs and noncomparative controlled studies evaluating abobotulinumtoxinA in adults with upper-limb spasticity due to stroke. Total botulinum toxin dose ranged from 500 to 1500 U. The authors did not pool study findings, but did report that most studies found a statistically significant benefit of botulinum toxin on functioning, as measured by the Modified Ashworth Scale.

A 2016 systematic review and meta-analysis by Baker and Pereira identified 25 RCTs that evaluated the efficacy of botulinum toxin type A for limb spasticity on improving activity restriction and quality of life (QOL) outcomes. Reviewers reported pooled analysis for 6 RCTs that included upper- and lower-limb trials but were unable to pool studies for QOL measures. Evidence quality for the upper-limb was low/very low. Pooled results showed a significant increase in active function with botulinum toxin type A at 4 to 12 weeks for the upper-limb (SMD=0.32; 95% CI, 0.01 to 0.62; p=0.04) and these effects were maintained for up to 6 months (mean difference [MD], 1.87; 95% CI, 0.53 to 3.21; p=0.006). Reviewers reported no conclusion for efficacy in lower-limb or for QOL measures in either limb. A 2017 systematic review and meta-analysis by Dong et al identified 22 RCTs (total N=1804 participants) that evaluated the efficacy of botulinum toxin type A for upper-limb spasticity after stroke or traumatic brain injury. Compared with placebo, botulinum toxin type A treatment resulted in decrease of muscle tone after week 4 (SMD = -0.98, 95% CI, -1.28 to -0.68; I²=66%, p=0.004), week 6 (SMD = -0.85, 95% CI, -1.11 to -0.59; I²=1.2%; p=0.409), week 8 (SMD = -0.87, 95% CI, -1.15 to -0.6; I²=0%, p=0.713), week 12 (SMD = -0.67, 95% CI, -0.88 to -0.46; I²=0%; p=0.896), and week 12 (SMD = -0.73; 95% CI, -1.21 to -0.24; I²=63.5%; p=0.065).

Three relatively large RCTs are discussed as follows. The first published in 2011 by Shaw et al, randomized 333 patients with poststroke upper-limb spasticity to physical therapy plus Dysport (n=170) or to physical therapy alone (n=163). The primary outcome, improved function at 1 month according to the Action Research Arm Test, did not differ significantly among groups. Improved function using Action Research Arm Test scores also did not differ significantly between groups at 3 or 12 months. Change in muscle tone, based on mean change in the Motor

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Assessment Scale score significantly favored the Dysport group (-0.6) over the placebo group (-0.1) at 1 month ($p < 0.001$), but not at 3 and 12 months. The second double-blind RCT published in 2015 by Gracies et al assigned 243 adults with a stroke or brain trauma in the last 5 months to a single injection of abobotulinumtoxinA 500 U ($n=81$) or 1000 U ($n=81$) or placebo ($n=81$). The primary end point was the change in muscle tone in the primary target muscle group from baseline to 4 weeks as measured by Modified Ashworth Scale. At both doses, abobotulinumtoxinA resulted in greater tone reduction as evidenced by statistically significant reduction in placebo-corrected Ashworth Scale scores from baseline to week 4; abobotulinumtoxinA 500 U group (-0.9; 95% CI -1.2 to -0.6; $p < 0.001$), and abobotulinumtoxinA 1000 U group (-1.1; 95% CI, -1.4 to -0.8; $p < 0.001$ vs placebo). Authors recommended that future trials use active movement and function as primary outcome measures. The third RCT, published in 2016 by Wissel et al, assigned 273 poststroke adults to a 22- to 34-week treatment with onabotulinumtoxinA or placebo and subsequently open-label onabotulinumtoxinA up to 52 weeks. End points included change in pain and responder analysis (defined as proportion of patients with baseline pain ≥ 4 achieving a $\geq 30\%$ improvement in pain and a $\geq 50\%$ improvement in pain interference with work at week 12). Mean pain reduction from baseline at week 12 was -0.77 (95% CI, -1.14 to -0.40) with onabotulinumtoxinA compared with -0.13 (95% CI, -0.51 to 0.24; $p < 0.05$) with placebo. Respective proportion of responders was 53.7% and 37.0%. A European trial evaluated Xeomin for poststroke upper-limb spasticity. Kanovsky et al (2009) randomized 148 patients with poststroke upper-limb spasticity to botulinum toxin or placebo. After 4 weeks, a significantly higher response rate was found in all treated flexor muscle groups among patients given Xeomin. The treatment benefit lasted through the week-12 visit. An open-label extension of this trial with 145 participants was published in 2011. Patients received up to 5 additional sets of Xeomin injections, with 12-week intervals between injections. A total of 111 (77%) patients had at least 3 injections, and 72 (50%) had 4 injections. Outcomes were assessed 4 weeks after each injection. Compared with baseline, patients consistently showed improved outcomes at each posttreatment visit. None of the patients developed neutralizing antibodies in the double-blind or extension phases of the study.

Most trials that established the efficacy of abobotulinumtoxinA in treating focal spasticity in patients with cerebral palsy were small. Delgado et al (2016) reported on a relatively larger RCT in which 249 cerebral palsy children with dynamic equinus foot deformity were randomized to abobotulinumtoxinA 10 or 15 U/kg per leg, or placebo. The primary outcome measure was change in Modified Ashworth Scale score from baseline to week 4. Of the 246 patients randomized, 226 completed the trial and analysis included 235 (98%) patients. Results showed that both doses of abobotulinumtoxinA resulted in greater improvement in placebo-corrected Ashworth Scale scores (-0.49; 95% CI, -0.75 to -0.23; $p < 0.001$; -0.38; (95% CI, -0.64 to -0.13; $p = 0.003$ respectively).

In 2016, Botox gained an indication for lower limb spasticity. The efficacy and safety of Botox for the treatment of lower limb spasticity was evaluated in a randomized, multi-center, double-blind, placebo-controlled study. The study included 468 post-stroke patients (233 Botox and 235 placebo) with ankle spasticity (modified Ashworth Scale ankle score of at least 3) who were at least 3 months post-stroke. A total dose of 300 Units of Botox or placebo were injected intramuscularly and divided between the gastrocnemius, soleus, and tibialis posterior, with optional injection into the flexor hallucis longus, flexor digitorum longus, flexor digitorum brevis, extensor hallucis, and rectus femoris with up to an additional 100 Units (400 Units total dose). Patients were followed for 12 weeks. The co-primary endpoints were the average of the change from baseline in modified Ashworth Scale (MAS) ankle score at Week 4 and Week 6, and the average of the Physician Global Assessment of Response (CGI) at Week 4 and Week 6. The CGI evaluated the response to treatment in terms of how the patient was doing in his/her life using a 9-point scale

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from -4 = very marked worsening to +4 = very marked improvement). Statistically significant between-group differences for Botox over placebo were demonstrated for the co-primary efficacy measures of MAS and CGI. Compared to placebo, significant improvements in MAS change from baseline for ankle plantar flexors and CGI were observed at Week 2, Week 4, and Week 6 for patients treated with Botox.

Summary: Multiple RCTs and meta-analyses support the efficacy of botulinum toxin for treating dystonia/spasticity, which is a labeled indication.

Strabismus

Strabismus is a condition in which the eyes are not in proper alignment with one another. In 2012, a Cochrane review was published by Rowe and colleagues evaluating the literature on botulinum toxin for strabismus. The investigators identified 4 RCTs, all of which were published in the 1990s. Three trials compared botulinum toxin injection to surgery, and 1 compared botulinum toxin injection to a noninvasive treatment control group. Among the trials that used surgery as a comparison intervention, 2 studies found no statistically significant differences in outcomes between the 2 groups, and 1 found a higher rate of a satisfactory outcome in the surgery group. The study comparing botulinum toxin to no intervention did not find a significant difference in outcomes in the 2 groups. Complications after botulinum toxin included transient ptosis and vertical deviation; combined complication rates ranged from 24% to 56% in the studies.

For patients who failed prior surgery, Tejedor and Rodriguez conducted a trial in 1999 that included 55 children with strabismus who remained symptomatic after surgical alignment. Patients were randomly assigned to receive a second operation (28 patients) or botulinum toxin injection (n=27). Motor and sensory outcomes did not differ significantly in the 2 groups. At 3 years, for instance, 67.8% of children in the reoperation group and 59.2% of children in the botulinum toxin group were within 8 prism diopters of orthotropias (p=0.72). In 1994, Lee and colleagues randomized 47 patients with acute unilateral sixth nerve palsy to botulinum toxin treatment or a no treatment control group. The final recovery rate was 20 of 25 (80%) in the botulinum toxin group and 19 of 22 (80%) in the control group.

Summary: Several RCTs from the 1990s had mixed results on the efficacy of botulinum toxin for strabismus. This evidence has not established that botulinum toxin improves outcomes for patients with strabismus. However, treatment is a noninvasive alternative to surgery.

Blepharospasm

Blepharospasm is a progressive neurologic disorder characterized by involuntary contractions of the eyelid muscles; it is classified as a focal dystonia. RCTs have evaluated Botox, Dysport, and Xeomin for the treatment of blepharospasm and found these agents to be effective at improving symptoms. No RCTs evaluating Myobloc for treating blepharospasm were identified in literature searches. Dashtipour et al (2015) reported on the results of a systematic review that included 5 RCTs (374 with blepharospasm, 172 with hemifacial spasm) of abobotulinumtoxinA. All trials showed statistically significant benefits for the treatment of blepharospasm and hemifacial spasm.

Summary: Multiple RCTs and a systematic review have found that botulinum toxin injection is an effective treatment of blepharospasm.

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Headache

Botulinum toxin for treatment of pain from migraine and from chronic tension-type headaches was addressed in a 2004 TEC Assessment. Both Assessments concluded that the evidence was insufficient for either indication. Because the placebo response rate is typically high in patients with headache, assessment of evidence focuses on randomized, placebo-controlled trials. More recent literature is discussed below, organized by type of headache. Recent studies have focused on frequency of headache as an outcome measure in addition to pain and headache severity.

Migraine Headache

Migraines can be categorized by headache frequency. According to the Third Edition of the International Headache Classification (ICHD-3), migraine without aura (previously known as common migraine) is defined as at least 5 attacks per month meeting other diagnostic criteria. Chronic migraine is defined as attacks on at least 15 days per month for more than 3 months, with features of migraine on at least 8 days per month.

Several RCTs and systematic reviews of RCTs have been published. In 2013, the Agency for Healthcare Research and Quality published a comparative effectiveness review on preventive pharmacologic treatments for migraine in adults. The investigators identified 15 double-blind RCTs evaluating botulinum toxin for migraine prevention: 13 used onabotulinumtoxinA and 2 used abobotulinumtoxinA. In a meta-analysis of 3 RCTs, onabotulinumtoxinA was more effective than placebo in reducing the number of chronic migraine episodes per month by at least 50% (relative risk, 1.5; 95% CI, 1.2 to 1.8). In another pooled analysis, onabotulinumtoxinA was associated with a significantly higher rate of treatment discontinuation due to adverse effects than placebo (relative risk, 3.2; 95% CI, 1.4 to 7.10). Five RCTs compared the efficacy of onabotulinumtoxinA with another medication (topiramate or divalproex sodium). Findings were not pooled, but, for the most part, there were no statistically significant differences in outcomes between the 2 drugs.

In 2012, Jackson et al conducted a meta-analysis of RCTs on botulinum toxin type A for the prophylactic treatment of headache in adults; the analysis addressed migraines and other types of headache. The investigators included RCTs that were at least 4 weeks in duration, had reduction in headache frequency or severity as an outcome, and used patient-reported outcomes. The investigators categorized eligibility criteria as addressing episodic (<15 headaches/month) or chronic headache (≥ 15 days/month). A total of 10 trials on episodic migraine and 7 trials on chronic migraine were identified. All trials on episodic migraine and 5 of 7 trials on chronic migraine were placebo-controlled; the other 2 trials compared botulinum toxin injections with oral medication. A pooled analysis for chronic migraine (5 trials) found a statistically significantly greater reduction in the frequency of headaches per month with botulinum toxin than with a control intervention (absolute difference, -2.30; 95% CI, -3.66 to -0.94). In contrast, in a pooled analysis on episodic migraine (9 trials), there was no statistically significant difference between groups in the change in monthly headache frequency (absolute difference, -0.05; 95% CI, -0.25 to 0.36).

Previously, in 2009, Shuhendler et al conducted a meta-analysis of trials on botulinum toxin for treating episodic migraines. The investigators identified 8 randomized, double-blind, placebo-controlled trials evaluating the efficacy of botulinum toxin type A injections. A pooled analysis of the main study findings found no significant differences between the botulinum toxin type A and placebo groups in change in the number of migraines per month. After 30

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days of follow-up, the SMD was -0.06 (95% CI, -0.14 to 0.03; $p=0.18$). After 90 days, the SMD was -0.05 (95% CI, -0.13 to 0.04; $p=0.28$). A subgroup analysis examining trials using low-dose botulinum toxin type A (<100 U) compared to trials using high-dose botulinum toxin type A (≥ 100 U) did not find a statistically significant effect of botulinum toxin type A compared with placebo in either stratum.

A pair of multicenter RCTs that evaluated onabotulinumtoxinA (Botox) for chronic migraine was published in 2010. The trials reported findings from the double-blind portions of the industry-sponsored PREEMPT (Phase 2 Research Evaluating Migraine Prophylaxis Therapy) trials 1 and 2. Trial designs were similar. Both included a 24-week double-blind, placebo-controlled phase prior to an open-label phase. The trials recruited patients meeting criteria for migraine and excluded those with complicated migraine. To be eligible, patients had to report at least 15 headache days during the 28-day baseline period, each headache lasting at least 4 hours. At least 50% of the headaches had to be definite or probable migraine. The investigators did not require that the frequent attacks occurred for more than 3 months or exclude patients who overused pain medication, 2 of the ICHD-2 criteria for chronic migraine. Eligible patients were randomly assigned to receive 2 cycles of Botox injections 155 U or placebo, with 12 weeks between cycles. Randomization was stratified by frequency of acute headache pain medication used during baseline and whether patients overused acute headache pain medication. (Medication overuse was defined as baseline intake of simple analgesics on at least 15 days, or other medications for at least 10 days, and medication use at least 2 days per week.)

The primary end point in PREEMPT 1 was mean change from baseline in frequency of headache episodes for 28 days ending with week 24. A headache episode was defined as a headache with a start and stop time indicating that pain lasted at least 4 hours. Prespecified secondary outcomes included, among others, change in frequency of headache days (calendar days in which pain lasted at least 4 hours), migraine days (calendar days in which a migraine lasted at least 4 hours), and migraine episodes (migraine with a start and stop time indicating that pain lasted at least 4 hours). Based on availability of data from PREEMPT 1 and other factors, the protocol of the PREEMPT 2 trial was amended (after study initiation but before unmasking) to make frequency of headache days the primary end point of this study. The authors noted that, to control for potential type I error related to changes to the outcome measures, a more conservative p value (0.01) was used. Several quality-of-life (QOL) measures were also included in the trials, including the 6-item Headache Impact Test 6 (HIT-6) and the Migraine Specific Quality of Life Questionnaire (MSQ v.2). Key findings of the 2 studies are described below.

PREEMPT 1 randomly assigned 679 patients. Mean number of migraine days during baseline was 19.1 in each group. The mean number of headache episodes during the 28-day baseline period was 12.3 in the Botox group and 13.4 in the placebo group. Approximately 60% of patients had previously used at least 1 prophylactic medication and approximately 68% overused headache pain medication during baseline. A total of 296 (87%) of 341 patients in the Botox group and 295 (87%) of 338 patients in the placebo group completed the 24-week double-blind phase. The primary outcome (change from baseline in frequency of headache episodes over a 28-day period) did not differ significantly between groups. The number of headache episodes decreased by a mean of 5.2 in the Botox group and 5.3 in the placebo group ($p=0.344$). Similarly, the number of migraine episodes did not differ significantly. There was a decrease of 4.8 migraine episodes in the Botox group and of 4.9 in the placebo group ($p=0.206$). In contrast, there was a significantly greater decrease in the number of headache days and the number of migraine days in the Botox group than in the placebo group. The decrease in frequency of headache days was 7.8 in the Botox group and 6.4 in

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the placebo group, a difference of 1.4 headache days per 28 days ($p=0.006$). Corresponding numbers for migraine days were 7.6 and 6.1, respectively ($p=0.002$). There was significantly greater improvement in QOL in the Botox versus the placebo group. The proportion of patients with severe impact of headaches (ie, HIT-6 score, ≥ 60) in the Botox group decreased from 94% at baseline to 69% at 24 weeks; in the placebo group, it decreased from 95% at baseline to 80%, a between-group difference of 11% ($p=0.001$). The authors did not report MSQ scores, but stated that there was statistically significant greater improvement in the 3 MSQ role function domains at week 24 (restrictive, $p<0.01$; preventive, $p=0.05$; emotional, $p<0.002$). Adverse events were experienced by 203 (60%) patients in the Botox group and 156 (47%) patients in the placebo group. Eighteen (5%) patients in the Botox group and 8 (2%) in the placebo group experienced serious adverse events. Treatment-related adverse events were consistent with the known safety profile of Botox.

PREEMPT 2 randomly assigned 705 patients. Mean number of migraine days during baseline period was 19.2 in the Botox group and 18.7 in the placebo group. Mean number of headache episodes during the 28-day baseline period was 12.0 in the Botox group and 12.7 in the placebo group. Approximately 65% of patients had previously used at least 1 prophylactic medication and approximately 63% overused headache pain medication during baseline. A total of 311 (90%) of 347 patients in the Botox group and 334 (93%) of 358 patients in the placebo group completed the 24-week, double-blind phase. The primary outcome, change from baseline frequency of headache days over a 28-day period (a different primary outcome from PREEMPT 1), differed significantly between groups and favored Botox treatment. The number of headache days decreased by a mean of 9.0 in the Botox group and 6.7 in the placebo group, an absolute difference of 2.3 days per 28 days ($p<0.001$). Mean number of migraine days also decreased significantly, more in the Botox group (8.7) than in the placebo group (6.3; $p<0.001$). Unlike PREEMPT 1, there was a significantly greater decrease in headache episodes in PREEMPT 2 in the Botox group (5.3) than in the placebo group (4.6; $p=0.003$). Change in frequency of migraine episodes was not reported.

Similar to PREEMPT 1, quality-of-life measures significantly improved in the Botox group. The proportion of patients reporting that their headaches had a severe impact (score of at least 60 on the HIT-6) severe impact of headaches in the Botox group decreased from 93% at baseline to 66% at 24 weeks; in the placebo group, it decreased from 91% at baseline to 77%. There was a between-group difference of 10% ($p=0.003$). The authors reported statistically significantly greater improvement in the 3 MSQ role function domains at week 24 (restrictive, preventive, emotional, $p<0.001$ for each domain). Adverse events were experienced by 226 (65%) patients in the Botox group and 202 (56%) patients in the placebo group. Fifteen (4%) patients in the Botox group and 8 (2%) in the placebo group experienced serious adverse events. As in PREEMPT 1, treatment-related adverse events in PREEMPT 2 were consistent with the known safety profile of Botox.

Also published in 2010 was a pooled analysis of findings from the PREEMPT 1 and 2 trials; this analysis was also industry-sponsored. There were 688 patients in the Botox group and 696 in the placebo group in the pooled analysis of outcomes at week 24. In the combined analyses, there was a significantly greater reduction in change from baseline in frequency of headache days, migraine days, headache episodes, and migraine episodes in the Botox group than in the placebo group. For example, the pooled change in mean frequency of headache days was 8.4 in the Botox group and 6.6 in the placebo group ($p<0.001$). Mean difference in number of headache days over a 28-day data collection period was 1.8 (95% CI, 1.13 to 2.52). The pooled change in frequency of headache episodes was 5.2 in the Botox group and 4.9 in the placebo group, a relative difference of 0.3 episodes (95% CI, 0.17 to 1.17;

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$p=0.009$). Between-group differences, though statistically significant, were relatively small and may not be clinically meaningful. In the pooled analysis, the authors also reported the proportion of patients with at least a 50% decrease from baseline in the frequency of headache days at each time point (every 4 weeks from week 4 to week 24). For example, at week 24, the proportion of participants with at least a 50% reduction in headache days was 47.1% in the Botox group and 35.1% in the placebo group. In contrast, the difference in the proportion of patients experiencing at least a 50% reduction in headache episodes did not differ significantly between groups at 24 weeks or at most other time points, with the exception of week 8. The article did not report the proportion of participants who experienced at least a 50% reduction in migraine days or migraine episodes. The pooled analysis showed statistically significant differences for the change in proportion of patients with severe headache impact as assessed using the HIT-6 and change in MSQ questionnaire domains.

Several issues are worth noting about the methods and findings of the PREEMPT studies. There was a statistically significant difference in headache episodes in PREEMPT 2 but not PREEMPT 1 (for which it was the primary outcome); the primary outcome was changed after initiation of PREEMPT 1. Moreover, one of the main secondary outcomes in PREEMPT 1 (change in the number of migraine episodes) was not reported in the second trial; the authors did not discuss this omission. In addition, the individual studies did not include threshold response to treatment (eg, at least a 50% reduction in headache or migraine frequency) as a key outcome. The pooled analysis did report response rates, but as secondary efficacy outcomes.

Most patients in both trials fulfilled criteria for medication overuse headache, and therefore many may have been experiencing secondary headaches rather than chronic migraines. If patients had secondary headaches, detoxification alone might have been sufficient to change their headache pattern to an episodic one. The clinical relevance of less than a 2-day difference in reduction in number of headache days is uncertain, though consistent with reductions previously reported in several medication trials.

Another RCT assessed use of botulinum toxin for treating chronic migraine was published by Cady et al. The trial included patients who met ICHD-2 criteria for chronic migraine. Patients were randomized to receive treatment with Botox ($n=29$) or topiramate ($n=30$). At the 12-week follow-up, the end of the double-blind phase of the study, treatment effectiveness did not differ significantly between groups. For the primary end point (Physician Global Assessment at week 12), physicians noted improvement in 19 (79%) of 24 patients in the Botox group and 17 (71%) of 24 patients in the topiramate group; 9 patients (15%) were not available for this analysis.

Medication Overuse Headache

According to the ICHD-2, medication overuse headache is a different diagnostic classification than chronic migraine. In 2013, Silberstein et al published a subanalysis of pooled PREEMPT data limited to patients with headache medication overuse at baseline. A total of 904 patients who indicated they had medication overuse headache were included; 445 were randomized to the botulinum toxin group and 459 to the placebo group. At the end of week 24, there was a significantly greater reduction in outcomes, including headache days, headache episodes, and moderate-to-severe headache days, in the botulinum toxin group than in the placebo group. For example, the number of headache days per month decreased by a mean of 8.2 (SE=0.3) in the botulinum toxin group and 6.2 (SE=0.3) in the placebo group ($p<0.001$). This is a single analysis of RCT data and provides insufficient evidence that botulinum toxin is effective for patients with the diagnosis of medication overuse headache.

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Tension Headache

The 2012 meta-analysis by Jackson et al (discussed above) identified 7 RCTs evaluating botulinum toxin for treating chronic tension-type headaches; all were placebo-controlled. A pooled analysis of these 7 studies did not find a statistically significant difference in change in the monthly number of headache days in the botulinum toxin group versus the placebo group (difference, -1.43; 95% CI, -3.13 to 0.27). The trial with the largest sample size (Silberstein et al²⁸) included 300 patients randomized to 1 of 4 doses of botulinum toxin or placebo. Overall, there was no statistically significant difference between the botulinum toxin groups and the placebo group in mean change from baseline to 90 days in number of headache days per month.

Chronic Daily Headache

Although chronic daily headache is not recognized in the ICHD, it is commonly defined to include different kinds of chronic headache (eg, chronic or transformed migraine, daily persistent headache). It may also include chronic tension-type headache, addressed above. The meta-analysis by Jackson et al identified 3 RCTs comparing botulinum toxin type A with placebo in patients having at least 15 headaches per month. A pooled analysis of data from these 3 trials found a significantly greater reduction in the number of headaches per month with botulinum toxin than with placebo (absolute difference, -2.06; 95% CI, -3.56 to -0.56). Individually, only 1 (Ondo et al, 2004²⁹) of the 3 trials found a statistically significant benefit with botulinum toxin treatment. Ondo included 60 patients, some with chronic migraines and chronic tension-type headache. The Ondo study found significantly greater reduction in the number of headache-free days over weeks 8 to 12 with botulinum toxin than with placebo ($p < 0.05$), but there was no statistically significant between-group difference in reduction in headache-free days over the entire 12-week study period ($p = 0.07$). The other 2 studies evaluated more patients: 355 in Mathew et al and 702 in Silberstein et al. Neither found a statistically significant difference in the reduction in the number of headache days per month with botulinum toxin. The available evidence from RCTs is conflicting and insufficient for conclusions.

Cluster Headache

No controlled trials were identified for cluster headache.

Cervicogenic Headache

In 2011, Linde et al published a double-blind, placebo-controlled crossover study that included 28 patients with treatment-resistant cervicogenic headache. Patients were randomized to botulinum toxin type A or placebo; there was at least an 8-week period between treatments. The trial did not find significant differences between active and placebo treatment in the primary outcome, reduction in number of days with moderate-to-severe headache. Three other RCTs, published between 2000 and 2008, randomized patients with chronic, whiplash-related headache to botulinum toxin type A treatment or placebo. One trial reported trends toward improvement with treatment for various outcomes; most were not statistically significant. Another reported no significant differences for several pain-related outcomes. One trial reported a significant improvement in pain with treatment while the placebo group reported no improvement, but trial design was flawed because the placebo group reported less pain at baseline.³⁴ A Cochrane review of treatment of mechanical neck disorders, published in 2007, included 6 RCTs (total $N = 273$ patients) assessing botulinum toxin and placebo for chronic neck disorders with or without radicular findings or headache. A meta-analysis of 4 studies ($n = 139$ patients) for pain outcomes found no statistically significant results. The reviewers

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concluded that a range of doses have not shown significant differences compared with placebo or with other comparators.

Summary: For chronic migraine, a meta-analysis of RCTs found that onabotulinumtoxinA was more effective than placebo in reducing the number of chronic migraine episodes per month, although it was also associated with a significantly higher rate of treatment discontinuation due to adverse effects than placebo. For patients with an episodic pattern of migraine (ie, <15 episodes per month), the published evidence does not suggest that botulinum toxin improves net health outcome for patients. For tension headache, RCTs and systematic reviews do not indicate that botulinum toxin improves outcomes. For other headache types, the evidence is insufficient to form conclusions about efficacy.

Esophageal Achalasia

Esophageal achalasia is a primary motor disorder characterized by abnormal lower esophageal sphincter relaxation. A 2014 Cochrane review by Leyden et al identified 7 RCTs (total N=178 participants) on treatment of primary esophageal achalasia with botulinum toxin or endoscopic pneumatic dilation.³⁷ A pooled analysis of data from 5 trials did not find a statistically significant difference in the rate of initial remission with pneumatic dilation versus botulinum toxin injection (risk ratio [RR], 1.11; 95% CI, 0.97 to 1.27). Remission at 6 and 12 months favored the pneumatic dilation group. No serious adverse events were reported after botulinum toxin injection; however, there were 3 cases of perforation after pneumatic dilation.

A randomized controlled trial by Annese and colleagues in Italy with 78 patients found 100U of Botox and 250U of Dysport to have comparable efficacy for treating esophageal achalasia.

Summary: A systematic review of RCTs reported similar initial remission rates of esophageal achalasia after botulinum toxin injection and pneumatic dilation. Pneumatic dilation was associated with higher longer term remission rates but is more invasive, and perforation has been reported.

Sialorrhea (Drooling)

Parkinson's Disease/Atypical Parkinsonism/Stroke/Traumatic Brain Injury Related

The efficacy and safety of incobotulinumtoxin A for the treatment of chronic sialorrhea were evaluated in a double-blind, placebo-controlled clinical trial that enrolled a total of 184 patients with chronic sialorrhea resulting from Parkinson's disease, atypical parkinsonism, stroke, or traumatic brain injury, that was present for at least three months. Patients with a history of aspiration pneumonia, amyotrophic lateral sclerosis, salivary gland or duct malformation, and gastroesophageal reflux disease were excluded. The study consisted of a 16-week main phase, followed by an extension period of dose-blinded treatment with incobotulinumtoxin A. In the main phase, a fixed total dose of incobotulinumtoxin A (100 Units or 75 Units) or placebo was administered into the parotid and submandibular salivary glands in a 3:2 dose ratio. The co-primary efficacy variables were the change in unstimulated Salivary Flow Rate (uSFR) and the change in Global Impression of Change Scale (GICS) at week 4 post-injection. A total of 173 treated patients completed the main phase of the study. For both the uSFR and GICS, incobotulinumtoxin A 100 Units was significantly better than placebo. incobotulinumtoxin A 75 Units was not significantly better than placebo.

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Summary: RCTs have consistently found benefit of botulinum toxin injection on sialorrhea in patients with Parkinson disease.

Non-Parkinson's Disease/Non-Stroke/Non-Traumatic Brain Injury Related

Several systematic reviews have been published on botulinum toxin for treating sialorrhea in people with conditions other than Parkinson Disease. In 2014, Squires et al reviewed the research on botulinum toxin injections for drooling in patients with amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). The review included both RCTs and controlled and uncontrolled observational studies. The authors identified 12 studies of which 8 did not have a control group. There were 2 small RCTs, 1 had 20 patients and was placebo-controlled and the other had 14 patients and compared botulinum toxin with radiotherapy. Sample sizes in the non-RCTs ranged from 5 to 26. Due to heterogeneity, study findings were not pooled. As reported in the systematic review, only 1 of the 2 RCTs reported drooling outcomes; this study found a significantly greater reduction in saliva volume in the botulinum toxin group than the placebo group at 2 weeks.

In 2012, Rodwell and colleagues published a systematic review of published literature evaluating botulinum toxin injections in the salivary gland for treating sialorrhea in children with cerebral palsy and neurodevelopment disability. The authors identified 5 RCTs; sample sizes in individual trials ranged from 6 to 48 participants. One of the RCTs, which had 6 participants, was terminated due to adverse events. In a pooled analysis from 3 RCTs of data 4 weeks postintervention, the mean score on the Drooling Frequency and Severity Scale (DFSS) was significantly lower in children who received botulinum toxin injections compared to a control intervention (mean difference: -2.71 points, 95% CI: -4.82 to -0.60, $p < 0.001$). The clinical significance of this degree of difference in DFSS scores is not clear. Data were not pooled for other outcomes. The systematic review also identified 11 prospective case series. The rate of adverse events associated with botulinum toxin injection in the RCTs and case series ranged from 2% to 41%. Dysphagia occurred in 2 of the 6 participants in the RCT that was terminated early and in 2 of 126 patients in a case series. There was 1 reported chest infection, 1 case of aspiration pneumonia and, in 1 case series, 6 of 126 patients experienced an increased frequency of pulmonary infections. In 7 studies, there were reports of patients with difficulty swallowing and/or chewing following botulinum toxin treatment.

The largest RCT on botulinum toxin for treating sialorrhea in children with cerebral palsy was published in 2008 by Reid and colleagues. Forty-eight children with cerebral palsy ($n=31$) and other neurologic disorders were randomized to a single injection of 25 U botulinum toxin A compared to no treatment. Drooling was assessed by administering the Drooling Impact Scale. Scores were significantly different between groups at 1 month, and a beneficial effect of botulinum toxin injection remained at 6 months.

A 2013 article focused on the long-term safety of botulinum toxin A injection for treating sialorrhea in children. The study included 69 children; 47 (68%) had cerebral palsy. Children received their first injection of botulinum toxin at a mean age of 9.9 years and mean follow-up was 3.1 years. During the study period, the children received a total of 120 botulinum toxin injections. Complications occurred in 19 of 69 (28%) children and in 23 of 120 (19%) injections. Fifteen of 23 complications were minor, including 6 cases of dysphagia. There were 8 major complications. These included 3 cases of aspiration pneumonia, 2 cases of severe dysphagia, and 3 cases of loss of motor control of the head. Complications were associated with 5 hospitalizations and 2 cases of neogastric tube placement.

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Summary: Although there is evidence of improvement in drooling scales following botulinum toxin injections in children with cerebral palsy, the clinical significance is uncertain, and there are concerns about the safety of injecting botulinum toxin into the salivary gland in this population. The evidence on botulinum toxin for treating sialorrhea in patients with amyotrophic lateral sclerosis/motor neuron disease is insufficient due to the paucity of controlled studies, small sample sizes of available studies, and limited reporting of drooling outcomes.

Internal Anal Sphincter (IAS) Achalasia

Internal anal sphincter (IAS) achalasia is a defecation disorder in which the internal anal sphincter is unable to relax. Symptoms include severe constipation and soiling. A meta-analysis of studies on treatment of IAS achalasia was published in 2012 by Friedmacher and Puri. Reviewers did not identify any RCTs of Botox treatment. Two prospective case series and 14 retrospective case series (total N=395 patients) of IAS achalasia were identified. Most patients (229/395 [58%]) in the series were treated with posterior IAS myectomy and 166 (42%) were treated with intrasphincteric botulinum toxin injection. A meta-analysis of data from the observational studies found that regular bowel movements were more frequent after myectomy (odds ratio [OR], 0.53; 95% CI, 0.29 to 0.99; p=0.04). Moreover, the rate of transient fecal incontinence was significantly higher after botulinum toxin injection (OR=0.07; 95% CI, 0.01 to 0.54; p<0.01) and the rate of subsequent surgical intervention was higher after botulinum toxin injection (OR=0.18; 95% CI, 0.07 to 0.44; p<0.001). Other outcomes, including continued use of laxatives or rectal enemas and overall complication rates, did not differ between treatments. Emile et al (2016) reported the results of a systematic review that included 7 studies comprising 189 patients with a follow-up period greater than 6 months in each of the individual studies. Of the 7 included studies, 2 were RCTs and remaining were comparative and observational studies. Both RCTs were single site from the same author group and conducted in Egypt, enrolling 15 and 24 patients, respectively. Improvement was defined as patients returning to their normal habits. The first RCT used biofeedback and the other used surgery as the comparator. In the first RCT, 50% of individuals in the biofeedback group reported improvement initially at 1 month but it dropped down to 25% by the end of year. The respective proportions of patients in the botulinum toxin arm were 70.8% and 33.3%. In the second RCT, surgery led to improved outcomes in all patients at 1 month but that percentage dropped to 66.6% at 1 year. The respective proportions of patients in the botulinum toxin arm were 87% and 40%. While these results suggest temporary improvement, methodologic limitations, including small sample size, lack of blinded assessment, and use of validated outcome measure, limit the interpretation of these RCTs.

Summary: There is a lack of good quality RCTs evaluating botulinum toxin injection as a treatment of IAS achalasia. A meta-analysis of observational data and a systematic review suggested that posterior IAS myectomy results in greater improvement in health outcomes than botulinum toxin injections.

Anal Fissure

Chronic anal fissure is a tear in the lower half of the anal canal that is maintained by contraction of the internal anal sphincter, and is treated surgically with an internal sphincterotomy. Since the anal sphincter contraction could be characterized as a dystonia, botulinum toxin is a logical medical approach.

In 1998, Maria and colleagues randomized 30 patients with chronic anal fissure to receive either two injections of 20 units of botulinum toxin, on either side of the fissure, or two injections of saline. After two months, 11 patients in the treatment group reported healing, compared to only two in the control group. The four patients who still had fissures

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after two months underwent retreatment with botulinum toxin; two of these four patients reported healing scars and symptomatic relief. These results are consistent with earlier case series that reported a healing rate of 80%. Nitroglycerin ointment has also been used to successfully treat anal fissure. In 1999, Brisinda and colleagues in Italy compared the results of nitroglycerin ointment and botulinum toxin in a randomized trial of 50 patients. After two months, 96% of the fissures were healed in the botulinum group compared with 60% in the nitroglycerin group. The same group conducted a second, similar trial in 2007 with 92% versus 70% healing rates for botulinum toxin A-treated versus nitroglycerin ointment-treated patients ($p < 0.001$). Another trial by this research group found that Botox and Dysport used to treat anal fissures were similar in terms of efficacy and tolerability. Others have reported both supportive and contradictory data from randomized trials comparing the same treatments. Randomized, controlled trials of botulinum toxin vs. sphincterotomy have reported significantly better results with sphincterotomy but authors concluded that botulinum toxin was a viable first option for patients who are not good surgical candidates or who want to minimize the likelihood of incontinence.

A 2012 systematic review of the literature identified 2 RCTs comparing botulinum toxin with placebo, 1 RCT comparing botulinum toxin with lidocaine pomme, 5 RCTs comparing botulinum toxin with nitrates, and 8 RCTs comparing botulinum toxin with surgery. A meta-analysis was not performed due to heterogeneity among studies. The author noted that the studies tended to be small and of short duration, and superiority of botulinum toxin over surgery has not been demonstrated. However, due to the fact that it is a minimally invasive option that can be repeated, it is a reasonable option prior to surgery.

Summary: There is evidence on botulinum toxin for treatment of anal fissure from numerous small RCTs. Botulinum toxin has not been found to have better outcomes than surgery, but studies have found that healing rates after botulinum toxin are reasonably high and that it is a less invasive than surgery.

Urologic Applications

Overactive bladder/neurogenic detrusor overactivity.

Several meta-analyses of RCTs have been published on overactive bladder and neurogenic detrusor overactivity. Drake et al (2017) reported on the results of a network meta-analysis of 56 RCTs that compared the efficacy of onabotulinumtoxinA, mirabegron, and anticholinergics in adults with idiopathic overactive bladder. While all treatments were more efficacious than placebo after 12 weeks, patients who received onabotulinumtoxinA (100 U) reported the greatest reductions in urinary incontinence episodes, urgency episodes, and micturition frequency, and the highest odds of achieving decreases of 100% and 50% or greater from baseline in urinary incontinence episodes per day. The exclusion of studies with a high risk of bias had little impact on the conclusions. Freemantle et al (2016) also reported on the results of a network meta-analysis of 19 RCTs comparing any licensed dose of onabotulinumtoxinA, mirabegron, anticholinergic drugs, or placebo. Both onabotulinumtoxinA and mirabegron were more efficacious than placebo at reducing the frequency of urinary incontinence, urgency, urination, and nocturia. OnabotulinumtoxinA was more efficacious than mirabegron (50 mg and 25 mg) in completely resolving daily episodes of urinary incontinence and urgency and in reducing the frequency of urinary incontinence, urgency, and urination.

A 2016 network meta-analysis by Cheng et al assessed a total of 1915 patients with neurogenic detrusor overactivity from 6 RCTs. Using the mean number of urinary incontinence episodes per week as the primary outcome measure,

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reviewers reported that treatment with onabotulinumtoxinA 200 U and 300 U compared with placebo reduced the mean number of urinary incontinence episodes at week 6 by 10.72 (95% CI, -13.4 to -8.04; $p < 0.001$) and -11.42 (95% CI, -13.91 to -8.93; $p < 0.001$), respectively. Treatment with onabotulinumtoxinA was associated greater frequency of urinary tract infections (RR=1.47; 95% CI, 1.29 to 1.67; $p < 0.001$), urinary retention (RR=5.58, 95% CI, 3.53 to 8.83; $p < 0.001$), hematuria (RR=1.70; 95% CI, 1.01 to 2.85; $p = 0.05$), and muscle weakness (RR=2.59; 95% CI, 1.36 to 4.91; $p = 0.004$).

In 2015, Cui et al identified 6 double-blind RCTs comparing botulinum toxin type A with placebo for treating patients with idiopathic overactive bladder. In a pooled analysis of 3 studies, patients treated with botulinum toxin were significantly more likely to be incontinence-free at the end of the study (OR=4.89; 95% CI, 3.11 to 7.70). Moreover, a pooled analysis of 5 studies found significantly greater reduction in the number of incontinence episodes per day in the group treated with botulinum toxin (SMD = -1.68; 95% CI, -2.06 to -1.31). Previously, in 2011, Duthie et al published a Cochrane review of RCTs evaluating botulinum toxin injections for patients with idiopathic or neurogenic overactive bladder. Reviewers identified 19 trials that compared treatment using botulinum toxin with placebo or another intervention. Two studies included botulinum toxin type B; the remainder included botulinum toxin type A. Outcomes varied, which made it difficult to pool trial findings. A pooled analysis of 3 trials found change in urinary frequency episodes at 4 to 6 weeks reported a significantly better outcome with botulinum toxin injection than with placebo (pooled MD = -6.50; 95% CI, -8.92 to -4.07). A pooled analysis of 3 trials on change in incontinence episodes at 4 to 6 weeks also found a significantly greater improvement with botulinum toxin (MD = -1.58; 95% CI, -2.16 to -1.01).

Other systematic reviews have included both controlled and uncontrolled studies. A 2013 systematic review by Soljanik identified 28 studies evaluating onabotulinumtoxinA for the treatment of neurogenic detrusor overactivity/neurogenic overactive bladder; 6 of the studies were RCTs. The authors reported that studies with comparative data found superior outcomes with onabotulinumtoxinA compared to placebo. Data from the RCTs were not pooled. Serious adverse events were not reported. However, adverse events after intra-detrusor botulinum toxin injection include postvoid residual urine (50%), urinary retention (23.7%), and urinary tract infection (16.7%). Also in 2013, Mehta and colleagues identified 14 studies evaluating botulinum toxin A for treating neurogenic detrusor overactivity after spinal cord injury; only 1 was an RCT. The authors examined effect sizes interpreted as small, > 0.2 ; moderate, > 0.5 ; or large, > 0.8 . Studies tended to have large effect sizes for outcomes including bladder capacity and reflex detrusor volume. The mean proportion of patients who experienced episodes of incontinence decreased after treatment with botulinum toxin A from 23% to 1.3% per day. Previously in 2008, Karsenty et al. identified 18 studies evaluating botulinum toxin A to treat patients who were refractory to anticholinergics. Most of the studies reported statistically significant improvement in clinical and urodynamic outcomes, without major adverse events.

Representative large, double-blind RCTs are described below:

Nitti et al (2017) reported the results of open-label RCT in which 557 patients with overactive bladder, 3 or more urgency urinary incontinence episodes in 3 days, and 8 or more micturitions per day inadequately managed with anticholinergics were randomized to onabotulinumtoxinA 100 U or placebo. Coprimary end points were the change from baseline in the number of urinary incontinence episodes per day and the proportion of patients with a positive response on the treatment benefit scale at posttreatment week 12. OnabotulinumtoxinA significantly decreased the daily frequency of urinary incontinence episodes vs placebo (-2.65 vs -0.87, $p < 0.001$) and 22.9% vs 6.5% of patients

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became completely continent. A larger proportion of onabotulinumtoxinA than placebo-treated patients reported a positive response on the Treatment Benefit Scale (60.8% vs 29.2%, $p < 0.001$). Uncomplicated UTI was the most common adverse event.

Amundsen et al (2016) reported the findings of a multicenter open-label RCT that assigned 381 women with refractory urgency urinary incontinence to cystoscopic intradetrusor injection of onabotulinumtoxinA ($n=192$) or sacral neuromodulation ($n=189$).⁹² The primary outcome measure was change in the mean number of daily urgency urinary incontinence episodes from baseline to 6 months as measured with monthly 3-day diaries. Per protocol, analysis of data from 364 women showed that onabotulinumtoxinA group had statistically significant greater reduction in the primary outcome compared with sacral neuromodulation group (-3.9 vs -3.3 episodes per day, $p=0.01$). However, the mean difference of 0.63 (95% CI, 0.13 to 1.14) was of uncertain clinical importance. Additionally, urinary tract infections (35% vs 11%; risk difference, -23%; 95% CI, -33% to -13%; $p < 0.001$, respectively) and need for transient self-catheterization (8% and 2% at 1 and 6 months in the onabotulinumtoxinA group) were higher in the onabotulinumtoxinA group vs sacral neuromodulation group.

In 2013, Nitti et al published data from an industry-supported study that included 557 patients with overactive bladder and urinary incontinence inadequately controlled by anticholinergics. Patients were randomized to an intradetrusor injection of onabotulinumtoxinA 100 U or placebo. At the 12-week follow-up, there was a statistically significantly greater improvement in the daily frequency of urinary incontinence episodes in the group that received botulinum toxin (-2.65) than in the placebo group (0.87; $p < 0.001$). The other primary end point was the proportion of patients with a positive response at week 12 using the Treatment Benefit Scale. A significantly larger proportion of patients in the botulinum toxin group than in the placebo group reported a treatment benefit (60.8% vs 29.2%, $p < 0.001$). A total of 22.9% of patients in the botulinum toxin group and 6.5% of patients in the placebo group became completely continent. In the first 12 weeks after injection, UTIs occurred in 43 (15.5%) of 278 patients in the botulinum toxin group and 16 (5.9%) of 272 patients in the placebo group. Urinary retention was reported by 15 (5.4%) patients in the botulinum toxin group and 1 (0.4%) patient in the placebo group. Between-group p values were not reported for adverse events. A 2014 prespecified subanalysis of data from this RCT and another placebo-controlled trial (Chapple et al, 2013⁹⁴) evaluated the efficacy of onabotulinumtoxinA by number of anticholinergic therapies used. Patients had used a mean of 2.4 anticholinergic therapies before enrolling in the study. At week 12, reduction in the daily number of urinary incontinence episodes was significantly lower in the onabotulinumtoxinA group than in the control group, whether or not 1, 2, 3, or more prior anticholinergics had been used. Mean reduction in daily incontinence episodes for patients with 1 prior anticholinergic was 2.82 in the onabotulinumtoxinA group and 1.52 in the placebo group ($p < 0.001$); with 3 or more prior anticholinergics, it was 2.92 and 0.73, respectively ($p < 0.001$).

A 2012 industry-supported RCT by Ginsberg and colleagues included 416 patients with neurogenic detrusor activity associated with multiple sclerosis or spinal cord injury. Patients were randomized to receive injections with 200 U onabotulinumtoxinA, 300 U onabotulinumtoxinA or placebo. Decrease in the mean number of weekly incontinence episodes at week 6, the primary endpoint, was significantly greater in both active treatment groups (-21 in the 200 U group and -23 in the 300 U group) than in the placebo group (-9, $p < 0.001$). Urinary retention was a common adverse event. Among patients who did not catheterize at baseline, 35% in the 200 U group, 42% in the 300 U group and 10% on placebo initiated catheterization. A total of 329 of 416 patients (79%) completed the 52-week study, however, outcomes such as the number of weekly incontinence episodes were not reported at 52 weeks.

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Summary: Numerous RCTs, as well as observational data, have reported improvements in outcomes following botulinum toxin treatment in patients with neurogenic detrusor overactivity or OAB unresponsive to anticholinergic medication. Despite the risk of adverse events, including urinary retention and UTI, evidence suggests that botulinum toxin improves the net health outcome.

Detrusor sphincter dyssynergia.

In 2002, DeSeze and colleagues studied 13 patients with chronic urinary retention due to detrusor sphincter dyssynergia from spinal cord disease (traumatic injury, multiple sclerosis, congenital malformations), randomized to receive perineal botulinum toxin A or lidocaine injections into the external urethral sphincter. In the botulinum group, there was a significant decrease in the primary outcome of post-void residual volume compared to no change in the control group receiving a lidocaine injection. Improvements were also seen in the satisfaction scores and other urodynamic outcomes.

Systematic reviews had addressed this potential indication for botulinum toxin injection. Most recently, in 2012, Mehta and colleagues conducted a systematic review of literature on botulinum toxin injection as a treatment of detrusor external sphincter dysfunction and incomplete voiding after spinal cord injury. The authors identified 2 RCTs in addition to uncontrolled studies. The RCTs included the deSeze study, discussed above and a second study that included only 5 patients. A 2008 systematic review by Karsenty and colleagues reviewed trials of botulinum toxin A injected into the urethral sphincter to treat different types of lower urinary tract dysfunction, grouped into neurogenic detrusor-sphincter dyssynergia and non-neurogenic obstructive sphincter dysfunction. In the former group, the authors cite 10 small studies (n ranged from 3 to 53; 3 studies included patients in both categories). Most patients were quadriplegic men unable to perform self-catheterization or patients (of both genders) with multiple sclerosis. All except 2 studies were case reports or case series; the 2 controlled studies were the same ones included in the Mehta systematic review. Authors of both systematic reviews noted that, while most of the available studies have reported improvements with botulinum toxin injections, there are few published studies, and studies included small numbers of patients.

Summary: There is insufficient evidence from RCTs on the impact of botulinum toxin on health outcomes for patients with detrusor sphincter dyssynergia.

Benign prostatic hyperplasia

Use of botulinum toxin to treat symptoms of benign prostatic hyperplasia (BPH) is premised in part on a static component related to prostate size and a dynamic component related to the contraction of smooth muscle within the gland. Botulinum therapy addresses this latter component. In 2012, Marchal et al published a systematic review on use of botulinum toxin to treat BPH.⁶⁹ The authors identified 25 studies, including controlled and uncontrolled studies and abstracts in journal supplements. There were 6 RCTs, 3 published as full articles and 3 as abstracts. Two of published RCTs were included in a meta-analysis. The authors reported that pre- and posttreatment mean postvoiding residue did not differ significantly; pooled results were not reported for between-group outcomes. One of the RCTs by Maria et al, reported on 30 patients with BPH randomly assigned to receive intraprostatic botulinum toxin type A or saline injection.⁷⁰ Inclusion criteria were moderate-to-severe symptoms of BPH based on the

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American Urological Association (AUA) score and a mean peak urinary flow rate of no more than 15 mL per second with a void volume of 150 mL or less. After 2 months, the AUA symptom score decreased by 65% among those receiving botulinum toxin compared with no significant change in the control group. Mean peak urinary flow rate was significantly increased in the treatment group.

Summary: Given the prevalence of BPH, larger trials with good methodology that compare the role of botulinum toxin with other medical and surgical therapies for treating BPH are warranted before conclusions can be drawn about the impact of this technology on health outcomes.

Interstitial cystitis

Interstitial cystitis (IC) is a chronic condition characterized by pain, urgency, and frequent urination of small volumes. Several RCTs and a systematic review have been published. The 2010 systematic review by Tirumuru et al identified 3 RCTs and 7 prospective cohort studies evaluating intravesical botulinum toxin type A injections for IC/painful bladder syndrome (PBS).⁷¹ Sample sizes of all studies were relatively small (range, 10-67 patients; total N=260 patients). Treatment protocols varied (eg, dose of botulinum toxin, number of injection sites, location of injection sites). Meta-analyses were not performed due to heterogeneity among studies. All 3 RCTs were conducted outside of the United States. Two studies reported response rates as an outcome measure (both used a 7-point Global Response Assessment [GRA] scale). One study found a significantly higher response rate with botulinum toxin plus hydrodistension than with hydrodistension-only, and the other found a significantly higher response rate with bacillus Calmette-Guérin (BCG) therapy than with botulinum toxin. Some adverse events, in particular dysuria and voiding difficulty, were reported and 19 (7%) of 260 patients self-catheterized at some time after treatment.

Since publication of that systematic review, 3 RCTs evaluating botulinum toxin for treatment of IC and/or bladder pain syndrome were published. One, published in 2015 by Akiyama et al, lacked blinding and reported only 1 month of comparative data. The 2 recent double-blind, placebo-controlled studies are described next.

A 2016 RCT by Kuo et al, included 60 Taiwanese patients (52 women, 8 men) with IC/PBS who had failed at least 6 months of conventional therapy.⁷³ To be eligible, patients had to fail at least 2 types of treatment modalities (ie, oral medications, intravesical treatment with heparin or hyaluronic acid). Individuals with a variety of comorbid conditions were excluded, including those with urinary retention. Participants received intravesical injection of botulinum toxin type A (Botox 100 U) or normal saline (placebo), followed by hydrodistension under general anesthesia. The primary end point was the reduction in pain according to a 10-point visual analog scale (VAS) score 8 weeks after treatment. There was a significantly greater reduction in the mean VAS score in the botulinum toxin group (-2.6, SD=2.8) than in the placebo group (-0.9, SD=2.2; p=0.021). Secondary outcomes, including overall subjective success (assessed by a GRA), Interstitial Cystitis Symptom Index (ICSI), urinary frequency, and nocturia did not differ significantly between groups. The incidence of adverse events was significantly higher in the botulinum toxin group than in the placebo group at 8 weeks (p=0.033). For example, 16 (40%) patients in the botulinum group and 1 (5%) in the placebo group reported dysuria at 8 weeks.

A 2014 RCT by Manning et al included 54 women with IC/BPS refractory to at least 2 recognized treatments.⁷⁴ Patients with voiding difficulty, bladder malignancy, and recurrent UTI were excluded. The primary outcome was the O'Leary-Sant (OLS) Questionnaire score, which assesses on daytime frequency, nocturia, urgency, and bladder

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pain. Patients received hydrodistention under general anesthesia, with either an injection of botulinum toxin type A (Dysport 500 U) or normal saline (placebo). The OLS score at 3 months did not differ significantly between groups. Scores were 20.4 (95% CI, 17.1 to 23.7) in the botulinum toxin group and 25.3 (95% CI, 21.9 to 28.8) in the placebo group (MD=3.7; 95% CI, -0.34 to 7.6; p=0.12). However, in the subgroups of 42 patients without UTIs the OLS score was significantly improved with botulinum toxin than with placebo (MD=6.1; 95% CI, 2.5 to 9.6; p=0.02). Adverse events were not reported.

Wang et al (2016) reported the findings of meta-analysis that included 7 RCTs and 1 retrospective study. Reviewers rated only one of the 7 RCTs as high quality (ie, low risk of bias) while five were rated as moderate, and one was rated as a high risk of bias. Moreover, reviewers reported a statistically significant effect on multiple outcome measures (multiple outcome measurements assess a patient's relevant outcome measures, eg, pelvic pain, frequency of urination, symptoms [eg, Interstitial Cystitis Problem Index scores], impact of symptoms on patient lives [eg, Interstitial Cystitis Symptom Index scores], and certain physiological outcome measures [eg, postvoid residual urine and maximum cystometric capacity]). However, the trials that generated these data suffered from multiple sources of bias, leading reviewers to conclude that "further well-designed, large-scale RCTs are required to confirm the findings of this analysis."

Summary: There is insufficient evidence that botulinum toxin improves the net health outcome in patients with IC. RCTs have had mixed findings on efficacy outcomes and botulinum toxin has been associated with adverse events (eg, dysuria). Moreover, there is insufficient evidence comparing botulinum toxin injection to alternative treatments.

Tremor

A tremor can be defined as alternate or synchronous contractions of antagonistic muscles. Some patients may be disabled by severe or task-specific tremors. Tremors are also a frequent component of dystonias, and successful treatment of dystonias result in reduction in tremors. Botulinum toxin has been investigated in patients with tremors unrelated to dystonias in case reports and case series. Three randomized, placebo-controlled studies have addressed essential hand tremors; the 2001 trial enrolled 133 patients, and the 1996 trial enrolled 25 patients. These RCTs reported inconsistent findings using tremor symptom scales and neither reported functional outcomes. The third trial, published in 2017 by Mittal et al, randomized 30 patients with essential tremor and Parkinson disease tremor to incobotulinumtoxinA in a crossover design. Treatment efficacy was evaluated by the tremor subsets of the Unified Parkinson's Disease Rating Scale, the Patient Global Impression of Change 4, and an evaluation set for 8 weeks after each of the 2 sets of treatments. There were statistically significant improvements in clinical rating scores of rest tremor and tremor severity at 4 and 8 weeks after the incobotulinumtoxinA injection and of action/postural tremor at 8 weeks; however, there was no statistically significant difference in grip strength at 4 weeks between the 2 groups. Other studies have shown that 30% to 70% patients who receive onabotulinumtoxinA for tremor develop moderate-to-severe hand weakness.

Summary: The clinical significance of contradictory findings from 2 RCTs in patients with tremor are unclear. While a third small crossover trial has reported statistically significant reduction in tremors in patients with Parkinson disease, a larger trial with longer term follow-up is required to replicate these findings and provide long-term follow-up to mitigate the risk of developing hand weakness over the course of time.

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Chronic Low Back Pain

Only one randomized controlled study of botulinum toxin A treatment in patients with low back pain has been published. The trial, published in 2001, enrolled 31 consecutive patients with chronic low back pain of at least six months' duration and more predominant pain on one side. Patients were injected with 40 units of Botox (Allergan, Inc.) at five lumbosacral locations for a total of 200 U (treated group) or saline placebo (placebo group). Injections were made on one side of the back only, depending on predominance of pain. At eight weeks, 60% of treated patients and 12.5% of placebo patients showed improvement in VAS pain scores ($p=0.009$). Perceived functional status (Oswestry scale) at eight weeks showed that 66.7% of treated patients and 18.8% of placebo patients were responders ($p=0.011$).

Summary: The population with chronic low back pain is a heterogeneous population, and results in this small group of selected subjects cannot be used to generalize results for the whole population with chronic low back pain. Furthermore, studies should examine the long-term effectiveness of using repeated courses of botulinum toxin to determine the durability of repeated treatments.

Lateral Epicondylitis

In 2013, Krogh et al published a systematic review and meta-analysis on the comparative effectiveness of injection therapies for lateral epicondylitis.⁷⁸ Seventeen trials, 4 of which evaluated botulinum toxin, were identified. In a meta-analysis, botulinum toxin showed marginal benefit (SMD = -0.50; 95% CI, -0.81 to -0.08). All trials were at high risk of bias and the treatment was associated with temporary paresis of finger extension.

Another relevant systematic review, without meta-analysis, was published in 2014 by Sims et al. The systematic review addressed nonsurgical treatment of lateral epicondylitis. The authors identified 58 RCTs. Four addressed treatment with botulinum toxin, and the remainder addressed other treatments (eg, corticosteroid injection, iontophoresis, prolotherapy). All trials were placebo-controlled. Three of the trials did not report significant differences in pain scores or grip strength over 18 weeks. The other 3 RCTs found significant improvements in pain scores, but not in grip strength. All studies had patients in treatment groups who reported transient weakness in finger extension.

Summary: Several systematic reviews have been published, and they identified a small number of RCTs evaluating botulinum toxin for treating epicondylitis. The RCTs were generally considered to be at high risk of bias, had mixed findings, and all reported transient adverse effects for patients treated with botulinum toxin. The RCTs evaluating botulinum toxin were all placebo-controlled and potential alternative treatments are available for this condition that could have been compared with botulinum toxin. The evidence is insufficient to draw conclusions about the effect of botulinum toxin on the net health outcome.

Other Joint Pain

Two case series of patients with chronic joint pain refractory to conservative management studied the effect of botulinum toxin type A injections (1 series specified that Dysport was used) into several joints of patients with arthritis and into the knee joint of patients with chronic knee pain. Both reported significant improvement in joint pain and function compared with baseline, lasting for 3 to 12 months. Although the results of several trials of botulinum toxin injections into joints for chronic pain favored treatment, some did not.

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Summary: Due to the lack of consistent findings from well-designed studies, the evidence is insufficient that botulinum toxin for treatment of other joint pain improves the net health outcome.

Myofascial Pain Syndrome

Myofascial pain syndrome is characterized by painful muscles with increased tone and stiffness associated with myofascial trigger points. Patients are often treated with injections of the trigger points with saline, dilute anesthetics, or dry needling. These trigger-point injections, while considered established therapy, have been controversial, since it is unclear whether any treatment effect is due to the injection, dry needling of the trigger point, or a placebo effect. The optimal study to evaluate the efficacy of botulinum toxin injection for treating myofascial pain syndrome would be double-blind to minimize the placebo effect and would compare injections of botulinum toxin to dry needling and to anesthetic injection.

Several systematic reviews of RCTs have evaluated botulinum toxin injection for myofascial pain syndrome. Most recently, a 2014 Cochrane review by Soares et al identified 4 RCTs (total N=233 patients).⁸² All RCTs were placebo-controlled and double-blind. Three were prospective and 1 used a crossover design. Follow-up in the prospective studies was 12 weeks in 2 studies and 4 weeks in the third. Due to heterogeneity among studies, the investigators did not pool analyses. The primary outcomes were change in pain as assessed by validated instruments. Three of the 4 studies found that botulinum toxin did not significantly reduce pain intensity. A 2014 systematic review had similar findings.

A systematic review that included a meta-analysis was published in 2011 by Langevin et al. A pooled analysis from 4 placebo-controlled trials did not find a statistically significant benefit of botulinum toxin. The SMD was -0.21 (95% CI, -0.50 to 0.70).

A 2014 industry-sponsored RCT, not included in the systematic review, focused on patients with myofascial pain who had responded to an initial injection of botulinum toxin A. A total of 114 patients received an initial injection and 54 responders were subsequently randomized to receive a second injection of botulinum toxin or saline placebo 14 weeks after the initial injection. At week 26 after the initial injection, but not week 20, there was a significantly greater improvement in the mean visual numeric scores for pain in the botulinum toxin group than the placebo group ($p=0.019$). There was no significant difference between groups at week 26, compared to baseline, in quality of life using the SF-36 scale. Thus, this study had mixed outcomes and some limitations. Restricting study participation to a responder group could introduce bias, eg, it may increase the proportion of patients who initially experienced a placebo response and make blinding more difficult if patients are familiar with side effects of the active treatment.

Summary: Several RCTs have evaluated botulinum toxin for treatment of myofascial pain syndrome. Studies were double-blind, but compared botulinum toxin with placebo, rather than with a commonly used alternative treatment. Most of the individual trials, as well as a pooled analysis of study findings, did not find that botulinum toxin improved health outcomes.

Temporomandibular Joint Disorder

A 2015 systematic review by Chen et al evaluated the literature on botulinum toxin for treatment of temporomandibular joint disorders.⁸⁶ Eligibility included RCTs comparing any dose or type of botulinum toxin with

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any alternative intervention or placebo. Five RCTs met the inclusion criteria; 2 were parallel group studies and 2 were crossover studies. Study sizes tended to be small; all but 1 study included 30 or more participants. Three of the 5 studies were judged to be at high risk of bias. All studies administered a single injection of botulinum toxin and followed patients up at least 1 month later. Four studies used a placebo (normal saline) control group and the fifth used botulinum toxin to fascial manipulation. The primary outcome was a validated pain scale. Data were not pooled due to heterogeneity among trials. In a qualitative review of the studies, only 2 of the 5 trials found a significant short-term (1- to 2-month) benefit of botulinum toxin compared with control on pain reduction.

Summary: A systematic review of RCTs found insufficient evidence that botulinum toxin improves the net health outcome in patients with temporomandibular joint disorders. Studies tended to be small, have a high risk of bias, and only 2 of 5 RCTs found that botulinum toxin reduced pain more than a comparator.

Trigeminal Neuralgia

Three RCTs using botulinum toxin to treat trigeminal neuralgia were identified; all were double-blind and placebo-controlled. All studies were conducted in China and appear to have been done by the same research group. No industry funding was reported. Sample sizes in the studies were relatively small, with fewer than 30 in any one. Most recently, in 2014, an RCT by Zhang et al included 84 patients with trigeminal neuralgia for at least 4 months who had failed other treatments (most commonly carbamazepine, gabapentin, or opioids), had a mean pain intensity score of at least 4, and had a mean attack frequency of at least 4 for day.⁸⁷ Medication treatment remained unchanged during the study. Patients were randomized to 1 of 3 groups: a single injection of normal saline (placebo) (n=28), botulinum toxin 25 U/l (n=27), or botulinum toxin 75 U/l (n=29). The primary efficacy outcome was the proportion of responders, defined as at least a 50% reduction in the mean pain score from baseline to 8 weeks. Pain severity was measured on an 11-point VAS (0-10 points). Mean baseline VAS scores were similar among the 3 groups (range, 6.24-7.18). At week 8, the proportion of responders was 32.1% in the placebo group, 70.4% in the 25-U group, and 86.2% in the 75-U group. Response rates were significantly higher in the 2 active treatment groups than in the placebo group (p<0.002). No severe adverse events were reported and no patients discontinued study participation due to adverse events. No severe or long-lasting adverse events were reported.

A 2013 RCT by Shehata et al included 20 women with a diagnosis of intractable idiopathic trigeminal neuralgia, defined as insufficient response to medication treatments for 3 months prior to study participation. Patients were randomized to receive a single injection of botulinum toxin type A or placebo. The primary efficacy outcome was reduction in pain, as measured by a 10-point VAS, and change in frequency of paroxysms. Baseline VAS scores were similar (8.3 in the botulinum toxin group, 8.3 in the placebo group). At 12 weeks postinjection, the VAS score decreased by 6.5 points in the botulinum toxin group and by 0.3 points in the placebo group (p<0.001). Paroxysm frequency was a secondary outcome. The baseline frequency of paroxysm was 39.2 in the botulinum toxin group and 36.7 in the placebo group. After 12 weeks, the mean frequency of paroxysms per day was 4.0 per day and 36.1 per day, respectively (p<0.001).

The third trial, published in 2012 by Wu et al, included 42 patients with trigeminal neuralgia. To be eligible for participation, patients had to have a mean pain intensity of at least 4 and a mean attack frequency of at least 4 per day despite medication therapy. Most patients were taking medication at baseline (eg, opioids, carbamazepine, gabapentin); medications remained unchanged during the study. Patients were randomized to receive botulinum

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toxin type A 75 U or saline (placebo). They were followed for 12 weeks. The primary end points were pain severity and pain attack frequency. Symptoms were recorded by patients each morning, for the previous 24-hour period using a VAS. Both of the primary end points were statistically significantly better in the treatment group than in the control group. The proportion of patients with at least a 50% reduction in the mean pain score from baseline to 12 weeks (a secondary end point) was 15 (68%) of 22 in the botulinum toxin group and 3 (15%) of 20 in the placebo group ($p < 0.01$). No severe or long-lasting adverse events were reported.

Morra et al (2016) published a meta-analysis that included 4 RCTs (total $N=178$ patients). Pooled results showed that patients receiving botulinum toxin type A were 2.87 (95 % CI, 1.76 to 4.69; $p < 0.001$) times more likely to be responder (defined as patients with $>50\%$ reduction in mean pain score from baseline to end point) than the controls, with no significant detected heterogeneity ($p=0.31$; $I^2=4\%$). Further, there was reduction in the paroxysms frequency per day (MD = -29.79; 95 % CI, -38.50 to -21.08; $p < 0.001$).

Summary: Three small RCTs from China and one from Egypt included patients who had failed medication treatment; the RCTs found a statistically significant benefit for botulinum toxin type added to their medication regimen vs placebo on pain intensity and attack frequency. Limitations of the evidence base includes studies from only 1 research group, the small overall number of patients evaluated, relatively short follow-up (8-12 weeks), and lack of reported statistical power analysis. In the absence of power analysis, there is a higher change of spurious statistically significant findings.

Pain Control after Hemorrhoidectomy

Several small RCTs of botulinum toxin intrasphincter injection for controlling pain after hemorrhoidectomy have been published. A 2005 article described a study by Patti and colleagues ($n=30$) who randomly assigned patients to 20 U botulinum toxin or saline injection and reported significantly decreased duration of postoperative pain at rest and during defecation in the treated group. A 2006 study by Patti and colleagues, which also included 30 patients, found significant differences in postoperative maximum resting pressure change from baseline comparing botulinum toxin treatment to topical glyceryl nitrate ($p < 0.001$; resting pressure is increased after surgery and may be responsible for pain). In addition, there was a significant reduction in postoperative pain at rest ($p=0.01$) but not during defecation. There was no difference in healing.

Summary: RCTs evaluating botulinum toxin injection after hemorrhoidectomy have suggested improvement in pain control; however, findings need confirmation in larger trials.

Facial Wound Healing

In 2013, Ziade and colleagues reported on findings of a study including 30 adult patients presenting to the emergency department with facial wounds without tissue loss. Patients were assigned to have an injection of botulinum toxin ($n=11$) or no injection ($n=13$) within 72 hours of the suturing of the wounds. The primary outcomes were scores on the following scales at 1 year: Patient Scar Assessment Scale (PSAS), Observer Scar Assessment Scale (OSAS), Vancouver Scar Scale (VSS) and a 1 to 10 visual analogue scale (VAS). The PSAS was a patient-reported outcome, the OSAS and VSS were assessed clinically by a blinded independent evaluator and the VAS was assessed using photograph analysis by a team of 6 medical specialists. Patients were not blinded to treatment group, and thus the PSAS might be a more subjective outcome, whereas it is likely that the OSAS, VSS and VAS

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were all reasonably objectively assessed. Twenty-four of 30 patients (80%) were available for the 1-year follow-up. There were no significant differences between groups in the PSAS, OSAS and VSS scales. For example, the median OSAS score was 8 in the botulinum toxin group and 9 in the control group. However, a significant between-group difference was found on the 4th outcome, the VAS score, favoring the botulinum toxin group. The median VAS score was 8.25 for the botulinum group and 6.35 for the control group, $p < 0.001$. These results demonstrate a lack of consistency in finding a benefit across outcomes, i.e., there was no significant difference in the patient-reported or clinically assessed outcomes, only on the outcome based on photographic analysis. Previously, in 2006, Gassner and colleagues conducted a small RCT of botulinum toxin-induced immobilization of facial lacerations to improve wound healing compared to placebo ($n=31$). The outcome was determined by blinded assessment of photographs of wound healing at intervals using a VAS. The authors report enhanced wound healing in the treatment arm compared to the placebo arm (8.9 vs. 7.2, $p=0.003$).

Summary: There are few RCTs evaluating botulinum toxin for facial wound healing, and the available trials did not find consistent evidence of benefit.

Pelvic and Genital Pain in Women

One double-blind, randomized, placebo-controlled trial evaluated 60 patients with chronic pelvic pain and pelvic floor spasm. Patients received injections of botulinum toxin type A or placebo. Pain scores were reduced for both groups, but there were no significant differences between groups. The trial likely was underpowered to detect clinically significant differences in outcomes between groups. Other studies include a small, open-label trial from 2006 that tested botulinum toxin type A injections in painful vulvar tissue to alleviate provoked vestibulodynia ($n=19$).⁹⁵ Patients receiving up to 2 doses had significantly reduced pain compared with baseline for 8 (lower dose) to 14 weeks (higher dose). A prospective cohort study tested different doses of botulinum toxin in 12 women with pelvic floor muscle hypertonicity and history of chronic pelvic pain.⁹⁶ Compared with baseline, there were nonsignificant reductions in pelvic pain and nonsignificant improvements in QOL.

Summary: Evidence for the use of botulinum toxin to treat pelvic or genital pain in women is insufficient to form conclusions about the impact on health outcomes. Additional adequately powered RCTs are needed.

Neuropathic Pain after Neck Dissection

Two open-label trials of 16 and 23 patients who had failed conservative therapy investigated various doses of botulinum toxin A injected into the area of complaint. For both studies, which were conducted by the same group, results indicated significant reductions in pain compared to baseline, and trends toward improved quality of life.

Summary: However, lack of a randomized, placebo-controlled study design to control for strong placebo effects in pain therapy render these studies inconclusive.

Tinnitus

In 2005, Stidham and colleagues explored the use of botulinum toxin A injections for tinnitus treatment under the theory that blocking the autonomic pathways could reduce the perception of tinnitus. In this study, 30 patients were randomized in a double-blind study to receive either three subcutaneous injections of botulinum toxin A around the ear followed by placebo injections four months later, or placebo injections first followed by botulinum toxin A. The authors reported that seven patients had reduced tinnitus after the botulinum toxin A injections, which was

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statistically significant when compared to the placebo groups in which only two patients reported reduced tinnitus ($p < 0.005$). The tinnitus handicap inventory scores were also significantly decreased between pretreatment and four months post-botulinum toxin A injections. However, no other significant differences were noted when comparing the two treatments at one and four months after injections. The authors noted larger studies are needed. Also, study limitations including size and lack of intent-to-treat analysis limit interpretation of results.

Summary: Evidence is insufficient to show that botulinum toxin improves health outcomes in patients with tinnitus. Additional well-conducted RCTs with sufficiently large sample sizes are needed.

Pain Associated with Breast Reconstruction after Mastectomy

There are no published RCTs evaluating botulinum toxin for pain associated with breast reconstruction after mastectomy. A 2014 systematic review identified 7 studies on perioperative injection of botulinum toxin A following breast reconstruction surgery. These consisted of 2 prospective controlled cohort studies, 3 retrospective controlled cohort studies, and 2 case series. The studies were mainly small; only one, with a sample size of 293, had more than 50 participants. Three of the studies assessed postoperative pain and all of these found that at least some outcomes were significantly better in the botulinum toxin group than the comparison group.

Summary: The evidence on botulinum toxin for perioperative management of pain associated with breast reconstruction after mastectomy is insufficient due to a lack of RCTs or large observational studies.

Hirschsprung's Disease

The published literature consists of small case series. The largest prospective case series, published by Minkes and Langer in 2000, included 18 children (median age=4 years) with persistent obstructive symptoms after surgery for Hirschsprung's disease. Patients received injections of botulinum toxin (Botox) into 4 quadrants of the sphincter. The total dose of botulinum toxin during the initial series of injections was 15 U to 60 U. Twelve of 18 (67%) patients experienced improvement for more than 1 month and the remaining 6 (33%) either showed no improvement or improved for less than 1 month. Ten children had 1-5 additional injections due to either treatment failure or recurrence of symptoms; retreatment was not based on a standardized protocol.

A 2011 series by Patrus and colleagues retrospectively reviewed outcomes in 22 patients with Hirschsprung's disease treated over 10 years who had received a median of 2 (range 1-23) botulinum toxin injections for postsurgical obstructive symptoms. The formulation of botulinum toxin was not specified. Median follow-up (time from first injection to time of chart review) was 5.0 years (range 0 to 10 years). At the time of chart review, 2 of 22 patients (9%) had persistent symptoms. Eighty percent of children had a "good response" to the initial treatment (not defined) and 69% had additional injections. The authors reported that the number of hospitalizations for obstructive symptoms decreased significantly after botulinum toxin injection (median=0) compared to preinjection (median=1.5), $p=0.003$. The authors did not report whether or not patients received other treatments during the follow-up period in either case series.

Summary: There are no controlled trials of botulinum toxin for the treatment of Hirschsprung disease; however, guidelines for the management of postoperative obstructive symptoms in children with HD have been published by

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the American Pediatric Surgical Association. If increased internal anal sphincter tone is suspected, a trial of botulinum toxin injection may be helpful. In many cases, obstructive symptoms improve or resolve with time.

Gastroparesis

A 2010 systematic review of the literature identified 15 studies on botulinum toxin injection to treat gastroparesis. Two studies were RCTs; the remainder was case series or open-label observational studies. The authors stated that, while the nonrandomized studies generally found improvement in subjective symptoms and gastric emptying after botulinum toxin injections, the RCTs did not confirm the efficacy of botulinum toxin for treating gastroparesis. The authors concluded that there is insufficient evidence to recommend botulinum toxin for gastroparesis. Brief summaries of the 2 RCTs follow.

In 2007, Arts et al published a randomized crossover study with 23 patients. The study included consecutive patients at a single institution who had symptoms suggestive of gastroparesis and established delayed gastric emptying for solids and liquids. Patients received, in random order, injections of Botox or saline during gastrointestinal endoscopies, with a 4-week interval between injections. Symptoms were assessed using the Gastroparesis Cardinal Symptom Index (GCSI), which has a maximum score of 45. There were no statistically significant differences in improvement after botulinum toxin injection or saline injection for either solid or liquid emptying times. For example, liquid half-emptying time was 8.2 minutes (SD=13.7) after Botox injection and 22.5 minutes (SD=7.7) after saline injection ($p>0.05$). In addition, in pooled analyses, mean total GCSI score did not differ significantly after Botox (6.1) compared with saline treatment (3.8; $p>0.05$).

The other RCT, published in 2008, was a single-center, double-blind trial with 32 patients. Patients had delayed gastric emptying and GCSI scores of 27 or higher. They received an injection of Botox ($n=16$) or saline placebo ($n=16$). All patients completed the study. Patients were evaluated with gastric emptying scintigraphy prior to treatment and at a 1-month follow-up. The proportion of patients with at least a 9-point reduction in GCSI score at 1 month (the primary end point) was 6 (37.5%) of 16 in the Botox group and 9 (56.3%) of 16 in the placebo group; the difference between groups was not statistically significant. Improvement in gastric emptying after 1 month (a secondary end point) also did not differ significantly between groups.

Summary: Two small RCTs failed to show a benefit for treatment of gastroparesis. This evidence is insufficient to draw conclusions about the efficacy of botulinum toxin for this indication.

Depression

In 2015, Magid et al published a meta-analysis of 3 placebo-controlled RCTs evaluating botulinum toxin type A for treating unipolar major depressive disorder. Sample sizes were small; a total of 59 patients were treated with botulinum toxin and 75 with placebo. In a pooled analysis of individual patient data, there was a significantly higher response rate in the botulinum toxin group (54.2%) than in the placebo group (10.7%; OR=7.3; 95% CI, 2.4 to 22.5). Other outcomes also favored the botulinum toxin group. No RCTs compared botulinum toxin with antidepressant treatment, which is standard of care.

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Summary: A pooled analysis of 3 small RCTs showed a statistically significant benefit of botulinum toxin compared with placebo. Studies were small and did not compare botulinum toxin with antidepressants. This evidence is insufficient to draw conclusions about the efficacy of botulinum toxin for this indication.

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11/21/2002 Medical Policy Committee review
01/28/2003 Managed Care Advisory Council approval
11/02/2004 Medical Director review

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11/16/2004	Medical Policy Committee review. Format revision. Clinical criteria revision.
11/29/2004	Managed Care Advisory Council approval
06/21/2005	Medical Policy Committee review. Policy revision; palmar hyperhidrosis added to off label uses of botulinum toxin, subject case management.
07/15/2005	Managed Care Advisory Council approval
02/15/2006	Medical Policy Committee review. Refer to medical director for consideration under case management was deleted.
07/12/2006	Medical Director review
07/19/2006	Medical Policy Committee approval. Format changes. FDA information added.
09/06/2006	Medical Director review
09/20/2006	Medical Policy Committee approval. Treatment of incontinence due to detrusor overreactivity caused by spinal cord injury that is inadequately controlled with anticholinergic therapy was added to the list of off-label indications that are eligible for coverage. Rationale and Source was updated to include urologic applications.
01/17/2007	Medical Policy Committee approval. Policy format updated to reflect differentiation of botulinum toxin A and botulinum toxin B indications; coverage eligibility unchanged.
05/02/2007	Medical Director review
05/23/2007	Medical Policy Committee approval. Coverage eligibility unchanged.
05/07/2008	Medical Director review
05/21/2008	Medical Policy Committee approval. Coverage eligibility unchanged.
06/04/2009	Medical Director review
06/17/2009	Medical Policy Committee approval. Added bullet to "When Services Are Eligible for Coverage" section as follows: <ul style="list-style-type: none">• Incontinence due to detrusor overreactivity (urge incontinence), either idiopathic or due to neurogenic causes (e.g., spinal cord injury, multiple sclerosis), that is inadequately controlled with anticholinergic therapy. Deleted bullet from "When Services Are Considered Investigational" section as follows: <ul style="list-style-type: none">• Detrusor overactivity not due to spinal cord injury. Added to the existing bullet in the "When Services Are Considered Investigational" section as follows: <ul style="list-style-type: none">• Detrusor sphincteric dyssynergia (after spinal cord injury)
11/12/2009	Medical Policy Committee approval.
11/18/2009	Medical Policy Implementation Committee approval. Title changed to "Botulinum Toxins" to clarify that there are several of these drugs in the policy. Deleted Botox as a botulinum toxin Type A drug and Myobloc as a botulinum toxin Type B drug. Added Onabotulinum and Abobotulinum listed as botulinum toxin Type A drugs and Rimabotulinum listed as a botulinum toxin Type B drug.
08/05/2010	Medical Policy Committee review
08/18/2010	Medical Policy Implementation Committee approval. Added upper limb spasticity to patient selection criteria for coverage.
11/04/2010	Medical Policy Committee review
11/16/2010	Medical Policy Implementation Committee approval. Added new drug, Xeomin to policy. Format revised. New FDA approved indication for Botox for chronic migraine headaches added.
12/15/2010	Medical Policy Implementation Committee approval. Clarification of non-coverage for wrinkles and cosmetic uses.
10/06/2011	Medical Policy Committee review
10/19/2011	Medical Policy Implementation Committee approval. Added "Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., Spinal Cord Injury, Multiple Sclerosis)

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	in adults who have an inadequate response to or are intolerant of an anticholinergic medication” under the FDA approved indications due to recent FDA approval.
05/03/2012	Medical Policy Committee review
05/16/2012	Medical Policy Implementation Committee approval. Added a Note to the end of the coverage section that botulinum toxins are unique, non-interchangeable and there is no fixed dose ratio among toxins. Coverage eligibility unchanged.
01/23/2013	Coding updated
02/07/2013	Medical Policy Committee review
02/20/2013	Medical Policy Implementation Committee approval. Treatment of incontinence due to detrusor overactivity was moved from off-label to labeled indications.
02/06/2014	Medical Policy Committee review
02/19/2014	Medical Policy Implementation Committee approval. Added Prevention of pain associated with breast reconstruction after mastectomy, Hirschsprung’s disease, Gastroparesis, Facial wound healing, and Internal anal sphincter (IAS) achalasia to the investigational list (to track the BCBS policy). Updated background criteria for the indications that included new literature since last update or for indications deemed investigational. Also updated the references. Expanded the indications to allow for interchangeability of botulinum toxin Type A products.
02/05/2015	Medical Policy Committee review
02/18/2015	Medical Policy Implementation Committee approval. No change to coverage criteria. Updated background info with most up to date information from the BCBS policy.
02/04/2016	Medical Policy Committee review
02/17/2016	Medical Policy Implementation Committee approval. Temporomandibular joint disorders, trigeminal neuralgia, and depression added to investigational statement. Added FDA approved indication of lower limb spasticity and updated background info.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
02/02/2017	Medical Policy Committee review
02/15/2017	Medical Policy Implementation Committee approval. No change to coverage.
02/01/2018	Medical Policy Committee review
02/21/2018	Medical Policy Implementation Committee approval. Updated Rationale/Source, Background. Added re-authorization statement.
08/09/2018	Medical Policy Committee review
08/15/2018	Medical Policy Implementation Committee approval. Added coverage for a new FDA approved Indication (chronic sialorrhea in adults secondary to Parkinson’s Disease/atypical parkinsonism, stroke, or traumatic brain injury) and also coverage for Hirschsprung’s disease with obstructive symptoms cause by internal sphincter achalasia following a pull-through surgery
Next Scheduled Review Date:	08/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Louisiana

Botulinum Toxins

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code																																																																																																				
CPT	46505, 52287, 64611, 64612, 64615, 64616, 64617, 64640, 64642, 64643, 64644, 64645, 64646, 64647, 64650, 64653, 67345, 95873, 95874																																																																																																				
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Louisiana

Botulinum Toxins

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	R49.8	R51	R61	R68.2	S06.2-S06.3
	Z13.850	Z87.820			

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

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- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
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 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 - 3. Reference to federal regulations.

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- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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