Botulinum Toxins

Policy # 00012
Original Effective Date: 01/28/2003
Current Effective Date: 10/09/2023

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.*

Note: prabotulinumtoxinA-xvfs (Jeuveau®)‡ is a botulinum toxin Type A product, however it is only indicated for cosmetic purposes. For the purpose of this policy, it will not be mentioned in the coverage section.

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 ∞

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- 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, anticonvulsant medications, or calcitonin gene related peptide antagonists (CGRP inhibitors)] 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)
        - Laryngeal dystonia (adductor spasmodic dysphonia)
        - Idiopathic (primary or genetic) torsion dystonia
        - Symptomatic (acquired) torsion dystonia
    - 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

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- 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, pediatric neurodevelopmental delay (e.g., Cerebral Palsy), 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. ∞
- Chronic sialorrhea (drooling) associated with Parkinson disease, pediatric neurodevelopmental delay (e.g., Cerebral Palsy), atypical parkinsonism, stroke, or traumatic brain injury ∞
- 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

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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 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) or rimabotulinumtoxinB (Myobloc) in chronic sialorrhea (drooling) associated with any conditions OTHER than Parkinson disease, pediatric neurodevelopmental delay (e.g., Cerebral Palsy), 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

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- 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

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, pediatric neurodevelopmental delay (e.g., Cerebral Palsy), 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.* Five formulations of botulinum toxin have been approved by the U.S. Food and Drug Administration (FDA). Labeled indications of these agents differ; however, all but one are FDA-approved for treating cervical dystonia in adults. Botulinum toxin products are also used for a range of off-label indications.

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There are seven distinct serotypes designated as type A, B, C-1, D, E, F, and G. In the United States, five preparations of botulinum are commercially available; four 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 four formulations of botulinum toxin type A are currently called onabotulinumtoxinA (Botox), abobotulinumtoxinA (Dysport), incobotulinumtoxinA (Xeomin), and prabotulinumtoxinA-xvfs (Jeuveau). Xeomin 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. Jeuveau is the newest product marketed in the U.S. and is only indicated for cosmetic purposes.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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

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. AbobotulinumtoxinA (Dysport) is indicated for the treatment of cervical dystonia and the treatment of spasticity. RimabotulinumtoxinB (Myobloc) is indicated for the treatment of cervical dystonia as well as the treatment of chronic sialorrhea. PrabotulinumtoxinA-xvfs (Jeuveau) is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.

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Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

This evidence review was created in July 1997 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through August 15, 2021. In this section, evidence was only reviewed for clinical indications for which none of the four commercially available FDA approved botulinum toxin products are available in the U.S.

Strabismus

Strabismus is a condition in which the eyes are not in proper alignment.

A Cochrane review by Rowe and Noonan (2012) evaluated the literature on botulinum toxin for strabismus. Reviewers identified 4 RCTs, all of which were published in the 1990s. Three trials compared botulinum toxin injection with surgery, and one compared botulinum toxin injection with a noninvasive treatment control group. Among the trials that used surgery as a comparator, two found no statistically significant differences in outcomes between groups, and one found a higher rate of a satisfactory outcome in the surgery group (defined as <8 prism diopters). The trial comparing botulinum toxin with 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 (1999) conducted a trial that included 55 children with strabismus who remained symptomatic after surgical alignment. Patients were randomized to a second surgery (28 patients) or botulinum toxin injection (N=27). Motor and sensory outcomes did not differ significantly in the 2 groups. For instance, at 3 years, 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). Lee et al (1994) randomized 47 patients with acute unilateral sixth nerve palsy to botulinum toxin treatment or a no treatment control group. The final

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recovery rate was 20 (80%) of 25 in the botulinum toxin group and 19 (86%) of 22 in the control group.

Strabismus Summary
Several RCTs from the 1990s have reported 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 for strabismus 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.

Dashtipour et al (2015) reported on the results of a systematic review that evaluated 5 RCTs (374 patients with blepharospasm, 172 patients with hemifacial spasm) of abobotulinumtoxinA (Dysport). All trials showed statistically significant benefits for the treatment of blepharospasm and hemifacial spasm.

RCTs have evaluated onabotulinumtoxinA (Botox), abobotulinumtoxinA (Dysport), and incobotulinumtoxinA (Xeomin) for the treatment of blepharospasm and found these agents to be effective at improving symptoms. No RCTs evaluating rimabotulinumtoxinB (Myobloc) for treating blepharospasm were identified in literature searches.

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

Dystonia/Spasticity
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.

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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.

A Cochrane review by Castelão et al (2017), which was an update of a Cochrane Review first published in 2005, identified 8 double-blind randomized controlled trials (RCTs) (total N=1010 patients) with moderate overall risk of bias that compared the efficacy and safety of botulinum toxin type A with placebo in cervical dystonia. The primary efficacy outcome was reductions in cervical dystonia-specific impairment. The primary safety outcome was the proportion of participants with any adverse event. All RCTs evaluated the effect of a single botulinum toxin type A treatment session, using doses from 150 to 236 U of onabotulinumtoxinA (Botox), 120 to 240 U of incobotulinumtoxinA (Xeomin), or 250 to 1000 U of abobotulinumtoxinA (Dysport). Treatment resulted in reduction of 8.06 points (95% confidence interval [CI], 6.08 to 10.05; I^2=0%) on the Toronto Western Spasmodic Torticollis Rating Scale at week 4 after injection compared with placebo. While there were no differences in withdrawals due to adverse events between the active and placebo treatment groups, botulinum toxin type A was associated with an increased risk of an adverse event (relative risk [RR], 1.19; 95% CI, 1.03 to 1.36; I^2=16%) with dysphagia (9%) and diffuse weakness/tiredness (10%) the most common treatment-related adverse events.

A systematic review and meta-analysis by Dong et al (2017) 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 (standardized mean difference [SMD], -0.98; 95% CI, -1.28 to -0.68; I^2=66%, p=0.004), week 6 (SMD = -0.85; 95% CI, -1.11 to -0.59; I^2=1.2%; p=0.409),week 8 (SMD = -0.87; 95% CI, -1.15 to -0.6; I^2=0%, p=0.713), week 12 (SMD = -0.67; 95% CI, -0.88 to -0.46;I^2=0%; p=0.896), and week 12 (SMD = -0.73; 95% CI, -1.21 to -0.24; I^2=63.5%; p=0.065). A systematic review and meta-analysis by Baker and Pereira (2016) identified 25 RCTs that evaluated the efficacy of botulinum toxin type A for limb spasticity on reducing activity restriction and

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improving 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 Cochrane review of 4 RCTs (total N=441 participants) by Marques et al (2016) 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 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.

Another Cochrane review of 3 RCTs by Duarte et al (2016) 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 systematic review by Dashtipour et al (2015) identified 16 RCTs and noncomparative controlled studies evaluating abobotulinumtoxinA (Dysport) in adults with upper-limb spasticity due to stroke. Total botulinum toxin dose ranged from 500 to 1500 U. Reviewers did not pool study findings, but did report that most studies found a statistically significant benefit of botulinum toxin for functioning (as measured by the Modified Ashworth Scale).

A systematic review and meta-analysis by Marsh et al (2014) 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.

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In a systematic review, Foley et al (2013) identified 16 RCTs comparing injection of botulinum toxin with 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 (SMD=0.54; 95% CI, 0.35 to 0.71; p<0.001). In another systematic review, Baker et al (2013) 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.

This evidence review section is based on a TEC Assessment (1996, updated 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 AAN 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.

Post Stroke Related Spasticity

Wein et al (2018) reported on the results of a double-blind RCT that evaluated the efficacy and safety of onabotulinumtoxinA (Botox) in adults (N=468) with poststroke lower-limb spasticity. The primary end point was change in Modified Ashworth Scale score from baseline between onabotulinumtoxinA (Botox) and placebo arm at approximately 12-week intervals. Injections were into the ankle plantarflexors (onabotulinumtoxinA [Botox] 300 U into ankle plantarflexors; ≤100 U, optional lower-limb muscles). Of 468 enrolled, 413 (88%) completed the trial. At the end of blinded phase at 4 to 6 weeks, there were small but statistically significant improvements with onabotulinumtoxinA (Botox) during for the primary end point (onabotulinumtoxinA [Botox], -0.8; placebo, -0.6, p=0.01).

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Wissel et al (2016) assigned 273 poststroke adults to a 22- to 34-week treatment with onabotulinumtoxinA (Botox) or placebo and subsequently open-label onabotulinumtoxinA (Botox) up to 52 weeks. End points included change in pain and responder analysis (defined as proportion of patients with baseline pain ≥4 achieving a ≥30% improvement in pain and a ≥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 (Botox) 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 double-blind RCT published by Gracies et al (2015) assigned 243 adults with a stroke or brain trauma in the last 5 months to a single injection of abobotulinumtoxinA (Dysport) 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 (MAS). At both doses, abobotulinumtoxinA (Dysport) resulted in greater tone reduction as evidenced by statistically significant reduction in placebo-corrected MAS scores from baseline to week 4 (abobotulinumtoxinA [Dysport] 500 U group, -0.9; 95% CI -1.2 to -0.6; p<0.001; abobotulinumtoxinA [Dysport] 1000 U group, -1.1; 95% CI, -1.4 to -0.8; p<0.001 vs placebo).

Shaw et al (2011) randomized 333 patients with poststroke upper-limb spasticity to physical therapy plus abobotulinumtoxinA (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 Assessment Scale score significantly favored the abobotulinumtoxinA (Dysport) group (-0.6) over the placebo group (-0.1) at 1 month (p<0.001), but not at 3 and 12 months.

Other RCTs have shown that botulinum toxin injection improves outcomes in patients with poststroke upper-limb spasticity.

Cerebral Palsy

Most trials that established the efficacy of abobotulinumtoxinA (Dysport) in treating focal spasticity in patients with cerebral palsy have been 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 (Dysport) 10 or 15 U/kg per leg, or placebo. The primary outcome measure was change in MAS score from baseline to week 4. Of the 246 patients randomized, 226 completed the

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trial and analysis included 235 (98%) patients. Results showed that both doses of abobotulinumtoxinA (Dysport) resulted in greater improvement in placebo-corrected MAS 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).

Dystonia/Spasticity Summary
Multiple RCTs and systematic reviews with meta-analyses have supported the efficacy of botulinum toxin for treating dystonia and spasticity.

Hyperhidrosis
Hyperhidrosis, or excessive sweating, can lead to impairments in psychologic and social functioning. Various treatments for hyperhidrosis are available, such as topical antiperspirant agents (e.g., aluminum chloride 20% solution), oral medications, botulinum toxin, and surgical procedures.

The Wade et al (2017) systematic review identified 23 studies evaluating botulinum injections for the treatment of primary hyperhidrosis, 13 were RCTs, and 10 were nonrandomized comparative studies. Fourteen studies were considered high risk of bias, 8 studies unclear risk, and 1 study low risk. Twenty-one studies used botulinum type A (usually 50 U, though some studies used up to 250 U) and 2 studies used botulinum type B (2500 U or 5000 U). Comparators differed across studies: placebo (12 studies), no treatment (4 studies), curettage (4 studies), iontophoresis (2 studies), and topical glycopyrrolate (1 studies). Sixteen studies treated axillary hyperhidrosis, 5 palmar hyperhidrosis, and 2 studies reported on treating axillary and/or palmar hyperhidrosis. Meta-analyses were conducted on studies comparing botulinum type A with placebo for the treatment of axillary hyperhidrosis and all estimates favored the botulinum injections: reduction in Hyperhidrosis Disease Severity Scale (HDSS) score of 2 or more points: 3.3 (95% confidence interval [CI], 2.5 to 4.4); reduction in sweating by 50% or more at 2 to 4 weeks (3.3; 95% CI, 1.9 to 5.5); reduction in sweating by 75% or more at 2 to 4 weeks (6.7; 95% CI, 2.8 to 16.0); and reduction in sweating by 50% or more at 16 weeks (2.9; 95% CI, 1.9 to 4.3). The studies comparing botulinum injections with curettage were of very low quality, precluding meaningful conclusions. There is low-quality evidence for botulinum type A and B for treating palmar hyperhidrosis suggesting a positive effect; however, there was a high incidence of adverse events reported with botulinum type B.

Obed et al (2021) conducted a systematic review and meta-analysis assessing botulinum injections for the treatment of focal hyperhidrosis in adults.7, The review incorporated only placebo-controlled RCTs, as opposed to any comparator in the Wade et al (2017) systematic review. Eight (N=937)

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were identified, 6 evaluated axillary hyperhidrosis, 1 evaluated craniofacial hyperhidrosis, and 1 evaluated lower limb hyperhidrosis. Six studies used botulinum type A (most often onabotulinumtoxinA 50 U) and 2 studies used botulinum type B (rimabotulinumtoxinB 2250 U or 2500 U). The quality of the included studies was mixed, with only 5 of the studies at low risk of bias for attrition. Further, only 5 studies included enough information to assess blinding of personnel and patients, and the majority of trials had an unclear risk of selection and reporting bias. Reduction in sweating by 50% or more from baseline to weeks 2 to 6 was more likely with botulinum injections as compared to placebo for axillary hyperhidrosis (risk difference, 0.62; 95% CI, 0.51 to 0.76). Improvements in reducing HDSS score by at least 2 points (risk difference, 0.56; 95% CI, 0.42 to 0.69) and mean change in the Dermatology Life Quality Index (mean difference, -5.55; 95% CI, -7.11 to -3.98) also favored botulinum injections over placebo. The analysis was limited by the availability of predominately short-term (8 weeks) trials.

A retrospective chart review by Mirkovic et al (2018) focused on children receiving botulinum toxin for hyperhidrosis. Children receiving at least 1 botulinum treatment were included (N=323); mean age was 15 years (range, 5-17 years). Sixty percent of the children received more than 1 treatment of botulinum. Of 183 who completed a follow-up Global Assessment of Therapy scale at a subsequent visit, 176 (96%) reported that sweating disappeared completely between 2 to 4 months post treatment. No severe adverse events were reported. Several RCTs have addressed botulinum toxin injections in adults as treatment of axillary and palmar hyperhidrosis. The discussion below is grouped by hyperhidrosis site and toxin type as dictated by trial.

Axillary Hyperhidrosis (Botulinum Toxin vs. Placebo)

One of the larger RCTs was published by Lowe et al (2007). This industry-sponsored, multicenter, double-blind, placebo-controlled trial evaluated the efficacy and safety study of botulinum toxin type A in patients with persistent bilateral primary axillary hyperhidrosis. Enrollment criteria included a resting sweat production of at least 50 mg per axilla in 5 minutes and an HDSS score of 3 or 4. A total of 322 patients were randomized to botulinum toxin type A (onabotulinumtoxinA [Botox]) 50 U or 75 U or placebo. Retreatment after 4 weeks was allowed in patients with at least 50 mg of sweat (per axilla) over 5 minutes and an HDSS score of 3 or 4. Following the first injection, 75% of patients in the botulinum toxin type A groups showed at least a 2-point improvement in HDSS score, compared with 25% of patients in the placebo group. Sweat production decreased by 87% (75 U), 82% (50 U), and 33% (placebo). (Similar results were obtained in patients requiring a second treatment.) The median duration of effect was 197 (75 U), 205 (50 U), and 96 (placebo) days.

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Seventy-eight percent (N=252) of patients completed the 52-week trial: 96 (87%) of 110 in the 75-U group, 83 (80%) of 104 in the 50-U group, and 73 (68%) of 108 in the control group. An intention-to-treat analysis at 52 weeks showed more than 2-point improvement on HDSS score in 54 (49%) patients in the 75-U group, 57 (55%) in the 50-U group, and 6 (6%) in the placebo group. Injection-site pain was reported in approximately 10% of all groups, with a mean pain duration of 2.4 days (10-day maximum).

Axillary Hyperhidrosis (Types of Botulinum Toxin Type A)

Dressler (2010) reported on an RCT that assessed 46 patients with bilateral axillary hyperhidrosis and a previously stable onabotulinumtoxinA (Botox) treatment for at least 2 years. Patients received onabotulinumtoxinA (Botox) 50 U in randomly selected axilla and incobotulinumtoxinA (Xeomin) 50 mouse units in the other axilla. All patients completed the trial. According to patient self-report in structured interviews, there were no between-group differences in therapeutic effect, including onset latency, extent, and duration, and no differences in injection-site pain. Moreover, clinical examination did not identify any differences between the 2 sides in the diffuse sweating pattern.

A small, double-blind RCT, published by Talarico-Filho et al (2007), included 20 patients with primary axillary hyperhidrosis who had sweat production greater than 50 mg/min. Patients received injections of 2 types of botulinum toxin A: onabotulinumtoxinA (Botox) 50 U in 1 axilla and abobotulinumtoxinA (Dysport) 150 U in the other. Outcomes did not differ significantly between groups (e.g., sweat rate was reduced by a mean of 98% in the onabotulinumtoxinA (Botox) group and 99% in the abobotulinumtoxinA (Dysport) group; $p>0.05$).

Axillary Hyperhidrosis Summary

Evidence from RCTs supports the efficacy and safety of botulinum toxin for treating axillary hyperhidrosis. Most studies evaluated type A for axillary hyperhidrosis and a meta-analysis of these studies showed that botulinum toxin type A reduced sweating in the short (2 to 4 weeks) and long (16 weeks) term, and improved HDSS scores by 2 or more points.

Palmar Hyperhidrosis (Botulinum Toxin vs. Placebo)

Lowe et al (2002) conducted an RCT of 19 patients who received injections of botulinum toxin type A in 1 palm and placebo in the other. The mean percentage of sweat reduction in the toxin-treated palms was significant compared with baseline. The sweat reduction in the placebo-injected palms

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did not differ statistically from baseline. Both physician and patient assessments showed significant improvements in the botulinum-injected palms compared with the placebo injected palms.

Palmar Hyperhidrosis (Various Doses of Botulinum Toxin Type A)
Saadia et al (2001) conducted a single-blind (patients) randomized trial in which 24 patients received botulinum toxin type A 50 U or 100 U injected intradermally in 20 sites in each palm. Patients were evaluated every 2 weeks during the first month, then once every month up to month 6. Both groups experienced significant improvements in sweat reduction by month 1 of follow-up, lasting through 6 months. Temporary adverse events included pain and soreness. No significant adverse events were associated with the treatment by the end of 6 months.

Palmar Hyperhidrosis (Types of Botulinum Toxin Type A)
Two double-blind, randomized trials compared onabotulinumtoxinA (Botox) with incobotulinumtoxinA (Xeomin). Campanati et al (2014) included 25 patients with moderate-to-severe primary palmar hyperhidrosis resistant to aluminum chloride, or iontophoresis. Patients received injections of incobotulinumtoxinA (Xeomin) in a randomly selected hand and onabotulinumtoxinA (Botox) in the other hand. Botulinum toxin was given at a fixed dosage per square centimeter of the hand. There were no statistically significant differences in outcomes between groups, including changes in HDSS score (mean values significantly decreased by 2 points from baseline in each group), and the extent of sweating assessed using the Minor test (at both 4 weeks and 12 weeks).

Palmar Hyperhidrosis Summary
For palmar hyperhidrosis, evidence from RCTs supports the efficacy and safety of botulinum toxin type A for treating palmar hyperhidrosis. An additional RCT comparing types of botulinum type A reported similar effectiveness.

Hyperhidrosis Summary
There is evidence that botulinum toxin type A is effective for the treatment of palmar and/or axillary hyperhidrosis.

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 (Botox), mirabegron, and anticholinergics in adults

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with idiopathic OAB. While all treatments were more efficacious than placebo after 12 weeks, patients who received onabotulinumtoxinA (Botox) 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 onabotulinumtoxinA (Botox), mirabegron, anticholinergic drugs, or placebo. Both onabotulinumtoxinA (Botox) and mirabegron were more efficacious than placebo at reducing the frequency of urinary incontinence, urgency, urination, and nocturia. OnabotulinumtoxinA (Botox) 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 network meta-analysis by Cheng et al (2016) assessed 1,915 patients with neurogenic detrusor overactivity from 6 RCTs. Using the mean number of urinary incontinence episodes per week as the primary outcome measure, reviewers reported that treatment with onabotulinumtoxinA (Botox) 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 (Botox) 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; $p=0.004$).

Cui et al (2015) identified 6 double-blind RCTs comparing botulinum toxin type A with placebo for treating patients with idiopathic OAB. 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). Cui et al (2013) also published another systematic review evaluating botulinum toxin type for OAB. Previously, Duthie et al (2011) published a Cochrane review of RCTs evaluating botulinum toxin injections for patients with idiopathic or neurogenic OAB. 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

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findings. A pooled analysis of 3 trials found change in urinary frequency episodes at 4 to 6 weeks a significantly better outcome with botulinum toxin injection than with placebo (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 systematic review by Soljanik (2013) identified 28 studies evaluating onabotulinumtoxinA (Botox) for the treatment of neurogenic detrusor overactivity or neurogenic OAB; 6 studies were RCTs. The reviewer reported that studies with comparative data found superior outcomes with onabotulinumtoxinA (Botox) compared with placebo. Data from the RCTs were not pooled. Serious adverse events were not reported. However, adverse events after intradetrusor botulinum toxin injection included postvoid residual urine (50%), urinary retention (23.7%), and urinary tract infection (UTI; 16.7%). Also, Mehta et al (2013) identified 14 studies evaluating botulinum toxin type A for treating neurogenic detrusor overactivity after spinal cord injury; only one was an RCT. Studies tended to have large effect sizes (>0.8) for outcomes including bladder capacity and reflex detrusor volume. Rates of incontinence episodes decreased after treatment with botulinum toxin type A from 23% to 1.3% per day. Previously, Karsenty et al (2008) identified 18 studies evaluating botulinum toxin type A to treat patients who were refractory to anticholinergics. Most studies reported statistically significant improvements in clinical and urodynamic outcomes, without major adverse events.

Representative large, double-blind RCTs are described below. Herschorn et al (2017) reported on the results of a double-blind RCT that compared the efficacy and safety of onabotulinumtoxinA (Botox) or solifenacin vs placebo in patients with OAB, urinary incontinence, and an inadequate response to or were intolerant of an anticholinergic. The primary end point included change from baseline in the number of urinary incontinence episodes per day and the proportion of patients with a 100% reduction (dry) in the number of incontinence episodes per day. While both onabotulinumtoxinA (Botox) and solifenacin fared better than placebo in terms of change from baseline in incontinence episodes per day (-3.19 or -2.56 vs -1.33; both $p<0.001$), the incontinence reduction was significantly greater for onabotulinumtoxinA (Botox) vs solifenacin ($p=0.022$). At week 12, 33.8% (vs placebo $p<0.001$), 24.5% (vs placebo $p=0.028$), and 11.7% of patients receiving onabotulinumtoxinA (Botox), solifenacin, and placebo, respectively, were dry.

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Nitti et al (2017) reported on the results of open-label RCT in which 557 patients with OAB, 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 (Botox) 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 (Botox) 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 became completely continent. A larger proportion of onabotulinumtoxinA (Botox) 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 on the findings of a multicenter open-label RCT that assigned 381 women with refractory urgency urinary incontinence to cystoscopic intradetrusor injection of onabotulinumtoxinA (Botox) (N=192) or sacral neuromodulation (N=189)., 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 (Botox) 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, UTIs (35% vs 11%, respectively; risk difference, -23%; 95% CI, -33% to -13%; p<0.001) and need for transient self-catheterization (8% and 2% at 1 and 6 months in the onabotulinumtoxinA [Botox] group) were higher in the onabotulinumtoxinA (Botox) group than in the sacral neuromodulation group. Outcomes at 2 years of the open-label extension follow-up reported that no difference between the 2 therapies in reducing urgency urinary incontinence symptoms.

Nitti et al (2013) published data from an industry-supported study that included 557 patients with OAB and urinary incontinence inadequately controlled by anticholinergics. Patients were randomized to an intradetrusor injection of onabotulinumtoxinA (Botox) 100 U or placebo. At the 12-week follow-up, there was a statistically significantly greater reductions 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

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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.

In a prespecified subgroup analysis of data from this RCT and another placebo-controlled trial (Chapple et al [2013]), Sievert et al (2014) evaluated the efficacy of onabotulinumtoxinA (Botox) 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 greater in the onabotulinumtoxinA (Botox) 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 (Botox) 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). Results with a follow-up of 3.5 years (extension phase) reported durable and consistent mean reductions in urinary incontinence episodes ranging from -3.1 to -3.8.

An industry-supported RCT by Ginsberg et al (2012) included 416 patients with neurogenic detrusor activity associated with multiple sclerosis or spinal cord injury. Patients were randomized to injections with onabotulinumtoxinA (Botox) 200 U, onabotulinumtoxinA (Botox) 300 U, or placebo. Decrease in the mean number of weekly incontinence episodes at week 6 (the primary end point) was significantly greater in both active treatment groups (-21 in the 200-U group, -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% were in the 200-U group, 42% were in the 300-U group, and 10% were on placebo-initiated catheterization. A total of 329 (79%) of 416 patients completed the 52-week study; however, outcomes like the number of weekly incontinence episodes were not reported at 52 weeks.

Overactive Bladder and Neurogenic Detrusor Overactivity Summary

Numerous RCTs and observational data studies have reported improvements in outcomes following botulinum toxin treatment in patients with neurogenic detrusor overactivity or OAB unresponsive to

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anticholinergic medication. Despite the risk of adverse events, including urinary retention and UTI, evidence would suggest that botulinum toxin improves the net health outcome.

Headache

Botulinum toxin for treatment of pain from migraine and from chronic tension-type headaches was addressed in a TEC Assessment (2004). The Assessment 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 Headaches

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.

The Agency for Healthcare Research and Quality published a comparative effectiveness review, conducted by Shamliyan et al (2013), on preventive pharmacologic treatments for migraine in adults. The investigators identified 15 double-blind RCTs evaluating botulinum toxin for migraine prevention: 13 used onabotulinumtoxinA (Botox) and two used abobotulinumtoxinA (Dysport). In a meta-analysis of 3 RCTs, onabotulinumtoxinA (Botox) was more effective than placebo in reducing the number of chronic migraine episodes per month by at least 50% (RR=1.5; 95% CI, 1.2 to 1.8). In another pooled analysis, onabotulinumtoxinA (Botox) was associated with a significantly higher rate of treatment discontinuation due to adverse events than placebo (RR=3.2; 95% CI, 1.4 to 7.10). Five RCTs compared the efficacy of onabotulinumtoxinA (Botox) 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.

Jackson et al (2012) 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. Reviewers 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. Reviewers

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categorized eligibility criteria as addressing episodic (<15 headaches per month) or chronic headache (≥15 days per month). Ten 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 of 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, Shuhendler et al (2009) conducted a meta-analysis of trials on botulinum toxin for treating episodic migraines. Reviewers 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 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 with 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 occur for more than 3 months or exclude patients who overused pain medication, two of the ICHD-2 criteria for chronic migraine. Eligible patients were randomized to 2 cycles of onabotulinumtoxin A (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

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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 lasting 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 lasting 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. The trialists 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 QOL measures were also used 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 both trials are described below.

PREEMPT 1 randomized 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 onabotulinumtoxinA (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 onabotulinumtoxinA (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 onabotulinumtoxinA (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 onabotulinumtoxinA (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 onabotulinumtoxinA (Botox) group than in the placebo group. The decrease in frequency of headache days was 7.8 in the onabotulinumtoxinA (Botox) group and 6.4 in 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 onabotulinumtoxinA (Botox) group vs the placebo group. The proportion of patients with severe impact of headaches (i.e., HIT-6 score, ≥60) in the onabotulinumtoxinA (Botox) group decreased from 94% at baseline

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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 onabotulinumtoxinA (Botox) group and 156 (47%) patients in the placebo group. Eighteen (5%) patients in the onabotulinumtoxinA (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 onabotulinumtoxinA (Botox).

PREEMPT 2 randomized 705 patients. Mean number of migraine days during baseline period was 19.2 in the onabotulinumtoxinA (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 onabotulinumtoxinA (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 onabotulinumtoxinA (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 onabotulinumtoxinA (Botox) treatment. The number of headache days decreased by a mean of 9.0 in the onabotulinumtoxinA (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 onabotulinumtoxinA (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 onabotulinumtoxinA (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, QOL measures significantly improved in the onabotulinumtoxinA (Botox) group. The proportion of patients reporting that their headaches had a severe impact (score of at least 60 on the HIT-6) decreased in the onabotulinumtoxinA (Botox) group 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 trialists 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 onabotulinumtoxinA (Botox) group and 202 (56%) patients in the placebo group. Fifteen (4%)

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patients in the onabotulinumtoxinA (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 onabotulinumtoxinA (Botox).

Also published was a pooled analysis of findings from the PREEMPT 1 and 2 trials; this analysis by Dodick et al (2010) was also industry-sponsored. There were 688 patients in the onabotulinumtoxinA (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 onabotulinumtoxinA (Botox) group than in the placebo group. For example, the pooled change in mean frequency of headache days was 8.4 in the onabotulinumtoxinA (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 onabotulinumtoxinA (Botox) group and 4.9 in the placebo group, a relative difference of 0.3 episodes (95% CI, 0.17 to 1.17; $p=0.009$). Between-group differences, though statistically significant, were relatively small and might not be clinically meaningful. In the pooled analysis, the trialists 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 onabotulinumtoxinA (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 published report 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 domains. Pooled results of PREEMPT studies at 56 week also reported that repeated treatment (≤5 cycles) of onabotulinumtoxinA (Botox) was effective, safe, and well-tolerated in adults with chronic migraine.

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 trialists did not discuss this omission. In addition,

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the individual studies did not include threshold response to treatment (e.g., 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 might 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 that assessed use of botulinum toxin for treating chronic migraine was published by Cady et al (2011). The trial included patients who met ICHD-2 criteria for chronic migraine. Patients were randomized to treatment with onabotulinumtoxinA (Botox) (N=29) or topiramate (N=30). At the 12-week follow-up, the end of the double-blind phase of the trial, 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 onabotulinumtoxinA (Botox) group and 17 (71%) of 24 patients in the topiramate group; 9 patients (15%) were not available for this analysis.

Migraine Headaches Summary

For chronic migraine, a meta-analysis of RCTs found that onabotulinumtoxinA (Botox) 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 events than placebo.

Non-Migraine Headaches

Tension Headache

Tension-type headache is the most common type of headache. Depending on the frequency, there are infrequent episodic (less than 1 day of headache per month), frequent episodic (1 to 14 days of headache per month) and chronic (15 days or more per month). It is postulated that botulinum toxin A affects the neuronal signaling pathways activated during a headache and also has a blocking action on the parasympathetic nervous system and might inhibit the release of other neurotransmitters or affect the transmission of afferent neuronal impulses. The acute or abortive (symptomatic) therapy

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of tension-type headache ranges from nonpharmacologic therapies to simple and combination analgesic medications. Chronic tension-type headache is often associated with comorbid stress, anxiety, and depression. In this setting, simple analgesics are usually of little or no benefit. When acute treatment of tension-type headache is ineffective, other possible causes should be considered.

The meta-analysis by Jackson et al (2012) identified 8 RCTs evaluating onabotulinumtoxinA (Botox) (6 trials) and abobotulinumtoxinA (Dysport) (2 trials) for treating chronic tension-type headaches; all were placebo-controlled. A pooled analysis of these 8 studies did not find a statistically significant difference in change in the monthly number of headache days in the botulinum toxin group vs the placebo group (difference=-1.43; 95% CI, -3.13 to 0.27; p-value=0.02). Silberstein et al (2006) randomized 300 patients to onabotulinumtoxinA (Botox) (5 different doses) or placebo for the prophylaxis of chronic tension-type headache. The trial failed to demonstrate statistically significant difference between the onabotulinumtoxinA (Botox) groups and the placebo group in the number of headache free days per month.

Cervicogenic Headache

Cervicogenic headache is head pain caused by a disorder of the cervical spine and its component bone, disc and/or soft tissue elements. There is ongoing debate regarding the existence of cervicogenic headache as a distinct clinical disorder, as well as its underlying pathophysiology and source of pain. Botulinum toxin A has been evaluated as a potential treatment given its efficacy in migraine. There is no proven effective treatment for cervicogenic headache. However, a number of different treatment modalities are available. Physical therapy is the preferred initial treatment because it is noninvasive. The available evidence suggests that pharmacologic therapy and botulinum toxin injections are not beneficial.

Multiple RCT's with smaller sample size (<50) have evaluated the efficacy of onabotulinumtoxinA (Botox) in patients with cervicogenic headache but either reported a lack of treatment benefit or were methodological flawed (pain scores imbalanced at baseline) to derive meaningful conclusions.

Non-Migraine Headache Summary

For non-migraine headache types, the evidence is inconclusive to confirm efficacy.

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Esophageal Achalasia

Esophageal achalasia results from progressive degeneration of ganglion cells in the myenteric plexus in the esophageal wall, leading to failure of relaxation of the lower esophageal sphincter, accompanied by a loss of peristalsis in the distal esophagus. Treatment is aimed at decreasing the resting pressure in the lower esophageal sphincter to a level at which the sphincter no longer impedes the passage of ingested material and this can be achieved by two ways: 1) mechanical disruption of the muscle fibers of the lower esophageal sphincter pneumatic dilation (PD), surgical myotomy or peroral endoscopic myotomy and 2) Pharmacological reduction in lower esophageal sphincter pressure (e.g., injection of botulinum toxin or use of oral nitrates).

A Cochrane review by Leyden et al (2014) identified 7 RCTs (total N=178 participants) that compared onabotulinumtoxinA (Botox) with endoscopic PD. Outcomes reported was symptom remission rate at 1, 6 and 12 months. The meta-analysis of RCTs showed no difference in relative risk (RR) of symptom remission at one month between PD vs onabotulinumtoxinA (Botox). (RR=1.11, 95% confidence interval [CI]:0.97 to 1.27). However, at 6 and 12 months, PD resulted in higher symptom remission rates and the difference was statistically significant (RR=1.57, p<0.005; RR=1.88, p=<0.005). No serious adverse events were reported after onabotulinumtoxinA (Botox) injection; however, there were three cases of perforation after PD. Authors concluded that PD resulted in superior long-term efficacy compared with onabotulinumtoxinA (Botox) (at 6 and 12 months). While the overall methodological quality of the individual RCTs was reported to be good, the risk of bias was high. In particular, only one RCT was double blind, five RCTs were potentially at a risk of selection, performance or detection bias due to inappropriate allocation of concealment, blinding of participants and personnel, and outcome assessment.

Wang et al (2009) conducted a meta-analysis of RCTs that compared the efficacy of different treatments for primary achalasia. Five RCTs compared botulinum toxin A injection with PD in patients with untreated achalasia, and also examined both subjective and objective parameters of esophageal improvement in all patients over 12 months. Authors reported that symptom remission rate was significantly higher in patients treated with PD vs botulinum toxin A injection (65.8% vs 36% respectively. Proportion of patients who relapsed within a year was 16.7% with PD vs 50% with botulinum toxin injection. Moreover, relapse time of botulinum toxin injection was shorter than that of PD after first therapy. Two RCTs compared efficacy of laparoscopic myotomy with botulinum toxin A injection in patients with untreated achalasia. Authors reported that the symptom remission rate of botulinum toxin injection rapidly decreased and nearly 50% of patients were

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symptomatic again after 1 year of treatment. Laparoscopic myotomy had superior efficacy to botulinum toxin injection (laparoscopic myotomy 83.3% vs botulinum toxin injection 64.9%, RR 1.28; 95% CI 1.02–1.59; P=0.03). Patients treated with onabotulinumtoxinA (Botox) had more frequent relapse and shorter time to relapse than those treated with laparoscopic myotomy. Some limitations of this meta-analysis include small number of cohorts in each trial, poor randomization techniques, and inadequate follow-up.

While the evidence is suggestive that PD and surgical myotomy are definitive therapies for esophageal achalasia and associated with superior long-term outcomes compared with botulinum toxin A, in patients who are not good candidates for PD and/or surgical myotomy, botulinum toxin A may be a reasonable option. Further, botulinum toxin injection has the advantage of being less invasive as compared with surgery, can be easily performed during routine endoscopy. Initial success rates with botulinum toxin are comparable to PD and surgical myotomy. However, patients treated with botulinum toxin have more frequent relapses and a shorter time to relapse. Greater than 50% of patients with achalasia treated with botulinum toxin A require retreatment within 6 to 12 months. Repeated botulinum toxin injections may also make a subsequent Heller myotomy more challenging.

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

Esophageal Achalasia Summary

For the treatment of esophageal achalasia, two meta-analysis that included RCTs compared endoscopic PD or laparoscopic myotomy with botulinum toxin. Results showed that PD as well as laparoscopic myotomy afforded higher and statistically significant symptom remission rates. OnabotulinumtoxinA (Botox) was not associated with any serious adverse events while PD resulted in perforation in few cases. While the evidence is suggestive that PD and surgical myotomy are definitive therapies for esophageal achalasia and associated with superior long-term outcomes compared with botulinum toxin A, in patients who are not good candidates for PD and/or surgical myotomy, botulinum toxin A may be a reasonable option. Further, botulinum toxin injection has the advantage of being less invasive as compared with surgery, can be easily performed during routine endoscopy. Initial success rates with botulinum toxin are comparable to PD and surgical myotomy.

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Sialorrhea (Drooling) Associated with Parkinson Disease

Several RCTs have evaluated botulinum toxin injections in patients with Parkinson disease. For example, Lagalla et al (2006) randomized 32 patients with Parkinson disease to placebo or botulinum toxin type A; evaluation at 1 month post-injection resulted in significant improvements compared with placebo in drooling frequency, saliva output, and familial and social embarrassment. Dysphagia scores were not significantly improved. Moreover, Ondo et al (2004) randomized 16 patients with Parkinson disease to botulinum toxin type B or placebo. The botulinum toxin group had significantly better outcomes than the placebo group at 1 month on 4 drooling outcomes. Groups did not differ on salivary gland imaging or on a dysphagia scale. Mancini et al (2003) assigned 20 patients with Parkinson disease to injections of either a saline placebo or botulinum toxin type A. The treatment group had significantly better outcomes than the placebo group on a drooling scale at 1 week; the effect disappeared by 3 months.

Sialorrhea Section Summary

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

Sialorrhea NOT Associated with Parkinson Disease

Several systematic reviews have evaluated botulinum toxin for treating sialorrhea in people with conditions other than Parkinson disease. Squires et al (2014) reviewed the research on botulinum toxin injections for drooling in patients with amyotrophic lateral sclerosis/motor neuron disease. Reviewers included RCTs and controlled and uncontrolled observational studies. They identified 12 studies, of which 8 had no control groups. There were 2 small RCTs, each with fewer than 20 patients. Sample sizes in the non-RCTs ranged from 5 to 26 patients. Due to heterogeneity, study findings were not pooled. Only one of the 2 RCTs reported drooling outcomes; it found a significantly greater reduction in saliva volume with botulinum toxin than with placebo at 2 weeks.

Rodwell et al (2012) published a systematic review evaluating botulinum toxin injections in the salivary gland to treat sialorrhea in children with cerebral palsy and neurodevelopment disability. Reviewers identified 5 RCTs; trial sample sizes ranged from 6 to 48 participants. One of the RCTs (N=6) was terminated due to adverse events. In a pooled analysis of data 4 weeks post intervention in 3 RCTs, the mean score on the Drooling Frequency and Severity Scale was significantly lower in children who received botulinum toxin injections than a control intervention (MD = -2.71 points; 95% CI, -4.82 to -0.60; $p<0.001$). The clinical significance of this difference in Drooling Frequency

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and Severity Scale scores is unclear. 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 (33%) of the 6 participants in an RCT terminated early and in 2 (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 (5%) 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.

Gonzalez et al (2017) reported the results of an RCT in which 40 adults with cerebral palsy were randomized to onabotulinumtoxinA (Botox) or observation. The trial had greater than 80% power to detect a 39% difference in the proportion of patients who achieved at least a 50% reduction in drooling quotient. The primary efficacy outcome was drooling quotient. This quotient, measured as a proportion, is a semi-quantitative method that assesses the presence of newly formed saliva on the lips every 15 seconds with 40 observations in 10 minutes, expressed as a percentage based on the ratio between the number of observed drooling episodes and the total number of observations. The proportion of patients who achieved at least a 50% reduction in drooling quotient in the treated group vs control after 8 weeks and 80 weeks was 45% vs 0.0% (p=0.001) and 20% vs 0% (p=0.106). While the treatment effect was large, the trial did not use a placebo group and was unblinded.

A large RCT on botulinum toxin for treating sialorrhea in children with cerebral palsy was published by Reid et al (2008). Forty-eight children with cerebral palsy (n=31) and other neurologic disorders (n=17) were randomized to a single injection of botulinum toxin type A 25 U compared with no treatment. Drooling was assessed by using the Drooling Impact Scale. Scores differed significantly between groups at 1 month, and a beneficial effect of botulinum toxin injection remained at 6 months.

A retrospective review by Chan et al (2013) focused on the long-term safety of botulinum toxin type A injection for treating sialorrhea in children. Reviewers included 69 children; 47 (68%) had cerebral palsy. Children received their first injection of botulinum toxin type A at a mean age of 9.9 years; 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 (28%) of 69 children and in 23 (19%) of 120 injections. Fifteen of 23 complications were minor, including 6 cases of dysphagia. There were 8 major complications: 3 cases of aspiration pneumonia, 2 cases of severe dysphagia, and 3 cases of

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loss of motor control of the head. Complications were associated with 5 hospitalizations and 2 cases of nasogastric tube placement.

Sialorrhea NOT Associated with Parkinson Disease Summary
There is evidence of improvement as measured on drooling scales following botulinum toxin injections in children with cerebral palsy. The American Academy for Cerebral Palsy and Developmental Medicine includes botulinum toxin use in their sialorrhea treatment pathway. The evidence on botulinum toxin for treating sialorrhea in patients with amyotrophic lateral sclerosis/motor neuron disease is inconclusive due to the paucity of controlled studies, small sample sizes of available studies, and limited reporting of drooling outcomes.

Anal Fissure
An anal fissure is a tear or ulceration in the lining of the anal canal below the mucocutaneous junction. Chronic anal fissure is typically associated with anal spasm or high anal pressure. The initial treatment is medical management (combination of supportive measures such as high fiber diet, sitz bath, topical analgesic and one of the topical vasodilators such as nifedipine or nitroglycerin for one month). Patients who fail medical therapy are candidates for surgical therapy that includes lateral internal sphincterotomy or botulinum toxin injection. Patients who are at a high-risk for fecal incontinence such as women who have had multiple vaginal deliveries and older patients with may have a weak anal sphincter complex are advised to undergo surgical procedures that do not require division of the anal sphincter muscle (e.g., botulinum toxin injection, fissurectomy, or anal advancement flap). Patients who are not at risk for developing fecal incontinence may undergo lateral internal sphincterotomy, which is considered the most effective treatment for anal fissure.

Chen et al (2014) compared outcomes of onabotulinumtoxinA (Botox) injection with lateral internal sphincterotomy based on 7 RCTs. Treatment with botulinum toxin injection was associated with lower healing rate and a higher recurrence rate compared with lateral internal sphincterotomy. Sphincterotomy also resulted in higher complication rates but the difference was not statistically significant (p-value=0.35). The meta-analysis suggests that internal sphincterotomy is more effective to treat anal fissure but onabotulinumtoxinA (Botox) injection was associated with lower rates of incontinence. Authors reported multiple limitations in the evidence pooled for the meta-analysis including various dose of onabotulinumtoxinA (Botox) used in different trials, inconsistent definition of chronic anal fissure used in the RCTs and none of the included RCTs were blinded. In addition, results of included studies were not consistent. The total complication rate varied from 0

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to 64 % among the trials, while the incontinence rate varied from 0 to 48%. Nelson et al (2012) published a Cochrane review that compared multiple treatment options for chronic anal fissure. Reported results for comparison of botulinum toxin injection with sphincterotomy are consistent with those reported by Chen et al (2014). Botulinum toxin A injection is therefore preferably used for patients who are at a high-risk of developing fecal incontinence (e.g., multiparous women or older patients).

Anal Fissure Summary
Two meta-analysis suggests that sphicterotomy is a more effective treatment option for chronic anal fissure compared with botulinum toxin A and results in significantly higher healing rate as well lower recurrence rate. However, these meta-analysis report higher incontinence rate with surgical procedures. Since botulinum toxin A injections are less invasive and do not require the internal sphincter muscle to be divided and thereby reduce the risk of fecal incontinence, they are preferred for patients who are not good surgical candidates or who want to minimize the likelihood of incontinence.

Hirschsprung Disease
Hirschsprung disease is a rare genetic birth defect that results in motor disorder of the gut due to failure of neural crest cells (precursors of enteric ganglion cells) to migrate completely during intestinal development during fetal life. The resulting aganglionic segment of the colon fails to relax, causing a functional obstruction.

A retrospective cohort study by Svetanoff et al (2021) included 40 patients admitted for Hirschsprung-associated enterocolitis (HAEC) from January 2010 to December 2019.9, The aim of the study was to determine if botulinum toxin injection during HAEC episodes decreased the number of recurrent HAEC episodes and/or increased the interval between readmissions. In the 40 patients analyzed, a total of 120 episodes of HAEC occurred. Patients who received botulinum toxin during their inpatient HAEC episode had a longer median time between readmissions (p=.04) and trended toward an association with fewer readmissions prior to a follow-up clinic visit (p=.08). This study provides additional evidence that the use of botulinum injections for Hirschsprung disease among patients hospitalized for HAEC is associated with an increased time between recurrent HAEC episodes and trend toward decreasing recurrent enterocolitis incidence.

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A retrospective cohort study of 41 patients consecutively treated for Hirschsprung disease in 2 academic hospitals in Amsterdam with a follow-up duration of ≥1 year after corrective surgery were analyzed.10, All patients had obstructive defecation problems non-responsive to high-dose laxatives or rectal irrigation, 2 patients also had an episode of HAEC. Twenty-five (61%) of 41 patients had clinical improvement after a first injection. In 29 (71%) of the 41 patients, spontaneous defecation or treatment with laxatives only was achieved.

A retrospective case series by Han-Geurts et al (2014), included 33 children with surgically treated Hirschsprung disease treated with intrasphincteric botulinum toxin A injections for obstructive symptoms was analyzed with a retrospective chart review between 2002 and 2013 in the Netherlands. The mean age at time of botulinum toxin A treatment was 3.6 years and median follow-up was 7.3 years (range 1 to 24). A median of two (range 1–5) injections were given. Initial short-term improvement was achieved in 76%, with a median duration of 4.1 months (range 1.7 to 58.8). Proportion of children hospitalized for enterocolitis decreased after treatment from 19 to 7. More than half (51%) of patients reported good or excellent long-term outcomes after a median follow-up of 126 months. Two children experienced complications: transient pelvic muscle paresis with impairment of walking. In both children symptoms resolved within four months without treatment.

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

A retrospective case series by Patrus et al (2011) reviewed outcomes in 22 patients with Hirschsprung disease treated over 10 years; subject had received a median of 2 (range, 1-23) onabotulinumtoxinA (Botox) injections for postsurgical obstructive symptoms. Median follow-up (time from first injection to time of chart review) was five years (range, 0-10 years). At chart review, 2 (9%) of 22 patients had persistent symptoms. Eighteen (80%) children had a “good response” to the initial treatment (not defined), and 15 (68%) had additional injections. The authors reported that the number of hospitalizations for obstructive symptoms decreased significantly after

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onabotulinumtoxinA (Botox) injection (median, 0) compared with pre-injection (median, 1.5; p=0.003). The authors did not report whether patients received other treatments during the follow-up period in either case series.

Hirschsprung Disease Summary
Hirschsprung disease is a rare disease where the mainstay of treatment is surgery. However, patients may develop obstructive symptoms after surgery. The published literature on use of onabotulinumtoxinA (Botox) to treat Hirschsprung disease consists of case series with a total of 73 patients with median follow-up of more than 7 years in 2 out of 3 published case series. All case series report consistent short-term responses in more than 75% of patients in 2 of the 3, case series. Long-term follow-up is suggestive of durability of response.

Internal Anal Sphincter Achalasia
Internal anal sphincter achalasia is a clinical condition with presentation similar to Hirschsprung's disease, but with the presence of ganglion cells on rectal suction biopsy. The diagnosis is made by anorectal manometry, which demonstrates the absence of the rectosphincteric reflex on rectal balloon inflation. The recommended treatment of choice is posterior internal anal sphincter myectomy.

Friedmacher and Puri (2012) reported results of a meta-analysis that included 395 patients from 2 prospective and 14 retrospective case series that compared internal anal sphincter myectomy (n=229) with botulinum A injection (n=166). Regular bowel movements (odds ratio [OR]=0.53; 95% CI 0.29 to 0.99, p=0.04), short-improvements (OR=0.56; 95% CI 0.32 to 0.97, p=0.04) and long-term improvement (OR=0.25; 95% CI 0.15 to 0.41, p<0.0001) favored myectomy compared with botulinum toxin A injection. Further, rate of transient fecal incontinence (OR=0.07, 95% CI 0.01 to 0.54; p< 0.01), rate of non-response (OR 0.52, [95 % CI 0.27-0.99]; p=0.04) and subsequent surgical treatment (OR 0.18, [95% CI 0.07-0.44]; p<0.0001) was significantly higher with botulinum A injection compared with myectomy. There was no significant difference in continued use of laxatives or rectal enemas, overall complication rates, constipation and soiling between the two procedures. Authors concluded that myectomy was more effective treatment option compared with intrasphincteric botulinum toxin A injection.

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Internal Anal Sphincter Achalasia Summary
There is a lack of high-quality RCTs evaluating botulinum toxin injection as a treatment of IAS. A meta-analysis of observational data and a systematic review suggested that posterior IAS myectomy results in greater improvements in health outcomes than botulinum toxin injections.

Anismus
Anismus is the failure of the normal relaxation of pelvic floor muscles during attempted defecation. Symptoms include tenesmus (the sensation of incomplete emptying of the rectum after defecation has occurred) and constipation. Retention of stool may result in fecal loading (retention of a mass of stool of any consistency) or fecal impaction (retention of a mass of hard stool). This mass may stretch the walls of the rectum and colon, causing megarectum and/or megacolon. Anismus is usually treated with dietary adjustments, such as dietary fiber supplementation. Biofeedback therapy, during which a sensor probe is inserted into the person's anal canal in order to record the pressures exerted by the pelvic floor muscles and pressure readings are visually relayed to the patient via a monitor who has also been used.

Emile et al (2016) reported on the results of a systematic review that assessed 7 studies comprising 189 patients with a follow-up period greater than 6 months in each study. Of the seven studies, two were RCTs and the others 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 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%, respectively. While these results would suggest temporary improvement, methodologic limitations, including small sample size and lack of blinded assessment, limit the interpretation of these RCTs.

Anismus Summary
Studies with a larger sample size and blinded assessments need to be conducted before any clear outcome can be determined.

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Detrusor Sphincter Dyssynergia

Systematic reviews have addressed treating detrusor sphincter dyssynergia with botulinum toxin injection. Mehta et al (2012) conducted a meta-analysis on botulinum toxin injection as a treatment of detrusor external sphincter dysfunction and incomplete voiding after spinal cord injury. Reviewers identified 2 RCTs and multiple uncontrolled studies. The RCTs included the de Seze study (discussed below) and a second study of 5 patients.

A systematic review by Karsenty et al (2006) reviewed trials of botulinum toxin type 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, reviewers cited 10 small studies (N range, 3-53 patients; 3 studies included patients in both categories). Most patients were quadriplegic men unable to self-catheterize or patients (of both sexes) with multiple sclerosis. All studies except two were case reports or case series; both exceptions were controlled studies and included in the Mehta meta-analysis. The authors of both reviews noted that, while most of the available studies have reported improvements with botulinum toxin injections, there are few published studies, and those published have small sample sizes.

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

Detrusor Sphincter Dyssynergia Summary

There is a lack of adequately powered, scientifically rigorous RCTs to establish the efficacy of botulinum toxin in patients with detrusor sphincter dyssynergia.

Benign Prostatic Hyperplasia

Benign prostatic hyperplasia is an enlargement of prostate gland in men. The enlargement of prostate presses causes narrowing of the urethra and losing the inability to empty the bladder completely. The symptoms include urinary frequency, urinary urgency, nocturia, urinary retention, and urinary incontinence. Transperineal or transurethral (via cystoscope) injection of botulinum toxin A into the

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prostate has been evaluated for reduction in symptoms associated with benign prostatic hyperplasia. Medications commonly used to treat lower urinary tract symptoms associated with benign prostatic hyperplasia include alpha-1-adrenergic antagonists, 5-alpha-reductase inhibitors, anticholinergic agents and phosphodiesterase-5 inhibitors.

Marchal et al (2012) reported the results of a systematic review on use of onabotulinumtoxinA (Botox) and abobotulinumtoxinA (Dysport) to treat benign prostatic hyperplasia. Two clinical trials with sufficient quality were selected for meta-analysis reported no difference in pre- and post-treatment of maximum flow, prostate volume, International Prostate Symptom Score and prostate-specific antigen post-voiding residue.

Benign Prostatic Hyperplasia 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 is a chronic condition characterized by pain, urgency, and frequent urination of small volumes. Intravesical injection of botulinum toxin A has been evaluated in patients with interstitial cystitis/bladder pain syndrome for patients with symptoms that significantly affect quality of life, who have failed other measures, and who are aware of and willing to accept the risk of adverse effects. There are numerous treatments and management approaches are organized in the order of increasing risk. For most patients, it is reasonable to move from one level (e.g., first-line to secondline) when less risky approaches have failed. Less invasive treatments include self-care practices and behavior modifications, physical therapy, oral medications such as amitriptyline, pentosan polysulfate sodium antihistaminic agents. More invasive treatments include, bladder hydrodistention, resection, electrical cauterization, or injection of Hunner lesions with a corticosteroid and intravesical instillation of glycosaminoglycans or dimethyl sulfoxide.

The mechanism of the effect of intradetrusor botulinum toxin therapy for interstitial cystitis is likely the ability of botulinum toxin to modulate sensory neurotransmission. While botulinum toxin has been shown to alleviate symptoms in multiple studies mostly conducted outside of the U. S., there is a risk of urinary retention which may be particularly devastating for a patient with a painful bladder and therefore any patient considering this treatment must be willing and able to perform intermittent

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self-catheterization. A network meta-analysis of 16 trials including 905 patients published in 2016 indicated that botulinum toxin-A treatment had the highest probability of being the best treatment course based on global response assessment and significantly ameliorates bladder capacity in patients with interstitial cystitis. However, botulinum toxin A showed no treatment advantages with regard to pain, urinary frequency, and urgency results. Wang et al (2016) who reported the findings of a systematic review that included 7 RCTs and a retrospective study on onabotulinumtoxinA (Botox) and abobotulinumtoxinA (Dysport) rated only 1 of the 7 RCTs as high-quality (ie, low-risk of bias) while 5 were rated as moderate, and the other was rated as a high-risk of bias. Kuo et al (2016) reported the results of an RCT that included 60 Taiwanese patients (52 women, 8 men) with IC/painful bladder syndrome who had failed at least 6 months of conventional therapy. In this trial, at a higher dose (200 units of botulinum toxin A), adverse reactions occurred in 9 of 15 patients (4 patients had acute or chronic urinary retention, 7 had severe dysuria). Later, the dose was decreased to 100 units that resulted in reduction of adverse events but they still occurred more frequent than hydrodistention alone.

Interstitial Cystitis 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 (e.g., dysuria). Moreover, there is insufficient evidence comparing botulinum toxin injection with alternative treatments.

Tremor
Essential tremor is the most common cause of action tremor in adults. It classically involves the hands and is brought out by arm movement and sustained antigravity postures, affecting common daily activities such as writing, drinking from a glass, and handling eating utensils. Essential tremor is slowly progressive and can involve the head, voice, and rarely the legs, in addition to the upper limbs. Disability from the tremor can be significant, and a variety of symptomatic therapies are available. The initial approach to treatment is conservative measures such as pharmacotherapy with first-line treatment with propranolol and/or primidone. In case of inadequate response, second line agents include benzodiazepines, gabapentin, topiramate.

Botulinum toxin type A (BoNT-A) have been shown to provide benefit for limb tremor associated with essential tremor but have been associated with dose-dependent hand weakness. A systematic review published in 2011concluded that botulinum toxin A is possibly effective for the treatment of

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essential hand tremor, with a beneficial effect that was modest at best. The conclusion was drawn on the basis of 2 double-blind, placebo-controlled, parallel-design trials of botulinum toxin type A-one enrolled 25 patients and the other enrolled 133 patients. In the first trial, 11 of 12 treated patients reported mild (50%) or moderate (42%) wrist or finger weakness. In the second trial, symptomatic hand weakness occurred in 30% of the low-dose group and 70% of the high-dose group. Neither the investigators nor the patients reported any subjective benefit, and there was minimal (0·5 points) change at six weeks. Subsequent to this systematic review, Mittal et al (2017) published the results of a small randomized trial of 30 patients with essential tremor and Parkinson disease tremor to incobotulinumtoxinA (Xeomin) in a crossover design. Statistically significant improvements in clinical rating scores of rest tremor and tremor severity at four and eight weeks were reported in the treated patients and of action/postural tremor at eight weeks; however, there was no statistically significant difference in grip strength at four weeks between the two groups. The clinical significance of small benefits observed in trials that were offset by frequent adverse effects (hand weakness) do not permit conclusions about net heath benefit. 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.

Tremor Summary
The clinical significance of contradictory findings from 2 RCTs in patients with tremor are unclear. While a third small crossover trial has reported a 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.

Chronic Low Back Pain
Foster et al (2001) reported the findings of an RCT in which 31 consecutive patients with chronic low back pain of at least 6 months in duration were randomized to onabotulinumtoxinA (Botox) or saline. Botulinum toxin A was superior to placebo injection for pain relief and improved function at 3 and 8 weeks (50 % pain relief at 3 weeks 73.3 vs 25%; at 8 weeks 60 vs 16%, respectively). However, in most patients, benefits were no longer present after three to four months. These results should be considered preliminary, and further data from randomized trials are needed to confirm findings in a larger number of patients over a longer duration and to evaluate benefits and harms of repeated injections before this treatment can be recommended.

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Chronic Low Back Pain Summary
The population with chronic low back pain is heterogeneous. Results of a small RCT in a 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 repeated courses of botulinum toxin to determine the durability of repeated treatments.

Lateral Epicondylitis
Although the mechanism for action for botulinum toxin in epicondylitis is not clearly understood, it is thought to be as "proinflammatory". Botulinum toxin has been evaluated as a treatment for epicondylitis in a number of RCTs as summarized in a number of systematic reviews. In the systematic review and meta-analysis published by Lin et al (2019), authors included 6 RCTs (n=321) that comparing onabotulinumtoxinA (Botox) or abobotulinumtoxinA (Dysport) with placebo or corticosteroid injections in patients with lateral epicondylitis. Four of the 6 trials enrolled less than 30 participants per treatment arm and allocation concealment was unclear in 4 out of 6 trials. Results were reported as standardized mean differences and a negative number implied a favorable effect of botulinum toxin on pain reduction. Compared with placebo, botulinum toxin injection significantly reduced pain at all 3 time points (2 to 4 weeks, 8 to 12 weeks and at 16 weeks or more; standardized mean difference -0.73 (-1.29 to -0.17), -0.45 (-0.74 to -0.15) and -0.54 (-0.99 to -0.11) respectively. In contrast, botulinum toxin was significantly less effective than corticosteroid 2 to 4 weeks following injection; standardized mean difference 1.15 (0.57 to 1.34) with no difference at 8-12 weeks or 16 weeks or more time point. While the systematic reviews generally report pain relief in individual trials of botulinum toxin vs the comparator, treatment with botulinum toxin was associated with temporary paresis of finger extension.

Lateral Epicondylitis Summary
Several systematic reviews have 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 events 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. A systematic review that included trials comparing botulinum toxin with corticosteroid injections reported that botulinum toxin was less effective than corticosteroid at 2 to 4 weeks and both treatments appeared similar in efficacy after 8 weeks.

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Myofascial Pain Syndrome

Myofascial pain syndrome is characterized by muscle pain with increased tone and stiffness associated using myofascial trigger points. Patients are often treated with trigger point injections with saline, dilute anesthetics, or dry needling. These injections, while established therapy, have been controversial because 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 design to evaluate the efficacy of botulinum toxin injection for treating myofascial pain syndrome would be a double-blind RCT to minimize the placebo effect and would compare botulinum toxin injections with dry needling and/or with anesthetic injection.

Several systematic reviews of RCTs have evaluated onabotulinumtoxinA (Botox) and abobotulinumtoxinA (Dysport) for myofascial pain syndrome. The Cochrane systematic review by Soares et al (2014) identified 4 placebo-controlled, double-blind RCTs that included 233 participants with myofascial pain syndrome excluding neck and head muscles. Due to heterogeneity among studies, reviewers did not pool analyses. The primary outcomes were change in pain as assessed by validated instruments. Three of the four studies found that botulinum toxin did not significantly reduce pain intensity. Major limitations included high-risk of bias due to study size in three of the four studies and selective reporting in one study. Two other systematic reviews that focused on myofascial pain syndrome involving head and neck muscles reported similar findings. Systematic review by Desai et al (2014) included 7 trials that evaluated the efficacy of botulinum toxin type A in cervico-thoracic myofascial pain syndrome. Majority of studies found negative results and except for one, six identified trials had significant failings due to deficiencies in one or more major quality criteria.

Myofascial Pain 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 common alternative treatments. Most trials, as well as a pooled analysis of study findings, did not report improved health outcomes with botulinum toxin.

Temporomandibular Joint Disorders

Chen et al (2015) summarized the evidence assessing the efficacy of botulinum toxin A for treatment of temporomandibular joint disorders in a systematic review that included 5 RCTs. Sample size in majority of trials was 30 or less except for 1. Three of the five studies were judged to be at high-risk

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of bias. All studies administered a single injection of onabotulinumtoxinA (Botox) or abobotulinumtoxinA (Dysport) and followed patients up at least one month later. Four studies used a placebo (normal saline) control group and the fifth used abobotulinumtoxinA (Dysport) to fascial manipulation. Data were not pooled due to heterogeneity among trials. In a qualitative review of the studies, two of the five trials found a significant short-term (1-2 months) benefit of onabotulinumtoxinA (Botox) compared with control on pain reduction.

Temporomandibular Joint Disorders Summary
A systematic review of RCTs found insufficient evidence that botulinum toxin improves the net health outcome in patients with temporomandibular joint disorders. Studies have 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
Evidence for the efficacy and safety of botulinum toxin A for trigeminal neuralgia is limited and was summarized by Morral et al (2016) in a systematic review that included 4 RCTs (total n=178 patients). The largest trial randomly assigned 80 patients to either botulinum toxin A or placebo. While the meta-analysis reported significant reductions in mean pain scores and attack frequency in the botulinum toxin A compared with the placebo group, there are concerns about small patient numbers, limited durability and quality of evidence.

Trigeminal Neuralgia Summary
Three small RCTs from China and one from Egypt have assessed 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 included studies from only a single 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 chance 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 trial by Patti et al (2005) randomized 30 patients to onabotulinumtoxinA (Botox) 20 U or saline injection and reported a significantly shorter duration

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of postoperative pain at rest and during defecation in the treated group. A trial by Patti et al (2006), which also included 30 patients, found significant differences in postoperative maximum resting pressure change from baseline with onabotulinumtoxinA (Botox) vs topical glyceryl trinitrate ($p<0.001$). 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.

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

Facial Wound Healing
Ziade et al (2013) reported results of an RCT in which 30 adults presenting to the emergency department with facial wounds without tissue loss were assigned to single an injection of onabotulinumtoxinA (Botox) (N=11) or no injection (N=13) within 72 hours of the suturing of the wounds. Scars were assessed at a one-year follow-up visit by patients, an independent evaluator as well as board of six experienced medical specialists. There were no significant differences between the two groups in multiple outcomes that were assessed. Limitations of the study included relatively small sample size, lost to follow-up of 20% patients and lack of patients blinding. Gassner et al (2006) reported the results of another RCT that randomized 31 patients to onabotulinumtoxinA (Botox)- or placebo-induced immobilization of facial lacerations to improve wound healing. Blinded assessment of standardized photographs by experienced facial plastic surgeons using a 10-cm visual analog scale at six months served as the main outcome measure. The difference in visual scores was 8.9 in the treatment arm vs 7.2 in the placebo arm ($p=0.003$). Limitations of the study included a single-institution study, relatively small sample size, lack of clarity on number screened/randomized/excluded from the final analysis.

Facial Wound Healing Summary
There are few RCTs evaluating botulinum toxin for facial wound healing, and the available trials offer inconsistent evidence of benefit.

Pelvic and Genital Pain in Women
One double-blind, randomized, placebo-controlled trial by Abbott et al (2006) evaluated 60 women with chronic pelvic pain and pelvic floor spasm. Patients received injections of onabotulinumtoxinA (Botox) or placebo. Pain scores were reduced for both groups, but there were no significant

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differences between groups. The trial likely was underpowered to detect clinically significant differences in outcomes between groups.

Pelvic and Genital Pain in Women Summary
A single inadequately powered RCT that evaluated botulinum toxin to treat pelvic or genital pain in women failed to demonstrate statistically significant reduction in pain scores compared with placebo.

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

Neuropathic Pain After Neck Dissection Summary
Lack of a randomized, placebo-controlled trial, controlling for strong placebo effects in pain therapy, render the results of 2 open-label trials inconclusive for the use of botulinum toxin to treat neuropathic pain after neck dissection.

Tinnitus
Tinnitus is a perception of sound in proximity to the head in the absence of an external source. In patients with myoclonus of the palatal muscles or middle ear structures, botulinum toxin injections into the palate or sectioning of the tendons with the middle ear has been evaluated for symptomatic relief. Treatment for tinnitus includes correcting identified comorbidities as well as directly addressing the effects of tinnitus on quality of life. Several treatment modalities including behavioral treatments and medications have been studied but the benefit for most of these interventions has not been conclusively demonstrated in randomized trials.

Slengerik-Hansen et al (2016) reported the findings of a systematic review that included 22 studies, mainly case reports and case series with a total of 51 treated patients treated with onabotulinumtoxinA (Botox) for the treatment of tinnitus. A small (n=30) cross over prospective study by Stidham et al (2005) reported statistical significant decrease in tinnitus handicap inventory scores between pretreatment and 4 month post botulinum toxin A injection. Multiple other outcomes studies showed no difference. Well-conducted RCTs with sufficiently large sample sizes are needed.

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Tinnitus Summary
The evidence for botulinum toxin in patients with tinnitus consists mostly of case reports and case series. Well-conducted RCTs with sufficiently large sample sizes are needed to demonstrate that botulinum toxin improves the net health outcomes in patients with tinnitus.

Pain Associated With Breast Reconstruction After Mastectomy
There are no published RCTs evaluating botulinum toxin for pain associated with breast reconstruction after mastectomy. A systematic review by Winocour et al (2014) identified 7 studies on perioperative injection of botulinum toxin type A following breast reconstruction surgery. They consisted of 2 prospective controlled cohort studies, 3 retrospective controlled cohort studies, and 2 case series. Most studies were small; only 1 (N=293) had more than 50 participants. Three studies assessed postoperative pain and all three found that at least some outcomes were significantly better in the botulinum toxin group than in the comparison group.

Pain Associated With Breast Reconstruction After Mastectomy Summary
The evidence for botulinum toxin in patients with pain associated with breast reconstruction after mastectomy mostly consists of observational studies. Well-conducted RCTs with sufficiently large sample sizes are needed to demonstrate that botulinum toxin improves the net health outcomes in these patients.

Gastroparesis
Gastroparesis is a syndrome of objectively delayed gastric emptying in the absence of a mechanical obstruction and cardinal symptoms of nausea, vomiting, early satiety, belching, bloating, and/or upper abdominal pain. Initial management of gastroparesis consists of dietary modification, optimization of glycemic control and hydration, and in patients with continued symptoms, pharmacologic therapy with
prokinetic and antiemetics.

A systematic review by Bai et al (2010) identified 15 studies on onabotulinumtoxinA (Botox) to treat gastroparesis. Two studies were RCTs; the remainder was case series or open-label observational studies. Reviewers stated that, while the nonrandomized studies generally found improvements in subjective symptoms and gastric emptying after onabotulinumtoxinA (Botox) injections, the RCTs did not report treatment benefit with onabotulinumtoxinA (Botox) for treating

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gastroparesis. The 2 RCTs were inadequately powered RCTs; one included 23 patients and the other included 32 patients.

Gastroparesis Summary
Two small inadequately powered RCTs failed to show a benefit of botulinum toxin for treatment of gastroparesis. Additional adequately powered RCTs are needed.

Depression
Depression is common that affects US population and is also the leading cause of disability. It is postulated that treating the frown muscles of depressed patients with botulinum toxin A may improve depressive symptoms as it is hypothesized that facial expression influences emotional perception; producing an expression that is characteristic of a particular emotion can lead to experiencing that emotion (e.g., smiling can lead to happiness, scowling can lead to anger). Inhibiting the muscles responsible for expressions of anguish and sadness, one may decrease the patient's experience of these feelings. The goal of initial treatment for depression is symptom remission and restoring baseline functioning.

Magid et al (2015) published a pooled analysis of individual patient data from 3 randomized trials evaluating injections of onabotulinumtoxinA (Botox) in the glabellar region (forehead) for treating unipolar major depressive disorder as an adjunctive treatment. The response rate (defined as ≥ 50% improvement from baseline scores in the depression score) was higher in the onabotulinumtoxinA (Botox) group compared with placebo (54.2% vs 10.7%; OR=11.1; 95% CI 4.3 to 28.8). The respective remission rate (defined as score ≤ 7 for the Hamilton Depression Rating scales, ≤ 10 for the Montgomery-Asberg Depression Rating Scale) was 30.5% vs 6.7% (7.3; 95% CI, 2.4 to 22.5). While the effect size of the treatment observed in the pooled analysis and individual RCTs is clinically meaningful and large, there are multiple limitations that preclude drawing meaningful conclusions about net health benefit. Limitations in study design and conduct include potential of unblinding due to changes in cosmetic appearance, small sample size, lack of power analysis, short duration of follow-up in two out of three RCTs lack of clarity on allocation concealment and lack of intention to treat analysis. More importantly, patients with a history of major depressive order presenting with acute depression episode prior to enrollment in the trial were evaluated, it is unclear if botulinum toxin A treatment is intended to be used as a short-term treatment of a depressive episode or as a maintenance treatment for depression. Further, a large trial (NCT02116361) with 258 patients to evaluate the efficacy of onabotulinumtoxinA (Botox) as treatment for major

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depressive disorder in adult females was completed in 2016 but has not been published which raises concerns about potential for publication bias.

Depression Summary
Various limitations exist in studies of botulinum toxins in depression.

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Policy History

Original Effective Date: 01/28/2003
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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
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 overactivity 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.

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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:

- 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:

- Detrusor overactivity not due to spinal cord injury.

Added to the existing bullet in the "When Services Are Considered Investigational" section as follows:

- 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) in adults who have an inadequate

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	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

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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 Hirschprung's disease with obstructive symptoms cause by internal sphincter achalasia following a pull-through surgery
08/01/2019	Medical Policy Committee review
08/14/2019	Medical Policy Implementation Committee approval. Added coverage for sialorrhea in pediatric developmental delays (e.g., cerebral palsy). Added CGRP inhibitors to list of options for migraine prophylaxis agents. Updated background information and references.
09/03/2020	Medical Policy Committee review
09/09/2020	Medical Policy Implementation Committee approval. Expanded the indication for sialorrhea under Myobloc coverage. Updated the not medically necessary statement for sialorrhea other than Parkinson disease, pediatric neurodevelopmental delay (e.g., Cerebral Palsy), atypical parkinsonism, stroke, or traumatic brain injury to include Myobloc (in addition to Xeomin). Updated background information and references.
09/02/2021	Medical Policy Committee review
09/08/2021	Medical Policy Implementation Committee approval. No change to coverage.
09/01/2022	Medical Policy Committee review
09/14/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Updated background information to reflect availability of new botulinum toxin product, Jeuveau, which is only approved for cosmetic purposes. Updated literature review.
09/07/2023	Medical Policy Committee review
09/13/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/27/2024	Coding update

Next Scheduled Review Date: 09/2024

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 2022

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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.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

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

Code Type	Code
CPT	31573, 46505, 52287, 64611, 64612, 64615, 64616, 64617, 64642, 64643, 64644, 64645, 64646, 64647, 64650, 64653, 67345 Delete codes effective 10/01/2023: 64640, 95873, 95874
HCPCS	J0585, J0586, J0587, J0588, S2340, S2341 Add code effective 04/01/2024: J0589
ICD-10 Diagnosis	All related Diagnoses

*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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A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
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:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

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.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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