Botulinum Toxin

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Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for botulinum toxin A and B injections if it is determined to be medically necessary because the following criteria are met

When Policy Topic is covered
The use of botulinum toxin may be considered medically necessary for the following:

- 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, eg, sternocleidomastoid, splenius, trapezius, or posterior cervical muscles. (See additional details in Policy Guidelines section.)

- Upper-limb spasticity

- 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 (eg, 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 disease

- Strabismus

- Blepharospasm or facial nerve (VII) disorders (including hemifacial spasm)
• Prevention (treatment) of chronic migraine headache in the following situations:
  o Initial approval:
    ▪ meet International Classification of Headache Disorders diagnostic criteria for chronic migraine headache (see Policy Guidelines) and
    ▪ have symptoms that persist despite adequate trials of at least 2 agents from different classes of medications used in the treatment of chronic migraine headaches (eg, antidepressants, antihypertensives, antiepileptics). Patients who have contraindications to preventive medications are not required to undergo a trial of these agents.
  o Renewal authorizations:
    ▪ Migraine headache frequency reduced by at least 7 days per month compared with pretreatment level, or
    ▪ Migraine headache duration reduced at least 100 hours per month compared with pretreatment level.
• Esophageal achalasia in patients who have not responded to dilation therapy or who are considered poor surgical candidates
• Sialorrhea (drooling) associated with Parkinson disease
• Chronic anal fissure
• Urinary incontinence due to detrusor overactivity associated with neurogenic causes (eg, spinal cord injury, multiple sclerosis) in patients unresponsive to or intolerant of anticholinergics.
• Overactive bladder in adults unresponsive to or intolerant of anticholinergics.

Note: Botulinum toxin as a treatment of hyperhidrosis is considered separately in policy No. 8.01.19. Botulinum toxin as a treatment of tinnitus is considered separately in policy No. 8.01.39.

When Policy Topic is not covered
The use of botulinum toxin is considered investigational for other indications, including but not limited to:
• headaches, except as noted above for prevention (treatment) of chronic migraine headache
• chronic low back pain
• joint pain
• mechanical neck disorders
• neuropathic pain after neck dissection
• myofascial pain syndrome
• temporomandibular joint disorders
• trigeminal neuralgia
• pain after hemorrhoidectomy or lumpectomy
• tremors such as benign essential tremor (upper extremity)
• tinnitus
• sialorrhea (drooling) except that associated with Parkinson disease
• chronic motor tic disorder (ICD-9 307.22), and tics associated with Tourette syndrome (motor tics) (ICD-9 307.23)
• 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
• Gastroparesis
• facial wound healing
• Internal anal sphincter achalasia
• Depression

The use of botulinum toxin may be considered **not medically necessary** as a treatment of wrinkles or other cosmetic indications.

The use of assays to detect antibodies to botulinum toxin is considered **investigational**.

**Considerations**
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 contractions can cause sustained abnormal positions or posturing.

Sideways or lateral rotation of the head and twisting of the neck are the most common findings in cervical dystonia. Muscle hypertrophy occurs in most patients. When using botulinum toxin to treat cervical dystonia, postural disturbance and pain must be of such severity as 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 (eg, cervicogenic headaches) must have been considered and excluded.

International Classification of Headache Disorders (ICHD-3) diagnostic criteria for chronic migraine headache include the following:

Headaches at least 15 days per month for more than 3 months; have features of migraine headache on at least 8 days.

**Features of migraine headache:**
• Lasts 4 to 72 hours;
• Has at least 2 of the following 4 characteristics:
  • Unilateral
  • Pulsating
  • Moderate or severe pain intensity
  • Aggravates or causes avoidance of routine physical activity
• Associated with:
  • Nausea and/or vomiting
Photophobia and phonophobia.

(In ICHD-2, absence of medication overuse was one of the diagnostic criteria for chronic migraine. In the ICHD-3, this criterion was removed from the chronic migraine diagnosis and "medication overuse headache" is now a separate diagnostic category.)

For continued treatment of chronic migraines, the policy includes the requirement that migraine headache frequency be reduced by at least 7 days per month compared with pretreatment level, or that migraine headache duration be reduced by at least 100 hours per month compared with pretreatment level in order to continue treatment beyond 6 months. The 7 days per month represents a 50% reduction in migraine days for patients who have the lowest possible number of migraine days (ie, 15) that would allow them to meet the ICHD-3 diagnostic criteria fewest chronic migraine. A 50% reduction in frequency is a common outcome measure for assessing the efficacy of headache treatments and was one of the end points of the PREEMPT study.

This Blue Cross and Blue Shield of Kansas City policy statement is consistent with the Blue Cross and Blue Shield Association Policy 5.01.05.

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

Background
There are 7 distinct serotypes designated as type A, B, C-1, D, E, F, and G. In the U.S., 4 preparations of botulinum are commercially available, 3 using type A serotype and 1 using type B. The nonproprietary names of the botulinum toxin products were changed in 2009; trade names and product formulations did not change. The 3 formulations of botulinum toxin type A are currently called onabotulinumtoxinA (Botox®), abobotulinumtoxinA (Dysport®), and incobotulinumtoxinA (Xeomin®). It is important to note that class labeling states that “The potency Units of [each botulinum toxin product] are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of [each botulinum toxin product] cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method.” Botox has been available for the longest time in the United States and has been the most widely used. Xeomin, the newest product marketed in the U.S., consists of the pure neurotoxin without complexing proteins and is the only product that is stable at room temperature for up to 4 years. Myobloc contains botulinum toxin type B; the current nonproprietary name of this drug is rimabotulinumtoxinB.

All 4 products are approved by the U.S. Food and Drug Administration (FDA) for the treatment of cervical dystonia in adults; this is the only FDA-approved indication for Myobloc. Dystonia is a general term describing a state of abnormal or disordered tonicity of muscle. As an example, esophageal achalasia is a dystonia of the lower esophageal sphincter, while cervical dystonia is also known as torticollis. Spasticity is a subset of dystonia, describing a velocity-dependent increase in tonic-stretch reflexes with exaggerated tendon jerks. Spasticity typically is associated with injuries to the central nervous system. Spasticity is a common feature of cerebral palsy. Botox and Dysport are also approved for treating upper limb spasticity in adults.

Among the botulinum toxin products, onabotulinumtoxinA (Botox®) is FDA-approved for the largest number of indications. Other than the indications mentioned above, this includes indications in primary axillary hyperhidrosis, detrusor overactivity associated with a neurologic condition and overactive bladder in adults, and blepharospasm and strabismus in individuals at least 12 years of age. On October 15, 2010, the FDA approved Botox injection for prevention of chronic migraine. Chronic migraine is defined as headache lasting at least 4 hours on at least 15 days per month for more than 3
months, which has the features of migraine headache on at least 8 days per month. (Botulinum toxin for treatment of hyperhidrosis is addressed separately in policy 8.01.19). The newest product, Xeomin, is approved for treating blepharospasm.

Three products, Botox (marketed as Botox Cosmetic), Xeomin and Dysport, are approved for temporarily improving the appearance of glabellar (frown) lines in adults younger than 65 years of age.

The botulinum toxin products have also been used for a wide variety of off-label indications, ranging from achalasia, spasticity after strokes (other than upper limb spasticity), cerebral palsy, and anal fissures.

**FDA Indications of Botulinum Toxin Products**

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA-Approved Indications</th>
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| Botox  | • Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication  
• Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition in adults who have an inadequate response to or are intolerant of an anticholinergic medication  
• Prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer)  
• Treatment of spasticity in adult patients  
• Treatment of cervical dystonia in adult patients  
• Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients  
• Treatment of blepharospasm associated with dystonia in patients ≥12 years of age  
• Treatment of strabismus in patients ≥12 years of age |
| Dysport | • Treatment of cervical dystonia in adult patients  
• Treatment of upper limb spasticity in adult patients  
• Treatment of lower-limb spasticity in pediatric patients ≥ 2 years of age |
| Xeomin | • Treatment of cervical dystonia in adult patients  
• Treatment of upper limb spasticity in adult patients  
• Treatment of blepharospasm with onabotulinumtoxinA prior treatment  
• Treatment of chronic sialorrhea in adults |
| Myobloc | • Treatment of cervical dystonia in adults |
to reduce the severity of abnormal head position and neck pain

Regulatory Status
Botox (Allergan, Irvine, CA) was approved by the FDA in 1989, Myobloc (Solstice Neurosciences) in 2000, Dysport (Medicis Pharmaceutical Corporation, Scottsdale, AZ) in 2009, and Xeomin (Merz Pharmaceuticals) in 2010.

Rationale
Dystonia/Spasticity
This policy section is based on a 1996 TEC Assessment that focused on the use of botulinum toxin for the treatment of focal dystonia or spasticity (which was updated in 2004), the American Academy of Neurology (AAN) 2008 assessments of movement disorders and spasticity (1-4) and additional controlled trials identified by MEDLINE literature searches.

At the time of the 1996 TEC Assessment, only onabotulinumtoxinA (Botox) was commercially available. Based on the evidence, the TEC Assessment concluded that Botox therapy for the following indications met the BCBSA TEC Criteria:

- Children with cerebral palsy in whom dynamic joint deformity secondary to spasticity or athetosis produces pain and/or interferes with function; and
- Ambulatory and nonambulatory patients with chronic limb spasticity, in whom dynamic joint deformity produces pain and/or interferes significantly with supportive care and quality of life (sitting, balance, hygiene, pain control). (Note: evidence for this indication was derived from trials that enrolled patients with chronic spasticity due to stroke, multiple sclerosis, trauma, familial spastic paresis, Friedrich’s ataxia, hypoxic brain damage, motor neuron disease, and hemorrhage from aneurysm.)

A 1990 National Institutes of Health (NIH) Consensus Development Conference concluded that botulinum toxin therapy is safe and effective for the currently FDA-approved indications, as well as for adductor spasmodic dysphonia and jaw-closing oromandibular dystonia. (5) According to information provided by the NIH National Institute on Deafness and Other Communication Disorders (NIDCD), the only available treatments for all types of spasmodic dysphonia is surgery (improvement often temporary), or botulinum toxin therapy. (6)

Two recent trials evaluated botulinum toxin A for treating mobility limitations in patients with spastic cerebral palsy. In 2010, van der Houwen et al. in the Netherlands randomized 22 children who walked with flexion of the knee in midstance to standard rehabilitation with and without multilevel Botox injections. (7) Botox injection did not result in general improvement in lower limb muscle activation during gait 6 weeks after the intervention. A 2011 study, conducted in Norway, randomized 66 patients who had decreased walking ability to Botox or placebo injections. (8) No significant differences were found between groups in the primary outcomes, which included kinematics (joint angles) and the Norwegian version of the short form 36 (SF-36) quality-of-life scale. However, among the secondary outcomes, the Botox group had significantly more reduction in muscle stiffness/spasticity and significantly greater improvement in the global improvement scale than the placebo group at week 8; these effects were not sustained at week 16.

Randomized controlled trials (RCTs) were identified that evaluated Botox, Dysport, and Xeomin used to treat spasticity after stroke. In 2010, Kaji and colleagues reported the findings of a trial conducted in Japan with 120 patients who had post-stroke lower limb spasticity randomly assigned to receive a single injection of Botox or placebo. (9) The primary outcome, change from baseline in modified Ashworth scale (MAS) of muscle spasticity, indicated significantly greater improvement in the Botox group compared to the placebo group over 8 weeks. Bakheit and colleagues randomly assigned 83 patients with upper limb spasticity after stroke to receive 1 of 3 doses of Dysport or placebo. (10) All 3
doses of Dysport resulted in a statistically significantly greater reduction in the MAS score than placebo.

In 2011, Shaw and colleagues reported on results of a study randomizing 333 patients with post-stroke upper limb spasticity to physical therapy plus Dysport (n=170) or physical therapy alone (n=163). (11) The primary outcome, improved function at 1 month according to the Action Research Arm Test (ARAT), did not differ significantly among groups. Improved function according to ARAT scores also did not differ significantly between groups at 3 or 12 months. Change in muscle tone according to median change in the MAS significantly favored the Dysport group over the placebo group at 1 month (mean change= -0.6 and -0.1, respectively, p<0.001), but not at 3 and 12 months. Several European trials have evaluated Xeomin for post-stroke upper limb spasticity. Kanovsky and colleagues randomized 148 patients with post-stroke upper limb spasticity to treatment with either Xeomin or placebo. (12) After 4 weeks, a significantly higher response rate was found in all treated flexor muscle groups among patients treated with Xeomin compared to placebo. The treatment benefit lasted through the week-12 visit. An open-label extension of this study with 145 participants was published in 2011. (13) Patients received up to 5 additional sets of Xeomin injections, with 12-week intervals between injections. A total of 111 (77%) patients had at least 3 injections and 72 (50%) had 4 injections. Outcomes were assessed 4 weeks after each injection. Compared to baseline, patients consistently showed improved outcomes at each post-treatment visit. None of the patients developed neutralizing antibodies in either the double-blind or extension phases of the study.

A multicenter study by Barnes and colleagues randomly assigned patients with upper limb spasticity (88% post-stroke) to receive either 50 U/mL or 20 U/mL Xeomin and did not find a substantial difference in outcomes with the 2 doses. (14)

A 2010 Cochrane systematic review identified 5 double-blind RCTs comparing a single injection of botulinum toxin A to a placebo injection for the treatment of shoulder spasticity after stroke or hemiplegia. (15) A pooled analysis of data from 4 studies (3 using Dysport and 1 using Botox) found a significantly greater reduction in pain severity in the botulinum toxin group compared to the placebo group at a follow-up visit between 12 and 24 weeks (mean difference= -1.2, 95% confidence interval [CI]: -2.37 to -0.07). At 12 to 24 weeks, shoulder range-of-motion outcomes did not differ significantly between groups. Most of the studies included in the review were small, and the investigators rated the overall evidence as low to mediocre.

A 2007 systematic review identified 70 studies that examined 2 botulinum toxin agents used to treat cervical dystonia. (16) There were 30 studies on Botox, 24 on Dysport, 11 on Myobloc, and 5 combining 2 agents. Xeomin for treating cervical dystonia has been evaluated in an RCT that found it to be non-inferior to Botox. (17) There is evidence from multiple RCTs that botulinum toxin is an effective treatment for cervical dystonia; therefore, it is considered medically necessary.

**Blepharospasm**

Blepharospasm is a progressive neurologic disorder characterized by involuntary contractions of the eyelid muscles; it is classified as a focal dystonia. RCTs have evaluated Botox, Dysport, and Xeomin for the treatment of blepharospasm and found these agents to be effective at improving symptoms. (18-20) No RCTs that evaluated Myobloc for treating blepharospasm were identified in literature searches. Due to evidence indicating that at least 1 botulinum toxin agent is an effective treatment of blepharospasm, botulinum toxin is considered medically necessary for this indication.

**Achalasia**

Esophageal achalasia is a primary motor disorder characterized by abnormal lower esophageal sphincter relaxation. Randomized, placebo-controlled trials initially validated the efficacy of botulinum toxin in treating achalasia. In 1999, Vaezi and colleagues (21) reported a trial that randomly assigned 42 patients with achalasia to either receive botulinum toxin or undergo pneumatic dilation. Pneumatic dilation resulted in a significantly higher cumulative remission rate. At 12 months, 70% of patients in the dilation group were still in remission compared to 32% of those in the botulinum toxin group. These results reflect the fact that the effects of botulinum toxin are known to be reversible but also the fact
that pneumatic dilation can provide durable treatment effects. The authors conclude that while botulinum toxin is an effective therapy, pneumatic dilation is the preferred medical treatment option. This conclusion is supported by a 2006 Cochrane systematic review and meta-analysis of 178 patients treated with either botulinum toxin or pneumatic dilation. (22)

An RCT by Annese and colleagues in Italy with 78 patients found 100 U of Botox and 250 U of Dysport to have comparable efficacy for treating esophageal achalasia. (23) Due to evidence indicating that at least 1 botulinum toxin agent is an effective treatment of achalasia, botulinum toxin is considered medically necessary for this indication.

**Anal Fissure**

Chronic anal fissure is a tear in the lower half of the anal canal that is maintained by contraction of the internal anal sphincter and is treated surgically with an internal sphincterotomy. Since the anal sphincter contraction could be characterized as a dystonia, botulinum toxin is a logical medical approach. In 1998, Maria and colleagues randomly assigned 30 patients with chronic anal fissure to receive either 2 injections of 20 units of botulinum toxin, on either side of the fissure, or 2 injections of saline. (24) After 2 months, 11 patients in the treatment group reported healing, compared to only 2 in the control group. The 4 patients who still had fissures after 2 months underwent retreatment with botulinum toxin; 2 of these 4 patients reported healing scars and symptomatic relief. These results are consistent with earlier case series that reported a healing rate of 80%. (25) Nitroglycerin ointment has also been used to successfully treat anal fissure. In 1999, Brisinda and colleagues in Italy compared the results of nitroglycerin ointment and botulinum toxin in a randomized trial of 50 patients. (26) After 2 months, 96% of the fissures were healed in the botulinum group compared with 60% in the nitroglycerin group. Brisinda and colleagues conducted a second, similar trial in 2007 with 92% versus 70%, respectively, healing rates for botulinum toxin A-treated versus nitroglycerin ointment-treated patients (p<0.001). (27) Another trial by Brisinda and colleagues found that Botox and Dysport used to treat anal fissures were similar in terms of efficacy and tolerability. (28) Others have reported both supportive (29) and contradictory (30) data from randomized trials comparing the same treatments. RCTs of botulinum toxin versus sphincterotomy have reported significantly better healing rates with sphincterotomy, but authors concluded that botulinum toxin was a viable first option for patients who are not good surgical candidates or who want to minimize the likelihood of incontinence. (31, 32) A systematic review concluded that no single treatment was the best for all patients. (33) Due to evidence of effectiveness, botulinum toxin is considered medically necessary for treatment of anal fissure.

**Urologic Applications**

**Detrusor overactivity.**

In 2008, Karsenty et al. conducted a systematic review of studies of Botulinum toxin A intradetrusor injections in adults with neurogenic detrusor overactivity and urinary incontinence or overactive bladder symptoms of neurogenic origin. (34) The authors identified 18 studies evaluating Botulinum toxin A to treat patients who were refractory to anticholinergics. Most of the studies reported statistically significant improvement in clinical and urodynamic outcomes, without major adverse events. The authors concluded that botulinum toxin treatment results in a clinically significant improvement in outcomes in this group of patients. Randomized trials published in 2010 and 2011 evaluating Botox for treating overactive bladder or neurogenic detrusor activity refractory to anticholinergics have had similar findings. (35, 36) One of the trials was a dose-ranging study and found efficacy with Botox doses of 100 U or greater; the 100 U dose minimized adverse effects. (36) RimabotulinumtoxinB (Myobloc) has also been found in a randomized trial to improve outcomes in patients with overactive bladder. (37)

**Detrusor sphincter dyssynergia.** In 2002, deSeze and colleagues studied 13 patients with chronic urinary retention due to detrusor sphincter dyssynergia from spinal cord disease (traumatic injury, multiple sclerosis, congenital malformations), randomly assigned to receive perineal botulinum toxin A or lidocaine injections into the external urethral sphincter. (38) In the botulinum group, there was a significant decrease in the primary outcome of post-void residual volume compared to no change in
the control group receiving a lidocaine injection. Improvements were also seen in the satisfaction scores and other urodynamic outcomes.

In 2006, Karsenty and colleagues (39) reviewed trials of botulinum toxin A injected into the urethral sphincter to treat different types of lower urinary tract dysfunction, grouped into neurogenic detrusor-sphincter dyssynergia and nonneurogenic obstructive sphincter dysfunction. In the former group, the authors cite 10 small studies (n ranged from 3 to 53; 3 studies included patients in both categories). Most patients were quadriplegic men unable to perform self-catheterization or patients (of both genders) with multiple sclerosis. All except 2 studies were case reports or case series. The previously cited study by deSeze et al. (38) was included; the other RCT enrolled only 5 patients. While most studies report significant improvements, in this study, the small patient numbers, different causes of dysfunction, and different outcome measures, together with lack of control arms make it difficult to draw conclusions regarding this application.

**Benign prostatic hyperplasia.** The rationale for botulinum treatment is based on the theory that symptoms of benign prostatic hyperplasia (BPH) are in part due to a static component related to prostate size and a dynamic component related to the contraction of smooth muscle within the gland. Botulinum therapy addresses this latter component. In 2003, Maria and colleagues reported on 30 patients with BPH randomly assigned to receive either intraprostatic botulinum toxin A or saline injection. (40) Inclusion criteria for this trial included moderate-to-severe symptoms of BPH based on the American Urological Association (AUA) score and a mean peak urinary flow rate of no more than 15 mL per second with a voided volume of 150 mL or less. After 2 months, the AUA symptom score decreased by 65% among those receiving botulinum toxin compared to no significant change in the control group. The mean peak urinary flow rate was significantly increased in the treatment group. In 2006, Chuang and Chancellor (41) reviewed trials testing the use of botulinum toxin in benign prostatic hyperplasia. With the exception of the previously cited trial by Maria and colleagues, (40) all were small, open-label trials (sample sizes ranged from 8 to 52) that generally reported improvement in spontaneous voiding and decreases in post-void residual volume compared to baseline. No additional RCTs were found in a MEDLINE search through June 2008. Given the prevalence of BPH, larger trials that compare the role of BPH with other medical and surgical therapies are warranted.

**Interstitial cystitis.** Several case series (fewer than 20 participants) of botulinum toxin treatment of patients with interstitial cystitis for alleviation of chronic pain and improving bladder capacity have been published. (e.g., 42-44) All report subjective improvement in a majority of patients and statistically significant improvement in various measured parameters, such as pain rated by visual analog scale (VAS), frequency, nocturia, and functional bladder capacity. The results suggest efficacy but need confirmation in a larger population and preferably in controlled clinical trials.

There is evidence from multiple RCTs that botulinum toxin is an effective treatment for detrusor overactivity; therefore, this is considered medically necessary. There is insufficient evidence on other urologic applications; thus, for these, botulinum toxin is considered investigational.

**Tremor**

Tremor may be defined as alternate or synchronous contractions of antagonistic muscles. Some patients may be disabled by severe or task-specific tremors. Tremors are also a frequent component of dystonias, and successful treatment of dystonias resulted in an improvement in tremors. Botulinum toxin has been investigated in patients with tremors unrelated to dystonias; however, most reports are case reports or case series. Two randomized, placebo-controlled studies addressed essential hand tremors; the 2001 trial enrolled 133 patients, and the 1996 trial enrolled 25 patients. (45,46) In both studies, inconsistent significant advantages for botulinum toxin were found on tremor symptom scales, but none were shown on functional outcomes. Thus, the clinical significance of these findings is unclear, and botulinum toxin is considered investigational for treating tremors, such as benign essential tremor.

**Sialorrhea (Drooling)**

Five small (n ranged from 16 to 48) RCTs evaluated botulinum toxin injection into parotid/submandibular glands compared with placebo injection to control sialorrhea in patients with
neurologic diseases (e.g., Parkinson, cerebral palsy, amyotrophic lateral sclerosis [ALS]). Ondo and colleagues (47) randomly assigned 16 patients with Parkinson disease to receive placebo or 2,500 U of botulinum toxin B (Myobloc). The botulinum toxin group had significantly better outcome than the placebo group at 1 month on 4 drooling outcomes, but groups did not differ on salivary gland imaging and a dysphagia scale. Mancini and colleagues (48) assigned 20 patients to injections of either a saline placebo or 450 U of Dysport. The treatment group was significantly better than placebo on a drooling scale at 1 week; the effect disappeared by 3 months. Lipp and colleagues (49) randomly assigned 32 patients to either placebo or 3 different doses of Dysport: 37.5 U, 75 U, or 150 U. One outcome was an objective measure of drooling based on weight of dental rolls, which significantly favored botulinum toxin over placebo for only the 75 U dose. The same pattern was observed for a patient-measured count of sialorrhea-related acts. Loss to follow-up was 21% at 3 months and 44% at 6 months; it was unclear what follow-up period was represented in the statistical analyses.

In 2006, Lagalla et al. randomly assigned 32 patients with Parkinson disease to placebo or 50 U botulinum toxin A; evaluation at 1 month post-injection resulted in significant improvements compared with placebo, in drooling frequency, saliva output, and in familial and social embarrassment. (50) Dysphagia scores were not significantly improved. Reid et al. randomly assigned 48 children with cerebral palsy and other neurologic disorders to no treatment or to 25 U botulinum toxin A. (51) Maximal response on the Drooling Impact Scale questionnaire occurred at 1 month, but the difference between treatment arms remained statistically significant at 6 months. Sixteen of 24 treated were responders. A systematic review of botulinum toxin A for treatment of sialorrhea concluded that the ideal dose, injection location, and technique of injection administration remain to be determined. (52) While some questions remain, studies on those with Parkinson disease provide consistent findings related to impact on sialorrhea. Thus, for this specific disease indication, this use of botulinum toxin is considered medically necessary. For sialorrhea associated with other disorders, there is little evidence and additional studies are needed; these indications are considered investigational.

**Chronic Low Back Pain**

Only 1 randomized controlled study of botulinum toxin A treatment in patients with low back pain has been published. (53) The trial, published in 2001, enrolled 31 consecutive patients with chronic low back pain of at least 6 months’ duration and more predominant pain on one side. Patients were injected with 40 units of Botox (Allergan, Inc.) at 5 lumbosacral locations for a total of 200 U (treated group) or saline placebo (placebo group). Injections were made on one side of the back only, depending on predominance of pain. At 8 weeks, 60% of treated patients and 12.5% of placebo patients showed improvement in VAS pain scores (p=0.009). Perceived functional status (Oswestry scale) at 8 weeks showed that 66.7% of treated patients and 18.8% of placebo patients were responders (p=0.011). The population with chronic low back pain is a heterogeneous population, and results in this small group of selected subjects cannot be used to generalize results for the whole population with chronic low back pain. Furthermore, studies should examine the long-term effectiveness of using repeated courses of botulinum toxin to determine the durability of repeated treatments. Botulinum toxin is considered investigational for treatment of chronic low back pain.

**Headache**

The interest in using botulinum toxin as a treatment of headache stemmed from the observation that patients receiving pericranial injections of botulinum toxin for other reasons reported a decrease in the incidence in migraine. While it may exert its effect by relieving the muscle tension associated with migraine, others have proposed independent actions, none yet proven, that may directly affect pain. Research has also addressed other types of headache. Because of the typically high placebo response rate in patients with headache, assessment of evidence focuses on randomized, placebo-controlled trials.

Botulinum toxin for treatment of pain from migraine and from chronic tension-type headaches was addressed in a TEC Assessment that was completed in 2002 and updated in 2004. (2) Both TEC Assessments concluded that the evidence was insufficient for either indication.

More recent studies have focused on the use of botulinum toxin to reduce the frequency of headaches. The American Academy of Neurology (AAN) assessment from 2008 identified 3 trials on
botulinum toxin for episodic migraine, 4 studies on chronic daily headache, and 4 studies on chronic tension-type headaches. (54) Most of the studies identified by the assessment stated that botulinum toxin A was used, and several further specified that they used Botox. The assessment concluded that botulinum toxin should not be considered for episodic migraine and chronic tension-type headache and that the evidence was insufficient for treatment of chronic daily headache.

**Migraine headache.** Migraines can be categorized, among other characteristics, according to headache frequency. According to the Third Edition (beta) 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. (55) Chronic migraine is defined as headache attacks on at least 15 days per month for more than 3 months, which has the features of migraine headache on at least 8 days per month.

A systematic review and meta-analysis of trials on botulinum toxin for treating episodic migraines (fewer than 15 per month over 3 months) was published in 2009 by Shuhendler and colleagues. (56) The investigators identified 8 randomized double-blind placebo-controlled trials evaluating the efficacy of pericranial botulinum toxin A injections. Six additional randomized trials were identified, but they did not meet eligibility criteria because they were not double-blind (n=2), used a measurement scale that was different from other studies (n=1), was not randomized (n=1), included patients with chronic migraine (n=1), or was a subgroup study (n=1). The 8 eligible studies included a total of 1,601 patients. Overall, the mean frequency of migraines per month was 5.3. A pooled analysis of the main study findings found no significant differences between the botulinum toxin A and placebo groups in change in the number of migraines per month. After 30 days of follow-up, the standardized mean difference (SMD) was -0.06 (95% confidence interval [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 that separately examined trials using low-dose botulinum toxin A (less than 100 units) separately from trials using high-dose botulinum toxin A (100 units or more) did not find a statistically significant effect of botulinum toxin A compared to placebo in either strata.

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 II Research Evaluating Migraine Prophylaxis Therapy) studies 1 and 2. (57, 58) Study designs were similar. Both studies included a 24-week double-blind placebo-controlled phase prior to an open-label phase. (Findings from the open-label phases of the studies have not yet been published). The trials recruited patients meeting criteria for migraine and excluded those with complicated migraine. To be eligible for participation, patients needed 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 needed to be definite or probable migraine. The investigators did not require that the frequent attacks occurred for more than 3 months or exclude patients who overused pain medication, 2 of the ICHD-2 criteria for chronic migraine. Eligible patients were randomly assigned to receive 2 cycles of injections of Botox 155 U or placebo, with 12 weeks between cycles. Randomization was stratified based on the frequency of acute headache pain medication during baseline and whether or not they overused acute headache pain medication. (Medication overuse was defined as baseline intake of simple analgesics on at least 15 days or other medications for at least 10 days and medication use at least 2 days per week.) The primary endpoint in PREEMPT 1 was mean change from baseline in frequency of headache episodes for 28 days ending with week 24. A headache episode was defined as a headache with a start and stop time indicating that pain lasted at least 4 hours. Prespecified secondary outcomes included, among others, change in frequency of headache days (calendar days in which pain lasted at least 4 hours), migraine days (calendar days in which a migraine lasted at least 4 hours), and migraine episodes (migraine with a start and stop time indicating that pain lasted at least 4 hours). Based on availability of data from PREEMPT 1 and other factors, the protocol of the PREEMPT 2 trial was amended (after study initiation but before unmasking) to make frequency of headache days the primary endpoint of this study. The authors noted that, to control for potential type-1 error related to changes to the outcome measures, a more conservative p value, 0.01 instead of 0.05, was used. Several quality-of-life measures were also included in the trials. This includes the 6-item Headache Impact Test (HIT-6) and the Migraine Specific Quality of Life Questionnaire (MSQ v.2). Key findings of the 2 studies are described below.
PREEMPT 1 randomly assigned a total of 679 patients. (57) The mean number of migraine days during baseline was 19.1 in each group. The mean number of headache episodes during the 28-day baseline period was 12.3 in the Botox group and 13.4 in the placebo group. Approximately 60% of patients had previously used at least 1 prophylactic medication, and approximately 68% overused headache pain medication during baseline. A total of 296/341 (87%) in the Botox group and 295/338 (87%) in the placebo group completed the 24-week double-blind phase. The primary outcome, change from baseline in frequency of headache episodes over a 28-day period, did not differ significantly between groups. The number of headache episodes decreased by a mean of 5.2 in the Botox group and 5.3 in the placebo group (p=0.344). Similarly, the number of migraine episodes did not differ significantly. There was a decrease of 4.8 migraine episodes in the Botox group and 4.9 in the placebo group, p=0.206. In contrast, there was a significantly greater decrease in the number of headache days and the number of migraine days in the Botox group compared to the placebo group. The decrease in frequency of headache days was 7.8 in the 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 quality of life in the Botox versus the placebo group. The proportion of patients with severe impact of headaches (i.e., HIT-6 score at least 60) in the Botox group decreased from 94% at baseline to 69% at 24 weeks and in the placebo group decreased from 95% at baseline to 80%. There was a between-group difference of 11%, p=0.001. The authors did not report scores on the Migraine Specific Quality (MSQ) of Life Questionnaire 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), and emotional (p<0.002). Adverse events were experienced by 203 patients (60%) in the Botox group and 156 patients (47%) in the placebo group. Eighteen patients (5%) in the Botox group and 8 (2%) in the placebo group experienced serious adverse events. Treatment-related adverse events were consistent with the known safety profile of Botox.

PREEMPT 2 randomly assigned a total of 705 patients. (58) The mean number of migraine days during baseline period was 19.2 in the Botox group and 18.7 in the placebo group. The mean number of headache episodes during the 28-day baseline period was 12.0 in the Botox group and 12.7 in the placebo group. Approximately 65% of patients had previously used at least 1 prophylactic medication, and approximately 63% overused headache pain medication during baseline. A total of 311/347 (90%) in the Botox group and 334/358 (93%) 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 than PREEMPT 1) differed significantly between groups and favored Botox treatment. The number of headache days decreased by a mean of 9.0 in the Botox group and 6.7 in the placebo group, a difference of 2.3 days per 28 days (p<0.001). The number of migraine days also decreased significantly, more in the Botox compared to the placebo groups, a mean of 8.7 versus 6.3 (p <0.001). In contrast to PREEMPT 1, there was a significantly greater decrease in headache episodes in the Botox group than the placebo group, 5.3 versus 4.6, p=0.003. Change in frequency of migraine episodes was not reported.

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

Also published in 2010 was a pooled analysis of findings from the PREEMPT 1 and PREEMPT 2 studies; this analysis was also industry-sponsored. (59) There were 688 patients in the Botox group and 696 in the placebo group in the pooled analysis of outcomes at week 24. In the combined analyses, there was a significantly greater reduction in change from baseline in frequency of headache days, migraine days, headache episodes and migraine episodes in the Botox compared to placebo groups. For example, the pooled change in frequency of headache days was a mean of 8.4 in
the Botox group and 6.6 in the placebo group, p<0.001. The mean difference in number of headache days over a 28-day data collection period was 1.8 (95% CI: 1.13 to 2.52). The pooled change in frequency of headache episodes was 5.2 in the Botox group and 4.9 in the placebo group, a relative difference of 0.3 episodes (95% CI: 0.17 to 1.17, p=0.009). Between-group differences, though statistically significant, were relatively small and may not be clinically significant. In the pooled analysis, the authors also reported the proportion of patients with at least a 50% decrease from baseline in the frequency of headache days at each time point (every 4 weeks from week 4 to week 24). For example, at week 24, the proportion of participants with at least a 50% reduction in headache days was 47.1% in the Botox group and 35.1% in the placebo group. In contrast, the difference in the proportion of patients experiencing at least a 50% reduction in headache episodes did not differ significantly between groups at 24 weeks or at most other time points, with the exception of week 8. The article did not report the proportion of participants who experienced at least a 50% reduction in migraine days or migraine episodes. The pooled analysis had statistically significant findings for the change in proportion of patients with severe headache impact according to the HIT-6 and change in MSQ questionnaire domains.

There are several issues worth noting regarding the methodology 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, 1 of the main secondary outcomes in PREEMPT 1, change in the number of migraine episodes, was not reported in the second trial; the authors did not discuss this omission. In addition, the individual studies did not include threshold response to treatment, e.g., at least a 50% reduction in headache or migraine frequency, as a key outcome. The pooled analysis did report response rates, but these were presented as secondary efficacy outcomes.

An editorial that discusses the findings of the PREEMPT studies commented that the majority of patients in both trials fulfilled criteria for medication overuse headache, and therefore many patients may have been experiencing secondary headaches rather than chronic migraines. (60) If patients did have secondary headaches, detoxification alone may have been a sufficient treatment to change their headache pattern to an episodic one. Another opinion piece, published after the PREEMPT 1 and 2 studies, mentioned that the clinical relevance of less than a 2-day difference in reduction in number of headache days is uncertain. (61) The author of the second article noted, though, that this degree of reduction in headache days is similar to that previously found in several medication trials.

The published evidence does not suggest that botulinum toxin improves net health outcome for patients with an episodic pattern of migraines (i.e., fewer than 15 episodes per month); thus it is considered investigational. There were 2 published studies (PREEMPT 1 and 2) on Botox for chronic migraine (at least 15 episodes per month); these were conducted by the same research group, were industry-sponsored, and had nearly identical designs. The PREEMPT 1 and 2 had a number of statistically significant findings, but the clinical significance of these results was unclear. The proportion of patients who responded to treatment was reported in the pooled analysis but not in the individual trials. Based on data from the PREEMPT trials, FDA approval, and clinical input obtained in 2010, botulinum toxin is considered medically necessary for the prevention of chronic migraine in certain situations, i.e., patients diagnosed with chronic migraine who failed trials of other medications.

An RCT by Cady and colleagues that was identified in the 2011 literature search does not change previous conclusions about botulinum toxin for prevention of chronic migraine. (62) The study included patients who met ICHD-2 criteria for chronic migraine; patients were not required to have failed previous trials of medication. Patients were randomized to receive treatment with Botox (n=29) or topiramate (n=30). At the 12-week follow-up, the end of the double-blind phase of the study, treatment effectiveness did not differ significantly between groups. For the primary endpoint, Physician Global Assessment at week 12, physicians noted improvement in 19 of 24 (79%) in the Botox group and 17 of 24 (71%) in the topiramate group; 9 patients (15%) were not available for this analysis.

Tension headache. Nine RCTs of botulinum toxin for treatment of chronic tension-type headaches have been published. The studies included in the AAN assessment (63-66) are described in Table E-4 of the AAN supplemental information (available online at: http://www.neurology.org/content/vol70/issue19/images/data/1707/DC1/Tables_e-1_to_4.doc). The
type of agent was not specified for the headache trials. Other RCTs in the treatment of tension headache include Smuts et al. 1999, (67) Rollnik et al. 2000, (68) Rollnik et al. 2002, (69) Rollnik et al. 2001, (70) Schmitt et al. 2001, (71) and Straube et al. 2008. (72) Two were rated AAN Class I, 3 rated Class II, and 4 Class IV. Five trials enrolled fewer than 20 patients per treatment arm. One very small Class III trial reported statistically significant differences favoring treatment in change in mean tenderness and in headache severity; another small Class III trial reported a significantly higher percentage of patients with a greater than 50% decrease in headache score. All other trials reported no significant difference between trial arms for the primary outcome. Thus, the higher quality evidence for this indication shows no significant effect for botulinum toxin treatment of chronic tension-type headache, and botulinum toxin is considered investigational.

**Chronic daily headache.** Although this category is not recognized in the International Classification of Headache Disorders, it is commonly defined to include different kinds of chronic headache such as chronic or transformed migraine and daily persistent headache and may also include chronic tension-type headache, addressed separately here. The studies included in the AAN assessment (73-76) are described in Table E-4 of the AAN supplemental information (available online at: http://www.neurology.org/content/vol70/issue19/images/data/1707/DC1/Tables_e-1_to_4.doc). An additional RCT in the treatment of chronic daily headache published since the AAN assessment is Freitag et al. 2008. (77) All were rated AAN Class II, enrolled at least 20 patients per treatment arm, and administered botulinum toxin A, including doses in the range of 100–200 U. Two studies reported significant improvement in primary outcomes, while the other 3 reported no significant differences. The evidence is conflicting and insufficient for conclusions; thus this remains an investigational indication.

**Cluster headache.** No controlled trials have been reported on this type of headache.

**Cervicogenic Headache.** Three RCTs, published between 2000 and 2008, randomly assigned patients with chronic headache related to whiplash injury to botulinum toxin A treatment or placebo. (78-80) One trial reported trends toward improvement with treatment for various outcomes; most were not statistically significant. (80) Another reported no significant differences in any of several pain-related outcomes. (79) One trial reported a significant improvement in pain with treatment while the placebo group reported no improvement, but the study design was flawed in that the placebo group reported less pain at baseline. (78) The evidence from these trials is conflicting and insufficient for conclusions. A Cochrane Review of treatment of mechanical neck disorders, published in 2007, (81) included 6 RCTs (total N=273) of botulinum toxin compared to placebo for chronic neck disorders with or without radicular findings or headache. A meta-analysis of 4 studies (total N=139) for pain outcomes gave a nonsignificant result. The authors concluded that a range of doses have not shown significant differences compared to placebo or to each other. Thus, botulinum toxin is considered investigational for this indication.

**Myofascial Pain Syndrome**

Painful muscles with increased tone and stiffness containing trigger points characterize myofascial pain syndrome. Patients are often treated with injections of the trigger points with saline, dilute anesthetics, or dry needling. These trigger-point injections, while considered established therapy, have been controversial, since it is unclear whether any treatment effect is due to the injection, dry needling of the trigger point, or a placebo effect. Seven randomized, blinded, placebo-controlled clinical trials of botulinum toxin versus placebo for cervicothoracic myofascial pain syndrome have been reported. All trials injected botulinum toxin or placebo into trigger points in the upper back, shoulder, and/or cervical muscles. Total botulinum toxin doses varied considerably across trials as did numbers of patients enrolled (n=20 to 132) and methods of pain assessment. Five trials reported no significant differences in response between treatment and placebo. (82-86) The majority of trials specified that botulinum toxin A was used. One trial, administering high-dose botulinum toxin versus placebo, reported significant differences in pain relief at marginal p values. (87) The last trial reported significant differences in only a few of several outcome measures. (88)

Two RCTs compared botulinum toxin to dry needling and to lidocaine or bupivacaine injection. In one trial published in 2005, lidocaine trigger point injection was significantly more effective than dry
needling but significantly less effective than botulinum toxin. (89) In the other, both bupivacaine and botulinum toxin A were similarly effective and not significantly different. (90)

Three studies addressed another form of myofascial pain, piriformis syndrome, characterized by buttock tenderness and sciatica. One study of 9 patients compared botulinum toxin with placebo, finding that postinjection pain scores were significantly improved in the treatment group for only 1 of 4 pain domains, while none improved in the placebo group. (91) Another study of 36 patients had a high loss to follow-up (23%) and found that the botulinum toxin group had a significantly higher proportion, with 50% or greater reduction in pain on each of the last 2 follow-up visits, compared with placebo. (92) These small and flawed studies, both published in 2002, do not establish that the effects of botulinum toxin exceed those of placebo. A third study from 2000, comparing botulinum toxin with methylprednisolone, found better results for the former, but placebo effects were not considered. (93) The evidence for piriformis myofascial pain syndrome does not support conclusions about the effects of botulinum toxin.

One RCT enrolled patients with myofascial pain related to bruxism; while subjective and objective improvements in several outcomes measures were reported favoring treatment versus placebo, none was significant. (94)

A 2007 systematic review (95) selected RCTs of myofascial trigger-point injection; use of the Oxford Pain Validity Scale was also a selection criterion. Five trials were included; 1 trial resulted in a significant effect, whereas the other 4 did not. The data were described as “limited and clinically heterogeneous,” and the authors concluded that the evidence did not support the use of botulinum toxin A injections in trigger points for myofascial pain. A 2011 meta-analysis of four trials comparing botulinum toxin to placebo for chronic myofascial neck pain did not find a statistically significant short-term difference between groups. (96) The pooled standard mean difference (SMD) was -0.21 (95% CI=-0.50 to 0.70). These four trials were considered to have high validity; that is they scored at least 6 on a 12-point risk of bias instrument used by the Cochrane collaboration. All of the four trials were cited previously in this policy (83, 86-88). Due to the lack of consistent evidence of benefit, botulinum toxin is considered investigational for treatment of myofascial pain syndrome.

**Wound Healing and Pain Control**

Three small RCTs of botulinum toxin intrasphincter injection for controlling pain after hemorrhoidectomy have been published. Davies and colleagues evaluated 50 patients and showed marginal improvement in pain control at days 6 and 7 by patient visual analogy scale (p=0.05) with Botox injections; there was no significant difference in morphine or analgesic use. (97) A 2005 article describes a study by Patti and colleagues (n=30) who randomly assigned patients to 20 U botulinum toxin or saline injection and reported significantly decreased duration of postoperative pain at rest and during defecation in the treated group. (98) A 2006 study by Patti and colleagues, which also included 30 patients, found significant differences in postoperative maximum resting pressure change from baseline comparing botulinum toxin treatment to topical glyceryl nitrate (p<0.001; resting pressure is increased after surgery and may be responsible for pain). (99) In addition, there was a significant reduction in postoperative pain at rest (p=0.01) but not during defecation. There was no difference in time of healing. These small studies suggest improvement in pain control; however, differences may be small and need confirmation in larger trials.

In 2006, Gassner and colleagues conducted a small, RCT of botulinum toxin-induced immobilization of facial lacerations to improve wound healing compared to placebo (n=31). (100) The outcome was determined by blinded assessment of photographs of wound healing at intervals using a VAS. The authors report enhanced wound healing in the treatment arm (8.9 vs. 7.2, p=0.003). These results conflict with the wound-healing outcome after hemorrhoidectomy, as reported in 2006 by Patti and colleagues. Additional studies are necessary to identify indications and confirm improved outcomes; thus, botulinum toxin is considered investigational for wound healing.

**Pelvic and Genital Pain in Women**

One double-blind, randomized, placebo-controlled trial evaluated 60 patients with chronic pelvic pain and pelvic floor spasm. (101) Patients received injections of either botulinum toxin A or placebo. Pain
scores were reduced for both groups, but there were no significant differences between groups. The trial likely was underpowered to detect clinically significant differences in outcomes between groups. Other studies include a small, open-label trial from 2006 that tested botulinum toxin A injections in painful vulvar tissue to alleviate provoked vestibulodynia (n=19). (102) Patients receiving either of 2 doses had significantly reduced pain compared to baseline for 8 (lower dose) to 14 weeks (higher dose). A prospective cohort study tested different doses of botulinum toxin in 12 women with pelvic floor muscle hypertonicity and history of chronic pelvic pain. (103) Compared to baseline, there were nonsignificant reductions in pelvic pain and nonsignificant improvements in quality of life. The evidence is insufficient for this indication.

Neuropathic Pain after Neck Dissection

Two open-label trials of 16 and 23 patients who had failed conservative therapy investigated various doses of botulinum toxin A injected into the area of complaint. (104, 105) For both studies, which were conducted by the same group, results indicated significant reductions in pain compared to baseline and trends toward improved quality of life. However, lack of a randomized, placebo-controlled study design to control for strong placebo effects in pain therapy render these studies inconclusive.

Lateral Epicondylitis and Other Joint Pain

In 2005, Wong and colleagues reported on the results of a double-blind, placebo-controlled trial that randomly assigned 60 patients with lateral epicondylitis of at least 3 months’ duration to receive either a single intramuscular injection of botulinum toxin or placebo, targeted at the tender spot in the elbow. (106) In the botulinum group, the mean VAS improved from 65.5 mm to 25.3 mm at 4 weeks, compared to a change of 66.2 mm to 50.5 mm in the placebo group, a statistically significant difference. Mild paresis was reported in 4 patients in the botulinum group. In a similarly designed study of 40 patients, published in 2005, Hayton and colleagues reported no treatment effect at 3 months. (107) However, the injection site was targeted at 5 cm distal to the most tender spot and a different formulation of botulinum toxin was used. In a randomized, blinded, placebo-controlled trial of 130 patients, a single injection of botulinum toxin A into the painful origin of the forearm extensor muscles was tested versus placebo. (108) Treated patients were significantly improved overall at weeks 2, 6, 12, and 18. Continuous pain was significantly improved in the treated group only at weeks 6 and 18; maximum pain showed no improvement compared to placebo.

Two case series of patients with chronic joint pain refractory to conservative management studied the effect of botulinum toxin A injections (one series specified that Dysport was used) into several joints of patients with arthritis and into the knee joint of patients with chronic knee pain. (109, 110) Both reported significant improvement in joint pain and function compared to baseline, lasting for 3–12 months. Although the results of several trials of botulinum toxin injections into joints for chronic pain tend to favor treatment, some results are contradictory. Due to the lack of consistent findings from well-designed studies, botulinum toxin for treatment of lateral epicondylitis and other joint pain is considered investigational.

Tinnitus

In 2005, Stidham and colleagues explored the use of botulinum toxin A injections for tinnitus treatment under the theory that blocking the autonomic pathways could reduce the perception of tinnitus. (111) In this study, 30 patients were randomly assigned in a double-blind study to receive either 3 subcutaneous injections of botulinum toxin A around the ear followed by placebo injections 4 months later, or placebo injections first, followed by botulinum toxin A. The authors reported that 7 patients had reduced tinnitus after the botulinum toxin A injections, which was statistically significant when compared to the placebo groups in which only 2 patients reported reduced tinnitus (p<0.005). The tinnitus handicap inventory scores were also significantly decreased between pretreatment and 4 months post-botulinum toxin A injections. However, no other significant differences were noted when comparing the 2 treatments at 1 and 4 months after injections. The authors noted larger studies are needed. Also, study limitations, including size and lack of intention-to-treat analysis limit interpretation of results. Due to insufficient evidence from large randomized trials, botulinum toxin for tinnitus is considered investigational.
Antibody Testing for Botulinum Toxin Resistance

Rare patients have no response to initial administration of botulinum toxin (primary resistance) and a small percentage of adult patients develop secondary resistance after long-term treatment. Reasons for resistance include injection of incorrect muscles, unrealistic expectations of a complete cure, and interference from associated disorders that interfere with perception of response. (112) In approximately 3–10% of adult patients, true secondary resistance arises due to the development of antibodies that specifically neutralize the activity of botulinum toxin. (e.g., 113,114) That neutralizing antibodies directly cause resistance has been shown in a case study in which a patient with severe dystonia, secondary resistance, and detectable neutralizing antibodies was treated with repeated plasma exchange and depletion of serum antibodies; subsequent treatment with the same botulinum toxin type was successful. (115) Non-neutralizing antibodies may also develop in patients but have no effect on outcomes. The predisposing factors are not completely understood but include use of higher doses, shorter intervals between repeat treatments, and younger age. (116) In 2 studies of pediatric patients treated for spasticity, neutralizing antibodies were detected in 28–32% of patients. (117,118) Recommendations for avoiding eventual resistance are to use the lowest dose possible to obtain a clinical response, and schedule intervals of 10–12 weeks between injections, if possible.

Patients who develop secondary resistance to botulinum toxin A may stop treatment for several months and then undergo retreatment with likely success; however, the duration of response is often short, as neutralizing antibodies may re-develop quickly. (119) Alternatively, the patient may be administered botulinum toxin B, with which neutralizing antibodies to toxin A will not interfere. However, the duration of effect is shorter, and adverse effects have occurred at higher frequencies than for botulinum toxin A. (116,120)

Confirmation of neutralizing antibodies to botulinum toxin A in research studies has most often been accomplished with either protection of mice from lethal doses of toxin with injection of patient serum (121) or with an in vitro toxin-neutralizing assay based on a mouse diaphragm nerve-muscle preparation. (122) While sensitive, neither assay is appropriate for a clinical laboratory setting. Other assay formats have been explored, such as immunoprecipitation, Western blot, and enzyme-linked immunosorbent assay (ELISA). However, unless only the protein sequences that specifically react with neutralizing antibodies are employed, these formats detect both neutralizing and non-neutralizing antibodies (117,123,124) and would therefore result in significant numbers of false-positive results. Thus, the currently available testing approach is considered investigational. An option for some patients might be to inject toxin into the frontal muscle above one eyebrow; a toxin-responsive patient would have asymmetry of the forehead on attempted frowning, whereas, a nonresponsive patient would not. (123)

Chronic Pain after Lumpectomy

There are no relevant publications on the use of botulinum toxin for pain following lumpectomy.

Pain associated with breast reconstruction after mastectomy

No randomized controlled trials were identified evaluating botulinum toxin for pain control after mastectomy and expander reconstruction. One published study was identified, an observational study published by Layeeque and colleagues in 2004. (125) The study included 48 patients who were undergoing mastectomy with tissue expander placement. Treatment selection was based on physician preference; 22 (46%) patients had Botox injections to prevent postoperative pain and 26 (54%) patients were treated without Botox. Botulinum toxin was injected into the pectoralis major, serratus anterior and rectus abdominis insertion. Pain was scored using a VAS of 0 to 10.

Pain-related outcomes tended to be better among patients who received Botox injections. Mean immediate postoperative pain was 3.09 (standard deviation [SD]=0.92) in the botulinum toxin group and 6.80 (SD=1.98) in the standard treatment group, p<0.0001. The mean dose of morphine used during the first 24 hours was 3.27 mg (SD=3.18) in the Botox group and 17.15 (SD=10.40) in the standard treatment group, p<0.0001. Among the other outcomes, mean length of hospital stay was 26 hours (SD=8) in the Botox group and 37 hours (SD=19) in the standard treatment group; this difference was statistically significant, p=0.015. A limitation of the study was that it was not
randomized, and there may have been differences between groups that affected outcomes. Findings have not been replicated in large observational studies or RCTs using any of the FDA-approved formulations of botulinum toxin. Thus, botulinum toxin injection to prevent pain associated with breast reconstruction after mastectomy is considered investigational.

Hirschsprung’s Disease

The published literature consists of small case series. (126-128) The largest prospective case series, published by Minkes and Langer in 2000, included 18 children (median age=4 years) with persistent obstructive symptoms after surgery for Hirschsprung’s disease. (126) Patients received injections of botulinum toxin (Botox) into 4 quadrants of the sphincter. The total dose of botulinum toxin during the initial series of injections was 15 U to 60 U. Twelve of 18 (67%) patients experienced improvement for more than 1 month and the remaining 6 (33%) either showed no improvement or improved for less than 1 month. Ten children had 1-5 additional injections due to either treatment failure or recurrence of symptoms; re-treatment was not based on a standardized protocol.

A 2011 series by Patrus and colleagues retrospectively reviewed outcomes in 22 patients with Hirschsprung’s disease treated over 10 years who had received a median of 2 (range 1-23) botulinum toxin injections for post-surgical obstructive symptoms. (127) The formulation of botulinum toxin was not specified. Median follow-up (time from first injection to time of chart review) was 5.0 years (range 0 to 10 years). At the time of chart review, 2 of 22 patients (9%) had persistent symptoms. Eighty percent of children had a “good response” to the initial treatment (not defined) and 69% had additional injections. The authors reported that the number of hospitalizations for obstructive symptoms decreased significantly after botulinum toxin injection (median=0) compared to pre-injection (median=1.5), p=0.003. The authors did not report whether or not patients received other treatments during the follow-up period in either case series. A limitation of the case series study design is that it lacks a control group. Due to the lack of controlled studies showing benefit, this indication is considered investigational.

Gastroparesis

A systematic review of the literature, published in 2010, identified a total of 15 studies on botulinum toxin injection to treat gastroparesis. (129) Two of the studies were RCTs; the remainder were case series or open-label observational studies. The authors stated that, while the non-randomized studies generally found improvement in subjective symptoms and gastric emptying after botulinum toxin injections, the RCTs did not confirm the efficacy of botulinum toxin for treating gastroparesis. The authors concluded that there is insufficient evidence to recommend botulinum toxin for gastroparesis. Brief descriptions of the 2 RCTs are as follows:

In 2007, Arts and colleagues published a randomized cross-over study with 23 patients. (130) The study included consecutive patients at a single institution who had symptoms suggestive of gastroparesis and established delayed gastric emptying for solids and liquids. Patients received, in random order, injections of Botox or saline during gastrointestinal endoscopies, with a 4-week interval between injections. Symptoms were assessed using the Gastroparesis Cardinal Symptom Index (GCSI), which has a maximum score of 45. When data from both groups were combined, there were no statistically significant differences in improvement after botulinum toxin injection or saline injection for either solid or liquid emptying times. For example, liquid half emptying time was 8.2 (SD=13.7) minutes after Botox injection and 22.5 (SD=7.7) minutes after saline injection, p>0.05. In addition, in pooled analyses, the total GCSI score did not differ significantly after Botox compared to saline treatment (mean GCSI=6.1 and 3.8, respectively, p>0.05).

The other RCT, published in 2008, was a single center double-blind trial with 32 patients. (131) Patients had symptoms consisting of delayed gastric emptying and had a GCSI score of 27 or higher. They received an injection of either Botox (n=16) or saline placebo (n=16). All patients completed the study. Patients were evaluated with gastric emptying scintigraphy (GES) prior to treatment and at a 1-month follow-up. The proportion of patients with at least a 9-point reduction in the GES at 1 month, the primary endpoint, was 6 of 16 (37.5%) in the Botox group and 9 of 16 (56.3%) in the placebo group; the difference between groups was not statistically significant. Improvement in gastric emptying after 1 month, a secondary endpoint, also did not differ significantly between groups.
Physician Specialty Society and Academic Medical Center Input

In response to requests, clinical input was received on this policy when it was under review in 2008 and again in 2010. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. In 2008, input was received on a number of indications from 5 physician specialty societies and 3 academic medical centers while this policy was under review in 2008. Nearly all reviewers who provided input agreed with the investigational determination for use in headaches and on the investigational role for antibody testing. Among the 4 reviewers who commented on use in sialorrhea, 2 reviewers felt this was medically necessary and 2 disagreed. In 2010, input was received only on botulinum toxin for migraine from 4 physician specialty societies (7 reviews) and 4 academic medical centers. The majority of reviewers agreed with the investigational indication for episodic migraine. Several reviewers thought that botulinum toxin was medically necessary in patients with disabling and/or frequent episodic migraines that were refractory to other treatments. Clinical input was more divergent for use of botulinum toxin for chronic migraine; some agreed that use was investigational and others did not. Reviewers who thought that botulinum toxin was medically necessary for patients with chronic migraines generally thought its use should be limited to patients unresponsive to other treatments.

References:

65. Reid SM, Johnstone BR, Westbury C, et al. Randomized trial of botulinum toxin injections into the salivary glands to reduce drooling


<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>31513</td>
<td>Laryngoscopy, indirect, with vocal cord injection</td>
</tr>
<tr>
<td></td>
<td>31570</td>
<td>Laryngoscopy, direct, with injection into vocal cords, therapeutic</td>
</tr>
<tr>
<td></td>
<td>31571</td>
<td>Laryngoscopy, direct, with injection into vocal cords, therapeutic; with operating microscope or telescope</td>
</tr>
<tr>
<td></td>
<td>43201</td>
<td>Esophagoscopy, rigid or flexible; diagnostic with or without collection of specimen(s) by brushing or washing, with directed submucosal injection(s) any substance</td>
</tr>
<tr>
<td></td>
<td>43236</td>
<td>Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum or jejunum as appropriate; diagnostic, with or without washing, with directed submucosal injection(s) any substance</td>
</tr>
<tr>
<td></td>
<td>46505</td>
<td>Chemodenervation of internal anal sphincter</td>
</tr>
<tr>
<td></td>
<td>52287</td>
<td>Cystourethroscopy, with injection(s) for chemodenervation of the bladder (new code 1/1/13)</td>
</tr>
<tr>
<td></td>
<td>64611</td>
<td>Chemodenervation of parotid and submandibular salivary glands, bilateral (new code 1/1/11)</td>
</tr>
<tr>
<td></td>
<td>64612</td>
<td>Chemodenervation of muscle(s); innervated by facial nerve (e.g., for blepharospasm or hemifacial spasm)</td>
</tr>
<tr>
<td></td>
<td>64615</td>
<td>; muscle(s) innervated by facial, trigeminal, cervical spinal and accessory nerves, bilateral (e.g., for chronic migraine) (new code 1/1/13)</td>
</tr>
<tr>
<td></td>
<td>64616</td>
<td>; neck muscle(s), excluding muscles of the larynx, unilateral (e.g., for cervical dystonia, spasmodic torticollis) (new code 1/1/14)</td>
</tr>
<tr>
<td></td>
<td>64617</td>
<td>; larynx, unilateral, percutaneous (e.g., for spasmodic dysphonia), includes guidance by needle electromyography, when performed (new code 1/1/14)</td>
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<tr>
<td></td>
<td>64642-64645</td>
<td>Chemodenervation of one extremity code range (new codes 1/1/14)</td>
</tr>
<tr>
<td></td>
<td>64646-64647</td>
<td>Chemodenervation of trunk muscle(s) code range (new codes 1/1/14)</td>
</tr>
<tr>
<td></td>
<td>67345</td>
<td>Chemodenervation of extraocular muscle</td>
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<td>HCPCS</td>
<td>J0585</td>
<td>Injection, onabotulinumtoxinA, 1 unit</td>
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<td></td>
<td>J0586</td>
<td>Injection, abobotulinumtoxinA, 5 units</td>
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<tr>
<td></td>
<td>J0587</td>
<td>Injection, rimabotulinumtoxinB, 100 units</td>
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<tr>
<td></td>
<td>J0588</td>
<td>Injection, incobotulinumtoxinA, 1 unit</td>
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<td>ICD-10-CM (effective 10/1/15)</td>
<td>G11.4</td>
<td>Hereditary spastic paraplegia</td>
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<td>G24.01-G24.9</td>
<td>Dystonia code range (includes blepharospasm)</td>
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<td></td>
<td>G35</td>
<td>Multiple sclerosis</td>
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<tr>
<td></td>
<td>G51.0-G51.9</td>
<td>Facial nerve disorders (includes disorders of the 7th cranial nerve)</td>
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<td></td>
<td>G80.0-G80.9</td>
<td>Cerebral palsy code range</td>
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<td></td>
<td>G81.10-G81.14</td>
<td>Spastic hemiplegia code range</td>
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<tr>
<td></td>
<td>G82.50-G82.54</td>
<td>Quadriplegia</td>
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<td>G83.0</td>
<td>Diplegia, of upper limbs</td>
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<td></td>
<td>G83.20-G83.24</td>
<td>Monoplegia, of upper limb</td>
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<td></td>
<td>G83.30-G83.34</td>
<td>Monoplegia, unspecified</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
<td></td>
</tr>
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<td>------------------------------------------------------------------</td>
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<tr>
<td>G83.81</td>
<td>Brown-Sequard, syndrome</td>
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<td>G83.82</td>
<td>Anterior cord syndrome</td>
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<tr>
<td>G83.89</td>
<td>Other specified paralytic syndromes</td>
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<td>G83.9</td>
<td>Paralytic syndrome, unspecified</td>
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<td>G43.011;</td>
<td>Migraine without aura, intractable codes</td>
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<td>G43.019</td>
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<td>G43.111;</td>
<td>Migraine with aura, intractable codes</td>
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<td>G43.119</td>
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<td>G43.411;</td>
<td>Hemiplegic migraine, intractable codes</td>
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<td>G43.419</td>
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<td>G43.511;</td>
<td>Persistent migraine aura without cerebral infarction, intractable</td>
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<tr>
<td>G43.519</td>
<td>codes</td>
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<tr>
<td>G43.611;</td>
<td>Persistent migraine aura with cerebral infarction, intractable</td>
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<tr>
<td>G43.619</td>
<td>codes</td>
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<tr>
<td>G43.711;</td>
<td>Chronic migraine without aura, intractable codes</td>
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<tr>
<td>G43.719</td>
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<td></td>
</tr>
<tr>
<td>G43.701;</td>
<td>Chronic migraine without aura, not intractable</td>
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</tr>
<tr>
<td>G43.709</td>
<td></td>
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<tr>
<td>G43.b11;</td>
<td>Ophthalmoplegic migraine, intractable codes</td>
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<tr>
<td>G43.b19</td>
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<tr>
<td>G43.d11;</td>
<td>Menstrual migraine, intractable codes</td>
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<tr>
<td>G43.d19</td>
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<tr>
<td>G43.811;</td>
<td>Other migraine, intractable codes</td>
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<tr>
<td>G43.819</td>
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<tr>
<td>G43.911;</td>
<td>Migraine, unspecified, intractable codes</td>
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<td>G43.919</td>
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<tr>
<td>G80.0-G80.9</td>
<td>Cerebral palsy code range</td>
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<td>G81.10-G81.14</td>
<td>Spastic hemiplegia code range</td>
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<td>H49.00 –</td>
<td>Strabismus code range</td>
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<td>H50.9</td>
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<td>H51.0-H51.8</td>
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<td></td>
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<tr>
<td>I69.951 –</td>
<td>Hemiplegia and hemiparesis following unspecified cerebrovascular</td>
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<tr>
<td>I69.959</td>
<td>disease code range</td>
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<tr>
<td>K11.7</td>
<td>Disturbances of salivary secretion</td>
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</tr>
<tr>
<td>K22.0</td>
<td>Achalasia of cardia</td>
<td></td>
</tr>
<tr>
<td>K60.1</td>
<td>Chronic anal fissure</td>
<td></td>
</tr>
<tr>
<td>N31.9</td>
<td>Neuromuscular dysfunction of bladder, unspecified</td>
<td></td>
</tr>
<tr>
<td>N32.81</td>
<td>Overactive bladder</td>
<td></td>
</tr>
<tr>
<td>N39.81</td>
<td>Urge incontinence</td>
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<tr>
<td>R25.0 – R25.9</td>
<td>Abnormal involuntary movements code range</td>
<td></td>
</tr>
</tbody>
</table>

ICD-10-PCS codes are used for inpatient services only.

Administration, physiological systems and anatomical regions, introduction, muscle, percutaneous, codes for serum, toxoid and vaccine, or other therapeutic substance
This Medical Policy is designed for informational purposes only and is not an authorization, an explanation of benefits, or a contract. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there is any exclusion or other benefit limitations applicable to this service or supply. Medical technology is constantly changing and Blue Cross and Blue Shield of Kansas City reserves the right to review and revise medical policy. This information is proprietary and confidential and cannot be shared without the written permission of Blue Cross and Blue Shield of Kansas City.

**Appendix**
Listing of medically necessary indications with support from published studies, by agent:

<table>
<thead>
<tr>
<th>Agent</th>
<th>Botox (OnabotulinumtoxinA)</th>
<th>Dysport (AbobotulinumtoxinA)</th>
<th>Xeomin (IncobotulinumtoxinA)</th>
<th>Myobloc (RimabotulinumtoxinB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication (additional specificity included in policy)</td>
<td>Off-label</td>
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<td></td>
<td></td>
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<tr>
<td>--------------------------------------------------------</td>
<td>-----------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Esophageal achalasia</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Anal Fissure (chronic)</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Incontinence due to detrusor overactivity (urge): idiopathic causes</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Sialorrhea associated with Parkinson disease</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Focal dystonias**

<table>
<thead>
<tr>
<th>Focal upper limb dystonia</th>
<th>Yes</th>
<th>Yes</th>
<th>No</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laryngeal dystonia</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Condition</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td>-----------------------------------------------</td>
<td>-----</td>
<td>-----</td>
<td>----</td>
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</tr>
<tr>
<td>Idiopathic torsion dystonia</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Spastic conditions</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Spasticity related to stroke</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (upper limb)</td>
<td>No</td>
</tr>
<tr>
<td>Acquired spinal cord or brain injury</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Hereditary spastic paraparesis</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Spastic hemiplegia</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Neuromyelitis optica</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Labeled (at least one)</td>
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</tr>
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<td>No</td>
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<tr>
<td>Blepharospasm (Botox and Xeomin)</td>
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<tr>
<td>Cervical dystonia (All agents)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Strabismus (Botox)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Upper limb spasticity (Botox and Dysport)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (due to stroke)</td>
<td>No</td>
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<tr>
<td>Incontinence due to detrusor overactivity (urge): neurogenic causes (Botox)</td>
<td>Yes</td>
<td>Yes</td>
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<td>No</td>
</tr>
<tr>
<td>Incontinence due to detrusor overactivity (urge) idiopathic causes (Botox)</td>
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<td></td>
<td></td>
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<tr>
<td>Chronic migraine (Botox)</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
For articles published prior to 2000, if the abstract did not specify type of agent, it was assumed that Botox (OnabotulinumtoxinA) was used (the only FDA-approved agent until 2000). For articles published 2000 or later, if the text of the article only stated that botulinum toxin or botulinum toxin A was used, it was assumed that Botox was used.

The level of data in support of the agents was generally randomized controlled trials or other comparative studies; for rare conditions there were sometimes only case series. When randomized controlled trials using Botox were available, case series for other indications were acceptable. Case reports and a single small case series (i.e. less than n=20) were considered to be insufficient data.

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