Title: Botulinum Toxin (BT)

See also: Treatment of Hyperhidrosis medical policy
          Treatment of Tinnitus medical policy

Professional
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June 1, 1999; January 1, 2001;
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December 29, 2004; October 5, 2005;
November 3, 2005; December 15, 2005;
March 10, 2006; May 31, 2006;
July 18, 2006; October 1, 2006;
October 19, 2007; July 18, 2008
January 1, 2010; February 25, 2011;
May 13, 2011; December 9, 2011;
January 1, 2012; January 15, 2013;
January 30, 2014; April 15, 2014;
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March 29, 2017
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Original Effective Date: June 3, 2004
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January 1, 2012; January 15, 2013;
January 30, 2014; April 15, 2014;
January 1, 2015; February 19, 2016;
July 1, 2016; October 1, 2016;
March 29, 2017
Current Effective Date: March 29, 2017

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Medical Policies of that plan.
<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are: Botulinum toxin injections</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With dystonia or spasticity resulting in functional impairment and/or pain</td>
<td></td>
<td>• Conservative measures</td>
<td>• Symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Medication</td>
<td>• Functional outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Medication use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Treatment-related morbidity</td>
</tr>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are: Botulinum toxin injections</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With strabismus</td>
<td></td>
<td>• Conservative measures</td>
<td>• Symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Surgery</td>
<td>• Functional outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Treatment-related morbidity</td>
</tr>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are: Botulinum toxin injections</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With blepharospasm or facial nerve (VII) disorders</td>
<td></td>
<td>• Conservative measures</td>
<td>• Symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Surgery</td>
<td>• Functional outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Treatment-related morbidity</td>
</tr>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are: Botulinum toxin injections</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With chronic migraine headache</td>
<td></td>
<td>• Complementary treatment (eg, acupuncture)</td>
<td>• Symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Laparoscopic myotomy</td>
<td>• Medication use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Medication</td>
<td>• Treatment-related morbidity</td>
</tr>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are: Botulinum toxin injections</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With esophageal achalasia</td>
<td></td>
<td>• Pneumatic dilation</td>
<td>• Symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Laparoscopic myotomy</td>
<td>• Functional outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Medication</td>
<td>• Treatment-related morbidity</td>
</tr>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are: Botulinum toxin injections</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With sialorrhea associated with Parkinson disease</td>
<td></td>
<td>• Medication</td>
<td>• Symptoms</td>
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<tr>
<td></td>
<td></td>
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<td>• Functional outcomes</td>
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<td>• Treatment-related morbidity</td>
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<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
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<td>• Medication</td>
<td>• Symptoms</td>
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<td></td>
<td></td>
<td>• Functional outcomes</td>
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<td></td>
<td></td>
<td>• Treatment-related morbidity</td>
</tr>
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<td>Interventions of interest are: Botulinum toxin injections</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With internal anal sphincter achalasia</td>
<td></td>
<td>• Surgery</td>
<td>• Symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Health status measures</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Treatment-related morbidity</td>
</tr>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are: Botulinum toxin injections</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With chronic anal fissure</td>
<td></td>
<td>• Surgery</td>
<td>• Symptoms</td>
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<td></td>
<td></td>
<td></td>
<td>• Health status measures</td>
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<tr>
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<td></td>
<td></td>
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<tr>
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<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
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<td>• With urinary incontinence due to detrusor overactivity associated with neurogenic causes or overactive bladder</td>
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<td>• Conservative measures</td>
<td>• Symptoms</td>
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<td></td>
<td>• Medication</td>
<td>• Medication use</td>
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<tr>
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<tr>
<td>• With urologic issues other than detrusor overactivity or overactive bladder</td>
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<td>• Conservative measures</td>
<td>• Symptoms</td>
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<td>• Medication</td>
<td>• Medication use</td>
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<tr>
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<td>• With other indications (eg, musculoskeletal pain, postsurgical pain, neuropathic pain, tremors)</td>
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<td>• Conservative measures</td>
<td>• Symptoms</td>
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<td></td>
<td>• Medication</td>
<td>• Medication use</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>• Treatment-related morbidity</td>
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*Non–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 lypectomy, tremors such as benign essential tremor (upper extremity), tinnitus, chronic motor tic disorder and tics associated with Tourette syndrome, lateral epicondylitis, prevention of pain associated with breast reconstruction after mastectomy, Hirschsprung disease, gastroparesis, facial wound healing, and depression.
DESCRIPTION
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 drug 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®). Botox has been available for the longest time in the United States and has been the most widely used formulation. 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 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.

Among the botulinum toxin products, onabotulinumtoxinA (Botox) is FDA-approved for the largest number of indications. Other than the indications mentioned above, this includes axillary hyperhidrosis in adults and in individuals at least 12 years of age, blepharospasm and strabismus. On October 15, 2010, the FDA approved Botox injection for prevention of chronic migraine. Chronic migraine is defined as episodes that otherwise meet criteria for migraine (e.g., at least 4 hours in duration) that occur on at least 15 days per month for more than 3 months, in the absence of medication overuse. OnabotulinumtoxinA is also approved for treatment of urinary incontinence due to neurogenic conditions causing detrusor overactivity in patients unresponsive to or intolerant to anticholinergic medication. Most recently, in 2013, onabotulinumtoxinA received FDA approval for treatment of overactive bladder (OAB) in adults who are unresponsive to or intolerant to anticholinergic medication.

Xeomin is approved for treating blepharospasm in patients previously treated with onabotulinumtoxinA.
Three products, Botox (marketed as Botox Cosmetic) Dysport, and Xeomin are approved for temporarily improving the appearance of glabellar (frown) lines in adults. The botulinum toxin products have also been used for a wide variety of off-label indications.

**REGULATORY STATUS**

In 1991, Botox® (Allergan, Irvine, CA) was approved by the U.S. Food and Drug Administration (FDA). In 2000, Myobloc® (Solstice Neurosciences) was approved by FDA. In 2009, Dysport® (Medicis Pharmaceutical, Scottsdale, AZ) was approved by FDA. In 2010, Xeomin® (Merz Pharmaceuticals) was approved by FDA.¹
POLICY

A. The use of botulinum toxin may be considered **medically necessary** for the following:

1. 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*. (See additional details in Policy Guidelines.)

2. Strabismus*.

3. Blepharospasm or facial nerve (VII) disorders (including hemifacial spasm)*.

4. Upper limb spasticity*.

5. Dystonia/spasticity resulting in functional impairment (interference with joint function, mobility, communication, nutritional intake) and/or pain in patients with any of the following:
   a. Focal dystonias:  
      - Focal upper limb dystonia (e.g., organic writer’s cramp), or  
      - Oromandibular dystonia (orofacial dyskinesia, Meige syndrome), or  
      - Laryngeal dystonia (adductor spasmodic dysphonia), or  
      - Idiopathic (primary or genetic) torsion dystonia, or  
      - Symptomatic (acquired) torsion dystonia.
   b. Spastic conditions:  
      - Cerebral palsy, or  
      - Spasticity related to stroke, or  
      - Acquired spinal cord or brain injury, or  
      - Hereditary spastic paraparesis, or  
      - Spastic hemiplegia, or  
      - Neuromyelitis optica, or  
      - Multiple sclerosis or Schilder’s disease.

6. Esophageal achalasia in patients who have not responded to dilation therapy or who are considered poor surgical candidates.

7. Sialorrhea (drooling) associated with Parkinson’s disease.

8. Chronic anal fissure.

9. Urinary incontinence due to detrusor overreactivity associated with neurogenic causes (e.g., spinal cord injury, multiple sclerosis), that is inadequately controlled with anticholinergics*.

10. Prevention (treatment) of chronic migraine headaches in the following situations:*
   a. Initial 6-month trial. Adult patients who:
      - Meet International Classification of Headache Disorders (ICHD) 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 (e.g., antidepressants, antihypertensives, antiepileptics). Patients who have contraindications to preventive medications are not required to undergo a trial of these agents.

b. Continuing treatment beyond 6 months:
- 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.

11. Overactive bladder in adults unresponsive to or intolerant of anticholinergics*.

*FDA-approved indication for at least one of the agents.

B. With the exception of cosmetic indications, the use of botulinum toxin is considered experimental / investigational for all other indications not specifically mentioned above, including, but not limited to:
1. Headaches, except as noted above for prevention (treatment) of chronic migraine headaches.
2. Chronic low back pain.
4. Mechanical neck disorders.
5. Neuropathic pain after neck dissection.
7. Pain after hemorrhoidectomy or lumpectomy.
8. Tremors such as benign essential tremor (upper extremity).
9. Tinnitus (see separate policy on Treatment of Tinnitus).
10. Sialorrhea (drooling) except that associated with Parkinson's disease.
11. Chronic motor tic disorder (ICD-10 F95.1), and tics associated with Tourette's syndrome (motor tics) (ICD-10 F95.2).
12. Lateral epicondylitis.
15. Detrusor sphincteric dyssynergia (after spinal cord injury).
16. Anismus.
17. Gastroparesis.
18. Prevention of pain associated with breast reconstruction after mastectomy.
20. Facial wound healing.
22. Temporomandibular joint disorders.
23. Trigeminal neuralgia.
24. Depression.
C. The use of botulinum toxin as a treatment of wrinkles or other cosmetic indications is **noncovered**.

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

**Policy Guidelines**

1. **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.

2. **International Classification of Headache Disorders (ICHD-3)** diagnostic criteria for chronic migraine headache include the following:
   a. Headaches at least 15 days per month for more than 3 months; have features of migraine headache on at least 8 days.
   b. 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 photophonia

   (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.)

3. **Continuing treatment with botulinum toxin beyond 6 months for chronic migraine**: The policy includes the requirement that migraine headache frequency be reduced by at least 7 days per month compared to pretreatment level, or that migraine headache duration be reduced by at least 100 hours per month compared to 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 (15) that would allow them to meet the ICHD-2 diagnostic criteria for chronic migraine. A 50% reduction in frequency is a...
common outcome measure for assessing the efficacy of headache treatments and is one of the endpoints of the PREEMPT study.

**RATIONALE**

This policy was originally created in 1997 and was updated regularly with searches of the MEDLINE database. Most recently, the literature was reviewed through August 20, 2015. For studies published before 2000, it is assumed that Botox, the only FDA-approved agent at that time, was used.

**Dystonia/Spasticity**

This evidence review is based on a 1996 TEC Assessment (updated in 2004) that focused on the use of botulinum toxin for the treatment of focal dystonia or spasticity, the American Academy of Neurology (AAN) 2008 assessments of movement disorders and spasticity,2-4 and additional controlled trials and systematic reviews identified by MEDLINE literature searches.

The AAN assessments concluded that the evidence was AAN level A (established as effective, should be done) for equinus varus deformity in children with cerebral palsy and level B (probably effective, should be considered) for upper-extremity and 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.4

In a 2013 meta-analysis, Foley et al identified 16 randomized controlled trials (RCTs) comparing injection of botulinum toxin to placebo injections or a nonpharmacologic treatment of moderate-to-severe upper-extremity spasticity following stroke.5 Studies evaluated the impact of treatment on activity limitations. Ten trials with a total of 1000 patients had data suitable for pooling. In a pooled analysis of effect size, botulinum toxin was associated with a moderate treatment effect compared with other interventions (standardized mean difference [SMD], 0.54; 95% confidence interval [CI], 0.35 to 0.71; p<0.001). In another systematic review published in 2013, Baker et al pooled RCT data and found statistically significant benefit of botulinum toxin A for treating limb spasticity.6 Evidence was limited on botulinum toxin for spasticity-related pain.

A 2014 systematic review and meta-analysis by Marsh et al identified 18 studies evaluating botulinum toxin A for treatment of cervical dystonia; 5 were RCTs and the remainder were observational studies.7 A pooled analysis found the mean duration of effect of botulinum toxin to be 93.2 days (95% CI, 91.8 to 94.6 days) using the fixed-effects model and 95.2 days (95% CI, 88.9 to 101.4 days) using the random-effects model. Most studies included did not have control groups.

A 2015 systematic review by Dashtipour et al identified 16 RCTs and noncomparative controlled studies evaluating abobotulinumtoxinA (i.e., Dysport) in adults with upper-limb spasticity due to stroke.8 Total botulinum toxin dose ranged from 500 to 1500 U. The authors did not pool study
findings but did report that most studies found a statistically significant benefit of botulinum toxin on functioning, as measured by the Modified Ashworth Scale.

A relatively large RCT, published in 2011 by Shaw et al, randomized 333 patients with poststroke upper-limb spasticity to physical therapy plus Dysport (n=170) or physical therapy alone (n=163). 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 Motor Assessment Scale 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.

A European trial evaluated Xeomin for poststroke upper-limb spasticity. Kanovsky et al randomized 148 patients with poststroke upper-limb spasticity to Xeomin or placebo. After 4 weeks, a significantly higher response rate was found in all treated flexor muscle groups among patients given Xeomin compared with placebo. The treatment benefit lasted through the week-12 visit. An open-label extension of this study with 145 participants was published in 2011. Patients received up to 5 additional sets of Xeomin injections, with 12-week intervals between injections. A total of 111 patients (77%) had at least 3 injections and 72 (50%) had 4 injections. Outcomes were assessed 4 weeks after each injection. Compared with baseline, patients consistently showed improved outcomes at each posttreatment visit. None of the patients developed neutralizing antibodies in either the double-blind or extension phases of the study.

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

Strabismus
Strabismus is a condition in which the eyes are not in proper alignment. In 2012, a Cochrane review by Rowe et al evaluated the literature on botulinum toxin for strabismus. The investigators identified 4 RCTs, all of which were published in the 1990s. Three trials compared botulinum toxin injection with surgery, and 1 compared botulinum toxin injection with a noninvasive treatment control group. Among the trials that used surgery as a comparator intervention, 2 studies found no statistically significant differences in outcomes between the 2 groups, and 1 found a higher rate of a satisfactory outcome in the surgery group. The study comparing botulinum toxin 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 conducted a trial in 1999 that included 55 children with strabismus who remained symptomatic after surgical alignment. Patients were randomly assigned to receive a second surgery (28 patients) or botulinum toxin injection (n=27). Motor and sensory outcomes did not differ significantly in the 2 groups. At 3 years, for instance, 67.8% of children in the reoperation group and 59.2% of children in the botulinum toxin group were within 8 prism diopters of orthotropias (p=0.72). In 1994, Lee et al randomized 47 patients with acute unilateral sixth nerve palsy to botulinum toxin treatment or a
no treatment control group. The final recovery rate was 20 (80%) of 25 in the botulinum toxin group and 19 (86%) of 22 in the control group.

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

Blepharospasm
Blepharospasm is a progressive neurologic disorder characterized by involuntary contractions of the eyelid muscles; it is classified as a focal dystonia. RCTs have evaluated Botox, Dysport, and Xeomin for the treatment of blepharospasm and found these agents to be effective at improving symptoms. No RCTs that evaluated Myobloc for treating blepharospasm were identified in literature searches.

Section Summary: Blepharospasm
RCTs have found that botulinum toxin injection is an effective treatment of blepharospasm.

Headache
Botulinum toxin for treatment of pain from migraine and from chronic tension-type headaches was addressed in a 2002 TEC Assessment that was updated in 2004. Both Assessments concluded that the evidence was insufficient for either indication. Because of the typically high placebo response rate 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 variable in addition to pain or headache severity.

Migraine Headache
Migraines can be categorized according to headache frequency. According to the Second Edition of the International Headache Classification (ICHD-2), migraine without aura (previously known as common migraine) is defined as at least 5 attacks per month meeting other diagnostic criteria. Chronic migraine is defined as attacks on at least 15 days per month for more than 3 months, with features of migraine on at least 8 days per month.

Several RCTs and systematic reviews of RCTs have been published. In 2013, the Agency for Healthcare Research and Quality published a comparative effectiveness review on preventive pharmacologic treatments for migraine in adults. The investigators identified 15 double-blind RCTs evaluating botulinum toxin for migraine prevention: 13 used onabotulinumtoxinA and 2 used abobotulinumtoxinA. In a meta-analysis of 3 RCTs, onabotulinumtoxinA was found to be 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 was associated with a significantly higher rate of treatment discontinuation due to adverse effects than placebo (RR=3.2; 95% CI, 1.4 to 7.10). Five RCTs compared the efficacy of onabotulinumtoxinA with another medication (topiramate or divalproex sodium). Findings were not pooled, but, for the most part, there were no statistically significant differences in outcomes between the 2 drugs.
In 2012, Jackson et al conducted a meta-analysis of RCTs on botulinum toxin A for the prophylactic treatment of headache in adults; the analysis addressed migraines and other types of headache. The investigators included RCTs that were at least 4 weeks in duration, had reduction in headache frequency or severity as an outcome, and used patient-reported outcomes. The investigators categorized eligibility criteria as addressing episodic (<15 headaches/month) or chronic headache (at least 15 days/month). A total of 10 trials on episodic migraine and 7 trials on chronic migraine were identified. All trials on episodic migraine and 5 of 7 trials on chronic migraine were placebo-controlled; the other 2 trials compared botulinum toxin injections with oral medication. A pooled analysis for chronic migraine found a statistically significantly greater reduction in the frequency of headaches per month with botulinum toxin than a control intervention (absolute difference, -2.30; 95% CI, -3.66 to -0.94; 5 trials). In contrast, in a pooled analysis on episodic migraine, there was no statistically significant difference between groups in the change in monthly headache frequency (absolute difference, -0.05; 95% CI, -0.25 to 0.36).

Previously, in 2009, Shuhendler et al conducted a systematic review and meta-analysis of trials on botulinum toxin for treating episodic migraines. The investigators identified 8 randomized, double-blind, placebo-controlled trials evaluating the efficacy of botulinum toxin A injections. 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 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 that examined trials using low-dose botulinum toxin A (<100 U) separately from trials using high-dose botulinum toxin A (≥100 U) did not find a statistically significant effect of botulinum toxin 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) studies 1 and 2. Study 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 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 Botox injections 155 U or placebo, with 12 weeks between cycles. Randomization was stratified based on the frequency of acute headache pain medication used during baseline and whether patients overused acute headache pain medication. (Medication overuse was defined as baseline intake of simple analgesics on at least 15 days, or other medications for at least 10 days, and medication use at least 2 days per week.)

The primary end point in PREEMPT 1 was mean change from baseline in frequency of headache episodes for 28 days ending with week 24. A headache episode was defined as a headache with a start and stop time indicating that pain lasted at least 4 hours. Prespecified secondary outcomes included, among others, change in frequency of headache days (calendar days in which pain lasted at least 4 hours), migraine days (calendar days in which a migraine lasted at
least 4 hours), and migraine episodes (migraine with a start and stop time indicating that pain lasted at least 4 hours). Based on availability of data from PREEMPT 1 and other factors, the protocol of the PREEMPT 2 trial was amended (after study initiation but before unmasking) to make frequency of headache days the primary end point of this study. The authors noted that, to control for potential type I error related to changes to the outcome measures, a more conservative p value (0.01) was used. Several quality-of-life measures were also included in the trials. This included 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. 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 (87%) of 341 patients in the Botox group and 295 (87%) of 338 patients in the placebo group completed the 24-week double-blind phase. The primary outcome, change from baseline in frequency of headache episodes over a 28-day period, did not differ significantly between groups. The number of headache episodes decreased by a mean of 5.2 in the Botox group and 5.3 in the placebo group (p=0.344). Similarly, the number of migraine episodes did not differ significantly. There was a decrease of 4.8 migraine episodes in the Botox group and 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 with 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, ≥60) in the Botox group decreased from 94% at baseline to 69% at 24 weeks; in the placebo group, it decreased from 95% at baseline to 80%. There was a between-group difference of 11% (p=0.001). The authors did not report scores on the 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 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. Mean number of migraine days during baseline period was 19.2 in the Botox group and 18.7 in the placebo group. Mean number of headache episodes during the 28-day baseline period was 12.0 in the Botox group and 12.7 in the placebo group. Approximately 65% of patients had previously used at least 1 prophylactic medication and approximately 63% overused headache pain medication during baseline. A total of 311 (90%) of 347 patients in the Botox group and 334 (93%) of 358 patients in the placebo group completed the 24-week double-blind phase. The primary outcome, change from baseline frequency of headache days over a 28-day period (a different primary outcome from PREEMPT 1), differed significantly between groups and favored Botox treatment. The number of headache days decreased by a mean of 9.0 in the Botox group and 6.7 in the placebo group, a difference of 2.3 days per 28 days (p<0.001). The number of migraine days also decreased significantly, more in the Botox than in the placebo groups, a mean of 8.7 versus 6.3
In contrast to PREEMPT 1, there was a significantly greater decrease in headache episodes in the Botox group than in the placebo group (5.3 vs 4.6, p=0.003). Change in frequency of migraine episodes was not reported.

Similar to PREEMPT 1, quality-of-life measures significantly improved in the Botox group. The proportion of patients with severe impact of headaches in the Botox group decreased from 93% at baseline to 66% at 24 weeks; in the placebo group, it decreased from 91% at baseline to 77%. There was a between-group difference of 10% (p=0.003). The authors reported statistically significantly greater improvement in the 3 MSQ role function domains at week 24 (restrictive, preventive, emotional, p<0.001 for each domain). Adverse events were experienced by 226 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 2 studies; this analysis was also industry-sponsored.24 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 with placebo groups. For example, the pooled change in mean frequency of headache days was 8.4 in the Botox group and 6.6 in the placebo group (p<0.001). Mean difference in number of headache days over a 28-day data collection period was 1.8 (95% CI, 1.13 to 2.52). The pooled change in frequency of headache episodes was 5.2 in the Botox group and 4.9 in the placebo group, a relative difference of 0.3 episodes (95% CI, 0.17 to 1.17; p=0.009). Between-group differences, though statistically significant, were relatively small and may not be clinically meaningful. In the pooled analysis, the authors also reported the proportion of patients with at least a 50% decrease from baseline in the frequency of headache days at each time point (every 4 weeks from week 4 to week 24). For example, at week 24, the proportion of participants with at least a 50% reduction in headache days was 47.1% in the Botox group and 35.1% in the placebo group. In contrast, the difference in the proportion of patients experiencing at least a 50% reduction in headache episodes did not differ significantly between groups at 24 weeks or at most other time points, with the exception of week 8. The article did not report the proportion of participants who experienced at least a 50% reduction in migraine days or migraine episodes. The pooled analysis showed statistically significant differences for the change in proportion of patients with severe headache impact according to the HIT-6 and change in MSQ questionnaire domains.

Several issues are worth noting about the methods and findings of the PREEMPT studies. There was a statistically significant difference in headache episodes in PREEMPT 2 but not PREEMPT 1 (for which it was the primary outcome); the primary outcome was changed after initiation of PREEMPT 1. Moreover, one of the main secondary outcomes in PREEMPT 1, change in the number of migraine episodes, was not reported in the second trial; the authors did not discuss this omission. In addition, the individual studies did not include threshold response to treatment (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 majority of patients in both trials fulfilled criteria for medication overuse headache, and therefore many may have been experiencing secondary headaches rather than chronic migraines. If patients did have secondary headaches, detoxification alone may have been sufficient 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, though consistent with that previously reported in several medication trials.

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

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

This is a single analysis of RCT data and provides insufficient evidence that botulinum toxin is effective for patients with the diagnosis of medication overuse headache.

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

Chronic Daily Headache
Although chronic daily headache is not recognized in the ICHD, it is commonly defined to include different kinds of chronic headache such as chronic or transformed migraine and daily persistent headache. It may also include chronic tension-type headache, addressed separately here. The meta-analysis by Jackson et al identified 3 RCTs comparing botulinum toxin A with placebo in patients having at least 15 headaches per month. A pooled analysis of data from these 3 trials found a significantly greater reduction in the number of headaches per month.
with botulinum toxin than with placebo (absolute difference, -2.06; 95% CI, -3.56 to -0.56). Individually, only 1 of the 3 trials (Ondo et al, 2004) found a statistically significant benefit with botulinum toxin treatment.31 Ondo included 60 patients, some with chronic migraines and chronic tension-type headache. The Ondo study found significantly greater reduction in the number of headache-free days over weeks 8 to 12 with botulinum toxin than with placebo (p<0.05), but there was no statistically significant between-group difference in reduction in headache-free days over the entire 12-week study period (p=0.07). The other 2 studies evaluated more patients: 355 in Mathew et al32 and 702 in Silberstein et al.33 Neither found a statistically significant difference in the reduction in the number of headache days per month with botulinum toxin. The available evidence from RCTs is conflicting and insufficient for conclusions.

Cluster Headache
No controlled trials were identified for cluster headache.

Cervicogenic Headache
In 2011, Linde et al published a double-blind, placebo-controlled crossover study that included 28 patients with treatment-resistant cervicogenic headache.34 Patients were randomized to botulinum toxin A or placebo; there was at least an 8-week period between treatments. The trial did not find significant differences between active and placebo treatment in the primary outcome, reduction in number of days with moderate-to-severe headache. Three other RCTs, published between 2000 and 2008, randomized patients with chronic, whiplash-related headache to botulinum toxin A treatment or placebo.35-37 One trial reported trends toward improvement with treatment for various outcomes; most were not statistically significant.35 Another reported no significant differences for several pain-related outcomes.37 One trial reported a significant improvement in pain with treatment while the placebo group reported no improvement, but trial design was flawed because the placebo group reported less pain at baseline.36 A Cochrane review of treatment of mechanical neck disorders, published in 2007,38 included 6 RCTs (total N=273) of botulinum toxin compared with placebo for chronic neck disorders with or without radicular findings or headache. A meta-analysis of 4 studies (total N=139) for pain outcomes found no statistically significant results. The authors concluded that a range of doses have not shown significant differences compared with placebo or with other comparators.

Section Summary: Headache
A number of RCTs have suggested benefit of botulinum toxin for treating chronic migraine. The published evidence does not suggest that botulinum toxin improves net health outcome for patients with an episodic pattern of migraines (i.e., <15 episodes per month). For tension headache, RCTs and systematic reviews do not indicate that botulinum toxin improves outcomes. For other headache types, the evidence is insufficient to form conclusions about efficacy.

Esophageal Achalasia
Esophageal achalasia is a primary motor disorder characterized by abnormal lower esophageal sphincter relaxation. A 2014 Cochrane review by Leyden et al identified 7 RCTs with a total of 178 participants on treatment of primary esophageal achalasia with botulinum toxin or endoscopic pneumatic dilation.39 A pooled analysis of data from 5 studies did not find a statistically significant difference in the rate of initial remission with pneumatic dilation versus
botulinum toxin injection (risk ratio [RR], 1.11; 95% CI, 0.97 to 1.27). Remission at 6 and 12 months favored the pneumatic dilation group. No serious adverse events were reported after botulinum toxin injection; however, there were 3 cases of perforation after pneumatic dilation.

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

Sialorrhea (Drooling)
Sialorrhea Associated With Parkinson Disease
Several RCTs have evaluated botulinum toxin injection in patients with Parkinson disease. For example, in 2006, Lagalla et al randomly assigned 32 patients with Parkinson disease to placebo or botulinum toxin A 50 U; evaluation at 1 month postinjection 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 randomly assigned 16 patients with Parkinson disease to receive placebo or botulinum toxin B 2500 U (Myobloc). 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 assigned 20 patients with Parkinson disease to injections of either a saline placebo or Dysport 450 U. The treatment group was significantly better than placebo on a drooling scale at 1 week; the effect disappeared by 3 months.

Section Summary: Sialorrhea (Drooling) Associated With Parkinson Disease
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 been published on botulinum toxin for treating sialorrhea in people with conditions other than Parkinson disease. In 2014, Squires et al reviewed the research on botulinum toxin injections for drooling in patients with amyotrophic lateral sclerosis/motor neuron disease. The review included RCTs and controlled and uncontrolled observational studies. The authors identified 12 studies, of which 8 did not have control groups. There were 2 small RCTs, each with fewer than 20 patients. Sample sizes in the non-RCTs ranged from 5 to 26. Due to heterogeneity, study findings were not pooled. Only 1 of the 2 RCTs reported drooling outcomes; it found a significantly greater reduction in saliva volume in the botulinum toxin group than on the placebo group at 2 weeks.

In 2012, Rodwell et al published a systematic review evaluating botulinum toxin injections in the salivary gland to treat sialorrhea in children with cerebral palsy and neurodevelopment disability. The authors identified 5 RCTs; sample sizes in individual trials ranged from 6 to 48 participants. One of the RCTs (N=6 participants) was terminated due to adverse events. In a pooled analysis of data 4 weeks postintervention in 3 RCTs, the mean score on the Drooling Frequency and Severity Scale (DFSS) 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 DFSS scores is not clear. Data were not pooled for other outcomes. The systematic review also identified 11 prospective case series. The rate of adverse events associated with botulinum toxin injection in the RCTs and case
series ranged from 2% to 41%. Dysphagia occurred in 2 (33%) of the 6 participants in an RCT that was 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.

The largest RCT on botulinum toxin for treating sialorrhea in children with cerebral palsy was published in 2008 by Reid et al. Forty-eight children with cerebral palsy (n=31) and other neurologic disorders (n=17) were randomized to a single injection of botulinum toxin A 25 U compared with no treatment. Drooling was assessed by administering 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 2013 article focused on the long-term safety of botulinum toxin A injection for treating sialorrhea in children. The study included 69 children; 47 (68%) had cerebral palsy. Children received their first injection of botulinum toxin at a mean age of 9.9 years, and mean follow-up was 3.1 years. During the study period, the children received a total of 120 botulinum toxin injections. Complications occurred in 19 (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. These included 3 cases of aspiration pneumonia, 2 cases of severe dysphagia, and 3 cases of loss of motor control of the head. Complications were associated with 5 hospitalizations and 2 cases of nasogastric tube placement.

**Section Summary: Sialorrhea (Drooling) Not Associated With Parkinson Disease**

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

**Anal Applications**

**Internal Anal Sphincter (IAS) Achalasia**

IAS achalasia is a disorder of defecation in which the internal anal sphincter is unable to relax. Symptoms include severe constipation and soiling. A systemic review of studies on treatment of IAS achalasia was published in 2012 by Friedmacher and Puri. The authors did not identify any RCTs of botox treatment. Two prospective case series and 14 retrospective case series with a total of 395 patients with IAS achalasia were identified. The majority of patients in the series, 229 of 395 (58%) were treated with posterior IAS myectomy and 166 (42%) were treated with intraspincteric botulinum toxin injection. A meta-analysis of data from the observational studies found that regular bowel movements were more frequent after myectomy (OR: 0.53, 95% CI: 0.29 to 0.99, p=0.44, p=0.04). Moreover, the rate of transient fecal incontinence was significantly higher after botulinum toxin injection (OR: 0.07, 95% CI: 0.01 to 0.54, p=0.01) and the rate of subsequent surgical intervention was higher after botulinum toxin injection (OR: 0.18, 95% CI: 0.07 to 0.44, p<0.001). Other outcomes, including continued use of laxatives or rectal enemas, and the overall complication rates, did not differ with the 2 treatments.
Section Summary: Internal Anal Sphincter Achalasia
There is a lack of RCTs evaluating botulinum toxin injection as a treatment of IAS. A meta-analysis of observational data suggested that posterior IAS myectomy results in greater improvement in health outcomes than botulinum toxin injections.

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

In 1998, Maria et al randomly assigned 30 patients with chronic anal fissure to receive either 2 injections of 20 U of botulinum toxin, on either side of the fissure, or 2 injections of saline. After 2 months, 11 patients (73%) in the treated group and 2 patients (13%) in the control group had healed fissures (p=0.003); 13 patients (87%) in the treated group and 4 (26%) in the control group had symptomatic relief (p=0.003). Four patients in the treated group were later retreated. No relapses occurred during an average of 16 months of follow-up. Nitroglycerin ointment has also been used to successfully treat anal fissure. In 1999, Brisinda et al in Italy compared the results of nitroglycerin ointment and botulinum toxin in a randomized trial of 50 patients. After 2 months, 96% of the fissures were healed in the botulinum group compared with 60% in the nitroglycerin group. Brisinda et al conducted a similar study in 2007 with 92% versus 70%, respectively, healing rates for botulinum toxin A–treated versus nitroglycerin ointment–treated patients (p<0.001). Another trial by Brisinda et al found that Botox and Dysport used to treat anal fissures were similar in terms of efficacy and tolerability. Others have reported both supportive and contradictory data from randomized trials comparing the same treatments. RCTs of botulinum toxin versus sphincterotomy, and a meta-analysis of these studies, 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.

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

Section Summary: Anal Fissure
There is evidence on botulinum toxin for treatment of anal fissure from numerous small RCTs, and botulinum toxin is a less invasive option than surgery.

Urologic Applications
Overactive Bladder/Neurogenic Detrusor Overactivity
Several meta-analyses of RCTs have been published. In 2015, Cui et al identified 6 double-blind RCTs comparing botulinum toxin A with placebo for treating patients with idiopathic overactive bladder (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;
Moreover, a pooled analysis of 5 studies found significantly greater reduction in the number of incontinence episodes per day in the group treated with botulinum toxin (SMD = -1.68; 95% CI, -2.06 to -1.31). Previously, in 2011, Duthie et al published a Cochrane review of RCTs evaluating botulinum toxin injections for patients with idiopathic or neurogenic OAB. The authors identified 19 trials that compared treatment using botulinum toxin with placebo or another intervention. Two studies included botulinum toxin B; the remainder included botulinum toxin A. Outcomes varied, which made it difficult to pool study findings. A pooled analysis of 3 studies reporting change in urinary frequency episodes at 4 to 6 weeks reported a significantly better outcome with botulinum toxin injection compared with placebo (pooled mean difference [MD], -6.50; 95% CI, -8.92 to -4.07). A pooled analysis of 3 studies on change in incontinence episodes at 4 to 6 weeks also found a significantly greater improvement with botulinum toxin (MD = -1.58; 95% CI, -2.16 to -1.01).

Other systematic reviews have included both controlled and uncontrolled studies. A 2013 systematic review by Soljanik identified 28 studies evaluating onabotulinumtoxinA for the treatment of neurogenic detrusor overactivity/neurogenic overactive bladder; 6 of the studies were RCTs. The author reported that studies with comparative data found superior outcomes with onabotulinumtoxinA 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 in 2013, Mehta et al identified 14 studies evaluating botulinum toxin 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. Rate of incontinence episodes decreased after treatment with botulinum toxin A from 23% to 1.3% per day. Previously in 2008, Karsenty et al identified 18 studies evaluating botulinum toxin A to treat patients who were refractory to anticholinergics. Most studies reported statistically significant improvement in clinical and urodynamic outcomes, without major adverse events.

Representative large, double-blind RCTs are described below.

In 2013, Nitti et al published data from an industry-supported study that included 557 patients with OAB and urinary incontinence inadequately controlled by anticholinergics. Patients were randomized to receive an intradetrusor injection of onabotulinumtoxinA 100 U or placebo. At the 12-week follow-up, there was a statistically significantly greater improvement in the daily frequency of urinary incontinence episodes in the group that received botulinum toxin than in the placebo group (-2.65 vs -0.87, p<0.001). The other primary end point was the proportion of patients with a positive response at week 12 according to the Treatment Benefit Scale. A significantly larger proportion of patients in the botulinum toxin group than 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 patients (5.4%) in the botulinum toxin group and 1 patient (0.4%) in the placebo group. Between-group p values were not reported for adverse effects. A prespecified subanalysis of data from this RCT and another placebo-controlled trial (Chapple et al 2013) evaluated the efficacy of onabotulinumtoxinA by number of anticholinergic therapies used. Patients had used a mean of 2.4 anticholinergic therapies before enrolling in the study. At week
12, reduction in the daily number of urinary incontinence episodes was significantly lower in the onabotulinumtoxinA group versus the control group, regardless of whether 1, 2, 3, or more prior anticholinergics had been used. The mean reduction in daily incontinence episodes for patients with 1 prior anticholinergic was 2.82 in the onabotulinumtoxinA group and 1.52 in the placebo group (p<0.001); with 3 or more prior anticholinergics, it was 2.92 and 0.73, respectively (p<0.001).

A 2012 industry-supported RCT by Ginsberg et al included 416 patients with neurogenic detrusor activity associated with multiple sclerosis or spinal cord injury.67 Patients were randomized to receive injections with onabotulinumtoxinA 200 U, onabotulinumtoxinA 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% in the 200-U group, 42% in the 300-U group, and 10% 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.

Section Summary: Overactive Bladder/Neurogenic Detrusor Overactivity
Numerous RCTs, as well as observational data, report improvements in outcomes following botulinum toxin treatment in patients with neurogenic detrusor overactivity or OAB who are unresponsive to anticholinergic medication. Despite the risk of adverse events, including urinary retention and UTI, evidence suggests that botulinum toxin improves the net health outcome.

Detrusor Sphincter Dyssynergia
In 2002, de Seze et al studied 13 patients with chronic urinary retention due to detrusor sphincter dyssynergia from spinal cord disease (traumatic injury, multiple sclerosis, congenital malformations) who were randomly assigned to receive perineal botulinum toxin A or lidocaine injections into the external urethral sphincter.68 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 receiving a lidocaine injection. Improvements were also seen in the satisfaction scores and other urodynamic outcomes.

Systematic reviews have addressed treating detrusor sphincter dyssynergia with botulinum toxin injection. Most recently, in 2012, Mehta et al conducted a systematic review of literature on botulinum toxin injection as a treatment of detrusor external sphincter dysfunction and incomplete voiding after spinal cord injury.69 The authors identified 2 RCTs in addition to uncontrolled studies. The RCTs included the de Seze study, discussed above, and a second study of 5 patients. A 2006 systematic review by Karsenty et al reviewed trials of botulinum toxin A injected into the urethral sphincter to treat different types of lower urinary tract dysfunction, grouped into neurogenic detrusor sphincter dyssynergia and non-neurogenic obstructive sphincter dysfunction.70 In the former group, the authors cited 10 small studies (N range, 3-53; 3 studies included patients in both categories). Most patients were quadriplegic men unable to self-catheterize or patients (of both genders) with multiple sclerosis. All studies except 2 were case reports or case series; the 2 controlled studies were those included in the Mehta systematic review. Authors of both systematic reviews noted that, while most of the available studies have reported improvements with botulinum toxin injections, there are few published studies, and studies have small sample sizes.
Section Summary: Detrusor Sphincter Dyssynergia
There is insufficient evidence from RCTs on the impact of botulinum toxin on health outcomes for patients with detrusor sphincter dyssynergia.

Benign Prostatic Hyperplasia
Use of botulinum toxin to treat symptoms of benign prostatic hyperplasia (BPH) is premised in part on a static component related to prostate size and a dynamic component related to the contraction of smooth muscle within the gland. Botulinum therapy addresses this latter component. In 2012, Marchal et al published a systematic review of the literature on use of botulinum toxin to treat BPH.71 The authors identified 25 studies, including controlled and uncontrolled studies and abstracts in journal supplements. There were 6 RCTs, 3 published as full articles and 3 as abstracts. Two of published RCTs were included in a meta-analysis. The authors reported that pre- and posttreatment mean postvoiding residue did not differ significantly; pooled results were not reported for between-group outcomes. One of the RCTs by Maria et al, reported on 30 patients with BPH randomly assigned to receive intraprostatic botulinum toxin A or saline injection.72 Inclusion criteria were 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 void volume of 150 mL or less. After 2 months, the AUA symptom score decreased by 65% among those receiving botulinum toxin compared with no significant change in the control group. Mean peak urinary flow rate was significantly increased in the treatment group.

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

Interstitial Cystitis
Interstitial cystitis (IC) is a chronic condition characterized by pain, urgency, and frequent urination of small volumes. Several RCTs and a systematic review have been published. The 2010 systematic review by Tirumuru et al identified 3 RCTs and 7 prospective cohort studies evaluating intravesical botulinum toxin A injections for IC/painful bladder syndrome (PBS).73 Sample sizes of all studies were relatively small (range, 10-67 patients; total N=260 patients). Treatment protocols varied (e.g. dose of botulinum toxin, number of injection sites, location of injection sites). Meta-analyses were not performed due to heterogeneity among studies. All 3 RCTs were conducted outside of the United States. Two studies reported response rates as an outcome measure (both used a 7-point Global Response Assessment [GRA] scale). One study found a significantly higher response rate with botulinum toxin plus hydrodistension than hydrodistension-only, and the other found a significantly higher response rate with bacillus Calmette-Guérin (BCG) therapy than botulinum toxin. Some adverse events, in particular dysuria and voiding difficulty, were reported and 19 of 260 patients (7%) self-catheterized at some time after treatment.

Since publication of that systematic review, 3 RCTs evaluating botulinum toxin for treatment of IC and/or bladder pain syndrome were published. One, published in 2015 by Akiyama et al, lacked blinding and reported only 1 month of comparative data.74 The 2 recent double-blind, placebo-controlled studies are described next.
A 2015 RCT by Kuo et al, included 60 Taiwanese patients (52 women, 8 men) with IC/PBS who had failed at least 6 months of conventional therapy. To be eligible, patients had to fail at least 2 types of treatment modalities (i.e., oral medications, intravesical treatment with heparin or hyaluronic acid). Individuals with a variety of comorbid conditions were excluded, including those with urinary retention. Participants received intravesical injection of botulinum toxin A (Botox 100 U) or normal saline (placebo), followed by hydrodistention under general anesthesia. The primary end point was the reduction in pain according to a 10-point visual analog scale (VAS) score 8 weeks after treatment. There was a significantly greater reduction in the mean VAS score in the botulinum toxin group (-2.6, SD=2.8) than the placebo group (-0.9, SD=2.2; p=0.021). Secondary outcomes, including overall subjective success (assessed by a GRA), Interstitial Cystitis Symptom Index (ICSI), urinary frequency, and nocturia did not differ significantly between groups. The incidence of adverse events was significantly higher in the botulinum toxin group compared with the placebo group at 8 weeks (p=0.033). For example, 16 patients in the botulinum group (40%) and 1 in the placebo group (5%) reported dysuria at 8 weeks.

A 2014 RCT by Manning et al included 54 women with IC/BPS refractory to at least 2 recognized treatments. Patients with voiding difficulty, bladder malignancy, and recurrent UTI were excluded. The primary outcome was the O'Leary-Sant (OLS) Questionnaire score, which assesses on daytime frequency, nocturia, urgency, and bladder pain. Patients received hydrodistention under general anesthesia, with either an injection of botulinum toxin A (Dysport 500 U) or normal saline (placebo). The OLS score at 3 months did not differ significantly between groups. Scores were 20.4 (95% CI, 17.1 to 23.7) in the botulinum toxin group and 25.3 (95% CI, 21.9 to 28.8) in the placebo group (MD=3.7; 95% CI, -0.34 to 7.6; p=0.12). However, in the subgroups of 42 patients without UTIs the OLS score was significantly improved in the botulinum toxin compared with the placebo group (MD=6.1; 95% CI, 2.5 to 9.6; p=0.02). Adverse events were not reported.

**Section Summary: Interstitial Cystitis**

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 to alternative treatments.

**Other Indications**

**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 in case reports and case series. Two randomized, placebo-controlled studies have addressed essential hand tremors; the 2001 trial enrolled 133 patients and the 1996 trial enrolled 25 patients. These RCTs reported inconsistent findings using tremor symptom scales and neither reported functional outcomes.

**Section Summary: Tremor**

The clinical significance of contradictory findings from 2 RCTs is unclear.
Orthopedic Pain

**Chronic Low Back Pain**

Only 1 RCT of botulinum toxin A treatment in patients with low back pain has been published. The trial, published in 2001, enrolled 31 consecutive patients with chronic low back pain of at least 6 months in duration and more predominant pain on 1 side. Patients were injected with Botox 40 U (Allergan) at 5 lumbosacral locations for a total of 200 U (treated group) or saline placebo (placebo group). Injections were made on 1 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 Disability Index) at 8 weeks showed that 66.7% of treated patients and 18.8% of placebo patients were responders (p=0.011).

*Section Summary: Chronic Low Back Pain*

The population with chronic low back pain is heterogeneous. Results of 1 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**

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

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

*Section Summary: Lateral Epicondylitis*

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

**Other Joint Pain**

Two case series of patients with chronic joint pain refractory to conservative management studied the effect of botulinum toxin A injections (1 series specified that Dysport was used) into
several joints of patients with arthritis and into the knee joint of patients with chronic knee pain.82,83 Both reported significant improvement in joint pain and function compared with baseline, lasting for 3 to 12 months. Although the results of several trials of botulinum toxin injections into joints for chronic pain favored treatment, some did not.

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

Myofascial Pain Syndrome
Myofascial pain syndrome is characterized by 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 to evaluate the efficacy of botulinum toxin injection for treating myofascial pain syndrome would be double-blind RCTs 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 botulinum toxin injection for myofascial pain syndrome. Most recently, a 2014 Cochrane review by Soares et al identified 4 RCTs (total N=233 patients).84 All RCTs were placebo-controlled and double-blind. Three were prospective and 1 used a crossover design. Follow-up in the prospective studies was 12 weeks in 2 studies and 4 weeks in the third. Due to heterogeneity among studies, the investigators did not pool analyses. The primary outcomes were change in pain as assessed by validated instruments. Three of the 4 studies found that botulinum toxin did not significantly reduce pain intensity. A 2013 systematic review had similar findings.85 A systematic review that included a meta-analysis was published in 2011 by Langevin et al.86 A pooled analysis from 4 placebo-controlled trials did not find a statistically significant benefit of botulinum toxin. The SMD was -0.21 (95% CI, -0.50 to 0.70).

A 2014 industry-sponsored RCT, not included in the systematic review, focused on patients with myofascial pain who had responded to an initial injection of botulinum toxin A.87 A total of 114 patients received an initial injection and 54 responders were subsequently randomized to receive a second injection of botulinum toxin or saline placebo 14 weeks after the initial injection. At week 26 after the initial injection, but not at week 20, there was a significantly greater improvement in the mean visual numeric scores for pain in the botulinum toxin group than in the placebo group (p=0.019). There was no significant difference between groups at week 26, compared with baseline, in quality of life using the 36-Item Short-Form Health Survey. Thus, this study had mixed outcomes and restricted study participation to a responder group. This could have biased the proportion of patients who initially experienced a placebo response and made blinding more difficult for those familiar with side effects of the active treatment.

Section Summary: Myofascial Pain
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 Disorder
A 2015 systematic review by Chen et al evaluated the literature on botulinum toxin for treatment of temporomandibular joint disorders. Eligibility included RCTs comparing any dose or type of botulinum toxin with any alternative intervention or placebo. Five RCTs met the inclusion criteria; 2 were parallel group studies and 2 were crossover studies. Study sizes tended to be small; all but 1 study included 30 or more participants. Three of the 5 studies were judged to be at high risk of bias. All studies administered a single injection of botulinum toxin and followed patients up at least 1 month later. Four studies used a placebo (normal saline) control group and the fifth used botulinum toxin to fascial manipulation. The primary outcome was a validated pain scale. Data were not pooled due to heterogeneity among trials. In a qualitative review of the studies, only 2 of the 5 trials found a significant short-term (1- to 2-month) benefit of botulinum toxin compared with control on pain reduction.

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

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

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

The third trial, published in 2012 by Wu et al, included 42 patients with trigeminal neuralgia. To be eligible for participation, patients needed to have a mean pain intensity of at least 4 and a mean attack frequency of at least 4 per day despite medication therapy. Most patients were taking medication at baseline (e.g., opioids, carbamazepine, gabapentin); medications remained unchanged during the study. Patients were randomized to receive botulinum toxin A 75 U or saline (placebo). They were followed for 12 weeks. The primary end points were pain severity and pain attack frequency. Symptoms were recorded by patients each morning, for the previous 24-hour period using a VAS. Both of the primary end points were statistically significantly better in the treatment group than in the control group. The proportion of patients with at least a 50% reduction in the mean pain score from baseline to 12 weeks, a secondary end point, was 15 of 22 (68%) in the botulinum toxin group and 3 of 20 (15%) in the placebo group (p<0.01). No severe or long-lasting adverse events were reported.

Section Summary: Trigeminal Neuralgia
Three small RCTs from China in patients who had failed medication treatment found statistically significant benefit of botulinum toxin added to their medication regimen versus placebo on pain intensity and attack frequency. Limitations of the evidence base includes studies from only 1 research group, the small overall number of patients evaluated, relatively short follow-up (8-12 weeks), and lack of reported statistical power analysis. In the absence of power analysis, there is a higher 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 2005 article described a study by Patti et al (n=30) who randomly assigned patients to botulinum toxin 20 U or saline injection and reported significantly decreased duration of postoperative pain at rest and during defecation in the treated group. A 2006 study by Patti et al, which also included 30 patients, found significant differences in postoperative maximum resting pressure change from baseline comparing botulinum toxin treatment with topical glyceryl trinitrate (p<0.001; increased resting pressure after surgery and may be responsible for pain). In addition, there was a significant reduction in postoperative pain at rest (p=0.01) but not during defecation. There was no difference in healing.

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

Facial Wound Healing
In 2013, Ziade et al reported on a study including 30 adult patients presenting to the emergency department with facial wounds without tissue loss. Patients were assigned to have an injection of botulinum toxin (n=11) or no injection (n=13) within 72 hours of the suturing of the wounds. The primary outcomes were scores on the following scales at 1 year: Patient Scar Assessment Scale (PSAS), Observer Scar Assessment Scale (OSAS), Vancouver Scar Scale (VSS), and a 1 to 10 VAS. The PSAS was a patient-reported outcome, the OSAS and VSS were assessed clinically by a blinded independent evaluator, and the VAS was assessed using
photograph analysis by a team of 6 medical specialists. Patients were not blinded to treatment group, and thus the PSAS might have been a more subjective outcome, whereas it is likely that the OSAS, VSS, and VAS were objectively assessed. Twenty-four (80%) of 30 patients were available for the 1-year follow-up. There were no significant differences between groups in the PSAS, OSAS, and VSS scales. For example, the median OSAS score was 8 in the botulinum toxin group and 9 in the control group. However, a significant between-group difference was found for the VAS score, favoring the botulinum toxin group. The median VAS score was 8.25 for the botulinum group and 6.35 for the control group (p<0.001). These results demonstrated a lack of consistency in finding a benefit across outcomes—there was no significant difference in the patient-reported or clinically accessed outcomes, only in the outcome based on photographic analysis. Previously, in 2006, Gassner et al conducted a small RCT of botulinum toxin–induced immobilization of facial lacerations to improve wound healing compared with placebo (n=31). The outcome was determined by blinded assessment of photographs of wound healing at intervals using a VAS. The authors reported enhanced wound healing in the treatment arm compared with the placebo arm (8.9 vs 7.2, p=0.003).

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

Pelvic and Genital Pain in Women
One double-blind, randomized, placebo-controlled trial evaluated 60 patients with chronic pelvic pain and pelvic floor spasm. Patients received injections of botulinum toxin 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). Patients receiving up to 2 doses had significantly reduced pain compared with baseline for 8 (lower dose) to 14 weeks (higher dose). A prospective cohort study tested different doses of botulinum toxin in 12 women with pelvic floor muscle hypertonicity and history of chronic pelvic pain. Compared with baseline, there were nonsignificant reductions in pelvic pain and nonsignificant improvements in quality of life.

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

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

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

In 2005, Stidham et al explored the use of botulinum toxin A injections for tinnitus treatment under the theory that blocking the autonomic pathways would reduce the perception of tinnitus. 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 with the placebo groups in which only 2 patients reported reduced tinnitus (p<0.005). Tinnitus Handicap Inventory scores were also significantly decreased between pretreatment and 4 months after botulinum toxin A injections. However, no other significant differences were noted when comparing the 2 treatments at 1 and 4 months postinjection. The authors noted larger studies are needed. Study limitations included sample size and lack of intention-to-treat analysis.

Section Summary: Tinnitus

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

Antibody Testing for Botulinum Toxin Resistance

Rarely do patients have no response to initial administration of botulinum toxin (primary resistance) and a small percentage of adults 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. In approximately 3% to 10% of adult patients, true secondary resistance arises due to the development of antibodies that specifically neutralize the activity of botulinum toxin, (e.g., , ). 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. 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. In 2 studies of pediatric patients treated for spasticity, neutralizing antibodies were detected in 28% to 32% of patients. Recommendations for avoiding eventual resistance are to use the lowest dose possible to obtain a clinical response and to schedule intervals of 10 to 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, because neutralizing antibodies may redevelop quickly. 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.

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 or with an in vitro toxin-neutralizing assay based on a mouse diaphragm nerve-muscle preparation. 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. However, unless only the protein sequences that specifically react with neutralizing antibodies are employed, these formats detect both neutralizing and non-neutralizing antibodies\textsuperscript{107,113,114} and would therefore result in significant numbers of false-positive results. An option for some patients might be to inject toxin into the frontal muscle above 1 eyebrow; a toxin-responsive patient would have asymmetry of the forehead on attempted frowning, whereas, a nonresponsive patient would not.\textsuperscript{114}

**Section Summary: Antibody Testing for Botulinum Toxin Resistance**
Evidence for the use of assays to detect antibodies to botulinum toxin is insufficient to support its use in a clinical setting.

**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**
There are no published RCTs evaluating botulinum toxin for pain associated with breast reconstruction after mastectomy. A 2014 systematic review identified 7 studies on perioperative injection of botulinum toxin A following breast reconstruction surgery.\textsuperscript{115} They consisted of 2 prospective controlled cohort studies, 3 retrospective controlled cohort studies, and 2 case series. Most studies were small; only one (N=293) had more than 50 participants. Three assessed postoperative pain and all 3 found that at least some outcomes were significantly better in the botulinum toxin group than the comparison group.

**Section Summary: Pain Associated with Breast Reconstruction After Mastectomy**
The evidence on botulinum toxin for perioperative management of pain associated with breast reconstruction after mastectomy is insufficient due to a lack of RCTs or large observational studies.

**Hirschsprung Disease**
The published literature consists of small case series.\textsuperscript{116-118} 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 disease.\textsuperscript{117} 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 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 1 to 5 additional injections due to either treatment failure or recurrence of symptoms; retreatment was not based on a standardized protocol.

A 2011 series by Patrus et al retrospectively reviewed outcomes in 22 patients with Hirschsprung disease treated over 10 years who had received a median of 2 (range, 1-23) botulinum toxin injections for postsurgical obstructive symptoms.\textsuperscript{118} 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, 0-10 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 botulinum toxin injection (median, 0) compared with preinjection (median, 1.5; \(p=0.003\)). The authors did not report
whether or not patients received other treatments during the follow-up period in either case series.

**Section Summary: Hirschsprung Disease**
There are no controlled trials of botulinum toxin for the treatment of Hirschsprung disease; therefore, the evidence is insufficient to form conclusions on efficacy.

**Gastroparesis**
A 2010 systematic review of the literature identified 15 studies on botulinum toxin injection to treat gastroparesis.119 Two studies were RCTs; the remainder was case series or open-label observational studies. The authors stated that, while the nonrandomized studies generally found improvement in subjective symptoms and gastric emptying after botulinum toxin injections, the RCTs did not confirm the efficacy of botulinum toxin for treating gastroparesis. The authors concluded that there is insufficient evidence to recommend botulinum toxin for gastroparesis. Brief summaries of the 2 RCTs follow.

In 2007, Arts et al published a randomized crossover study with 23 patients.120 The study included consecutive patients at a single institution who had symptoms suggestive of gastroparesis and established delayed gastric emptying for solids and liquids. Patients received, in random order, injections of Botox or saline during gastrointestinal endoscopies, with a 4-week interval between injections. Symptoms were assessed using the Gastroparesis Cardinal Symptom Index (GCSI), which has a maximum score of 45. There were no statistically significant differences in improvement after botulinum toxin injection or saline injection for either solid or liquid emptying times. For example, liquid half-emptying time was 8.2 minutes (SD=13.7) after Botox injection and 22.5 minutes (SD=7.7) after saline injection (p>0.05). In addition, in pooled analyses, the total GCSI score did not differ significantly after Botox compared with saline treatment (mean GCSI score, 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.121 Patients had symptoms consisting of delayed gastric emptying and had GCSI scores 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 prior to treatment and at a 1-month follow-up. The proportion of patients with at least a 9-point reduction in the GCSI score at 1 month, the primary end point, was 6 (37.5%) of 16 in the Botox group and 9 (56.3%) of 16 in the placebo group; the difference between groups was not statistically significant. Improvement in gastric emptying after 1 month, a secondary end point, also did not differ significantly between groups.

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

**Depression**
In 2015, Magid et al published a meta-analysis of 3 placebo-controlled RCTs evaluating botulinum toxin A for treating unipolar major depressive disorder.122 Sample sizes were small; a total of 59 patients were treated with botulinum toxin and 75 were treated with placebo. In a pooled analysis of individual patient data, there was a significantly higher response rate in the botulinum toxin group than the placebo group (54.2% vs 10.7%; OR=7.3; 95% CI, 2.4 to
22.5). Other outcomes also favored the botulinum toxin group. No RCTs compared botulinum toxin with antidepressant treatment, which is standard of care.

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

**ONGOING AND UNPUBLISHED CLINICAL TRIALS**
Some currently unpublished trials that might influence this review are listed in Table 1.

<table>
<thead>
<tr>
<th>Table 1. Summary of Key Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT No.</td>
</tr>
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<td>NCT01905137</td>
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<tr>
<td>NCT02116361</td>
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<td>NCT02414425</td>
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</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

**SUMMARY OF EVIDENCE**
The evidence for botulinum toxin injections in individuals who have dystonia or spasticity resulting in functional impairment and/or pain includes multiple randomized controlled trials (RCTs) and meta-analyses. Relevant outcomes are symptoms, functional outcomes, medication use, and treatment-related morbidity. The studies support the efficacy of botulinum toxin for improving dystonia or spasticity in patients with various conditions. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for botulinum toxin injections in individuals who have strabismus includes several RCTs. Relevant outcomes are symptoms, functional outcomes, and treatment-related morbidity. RCTs evaluating botulinum toxin had mixed findings; treatment with botulinum toxin is a noninvasive alternative to surgery and is associated with fewer harms. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.
The evidence for botulinum toxin injections in individuals who have blepharospasm or facial nerve (VII) disorders includes several RCTs. Relevant outcomes are symptoms, functional outcomes, and treatment-related morbidity. RCTs have found symptom improvements in patients treated with botulinum toxin compared with an alternative intervention. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for botulinum toxin injections in individuals who have chronic migraine headache includes several RCTs and meta-analyses. Relevant outcomes are symptoms, medication use, and treatment-related morbidity. RCTs had mixed findings; a meta-analysis found that botulinum toxin reduced the frequency of headaches per month compared to placebo or medication. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for botulinum toxin injections in individuals who have chronic migraine headache includes several RCTs and meta-analyses. Relevant outcomes are symptoms, medication use, and treatment-related morbidity. RCTs had mixed findings; a meta-analysis found that botulinum toxin reduced the frequency of headaches per month compared to placebo or medication. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for botulinum toxin injections in individuals who have esophageal achalasia includes a number of RCTs and a systematic review of RCTs. Relevant outcomes are symptoms, functional outcomes, and treatment-related morbidity. The systematic review found similar efficacy and fewer harms with botulinum toxin than with pneumatic dilation. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for botulinum toxin injections in individuals who have sialorrhea associated with Parkinson disease includes several RCTs. Relevant outcomes are symptoms, functional outcomes, and treatment-related morbidity. RCTs have consistently found that botulinum toxin provides benefit. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for botulinum toxin injections in individuals who have sialorrhea not associated with Parkinson disease includes RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, and treatment-related morbidity. Available individual RCTs are small and do not consistently find a clinically meaningful improvement with botulinum toxin therapy. In several trials, rates of adverse events are notably high, making the risk-benefit ratio of botulinum toxin therapy uncertain. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for botulinum toxin injections in individuals who have internal anal sphincter achalasia includes nonrandomized studies, which have been summarized in a systematic review. Relevant outcomes are symptoms, health status measures, and treatment-related morbidity. In a systematic review of nonrandomized studies comparing botulinum toxin injection with myectomy, outcomes were more favorable after surgery. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for botulinum toxin injections in individuals who have chronic anal fissure includes a number of RCTs and a systematic review. Relevant outcomes are symptoms, health status measures, and treatment-related morbidity. Studies have found similar efficacy with botulinum toxin or surgery, and less potential harm with toxin injections. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.
The evidence for botulinum toxin injections in individuals who have urinary incontinence due to detrusor overactivity associated with neurogenic causes or overactive bladder includes numerous RCTs. Relevant outcomes are symptoms, medication use, and treatment-related morbidity. Studies have shown that botulinum toxin is effective at reducing symptoms in patients unresponsive to anticholinergic medications. There are adverse events associated with botulinum toxin (eg, urinary retention, urinary tract infection), but patients may find that benefits outweigh harms. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for botulinum toxin injections in individuals with urologic issues other than detrusor overactivity or overactive bladder (eg, detrusor sphincter dyssynergia, benign prostatic hyperplasia, and interstitial cystitis) includes RCTs and systematic reviews. Relevant outcomes are symptoms, medication use, and treatment-related morbidity. Available RCTs for these conditions are small and have mixed findings on the benefit of botulinum toxin. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for botulinum toxin injections in individuals who have other indications (eg, musculoskeletal pain, postsurgical pain, neuropathic pain, tremors) includes case series or a few small, flawed RCTs. Relevant outcomes are symptoms, functional outcomes, medication use, and treatment-related morbidity. Evidence of benefit from large well-conducted RCTs is lacking for these other indications. The evidence is insufficient to determine the effects of the technology on health outcomes.

**CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS**

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.

**2010 Input**

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 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.

**2008 Input**

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.
American Urological Association
In 2012, the American Urological Association (AUA) issued a guideline on non-neurogenic overactive bladder in adults. The guideline includes intradetrusor onabotulinumtoxinA injection as a third-line treatment option in “carefully selected and thoroughly-counseled” patients who are refractory to first- and second-line treatments and are willing to perform self-catheterization if needed for postvoid retention.

In 2014, AUA issued a guideline on diagnosis and treatment of interstitial cystitis/bladder pain syndrome. The guidelines include intradetrusor onabotulinumtoxinA injection as a fourth-line treatment, following conservative therapies, pain management, physical therapy, oral medications, intravesical treatments, cystoscopy, and fulguration. The guideline noted that some patients require intermittent self-catheterization after botulinum toxin injection and that the treatment is relatively contraindicated for patients with evidence of impaired bladder emptying.

American Academy of Neurology
In 2011, the American Academy of Neurology (AAN), Quality Standards Subcommittee, published an update of evidence-based recommendations for treating essential tremor. The report reaffirmed the Academy’s previous position that botulinum toxin is “possibly effective” and may be considered to reduce limb tremor associated with essential tremor.

In 2010, AAN’s Quality Standards Subcommittee and the Child Neurology Society’s Practice Committee published a practice parameter on the pharmacologic treatment of spasticity in children and adolescents with cerebral palsy. Botulinum toxin A was considered an effective and generally safe treatment for localized/segmental spasticity requiring treatment. There were insufficient data on use of botulinum toxin B.

In 2008, AAN’s Therapeutics and Technology Assessment Subcommittee published evidence-based recommendations on botulinum toxin for treatment of autonomic disorders and pain. The subcommittee recommended that botulinum toxin be offered as a treatment option for detrusor activity, should be considered for drooling and for detrusor sphincter dyssynergia after spinal cord injury, and may be considered for low back pain.

American Society of Colon and Rectal Surgeons
The 2010 revision of a practice parameter on treatment of anal fissures by the American Society of Colon and Rectal Surgeons states:

“Patients who do not respond to topical nitrates should be referred for botulinum toxin injections or surgery... Botulinum toxin injection has been associated with healing rates superior to placebo. There is inadequate consensus on dosage, precise site of administration, number of injections, or efficacy. Grade of Recommendation: Strong recommendation based on low-quality evidence 1C.”

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
No U.S. Preventive Services Task Force (USPSTF) recommendations for botulinum toxin have been identified.
CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

31513  Laryngoscopy, indirect; with vocal cord injection
31570  Laryngoscopy, direct, with injection into vocal cord(s), therapeutic;
31571  Laryngoscopy, direct, with injection into vocal cord(s), therapeutic; with operating microscope or telescope
43201  Esophagoscopy, flexible, transoral; with directed submucosal injection(s), any substance
43236  Esophagogastroduodenoscopy, flexible, transoral; with directed submucosal injection(s), any substance
46505  Chemodenervation of internal anal sphincter
52287  Cystourethroscopy, with injection(s) for chemodenervation of the bladder
64611  Chemodenervation of parotid and submandibular salivary glands, bilateral
64612  Chemodenervation of muscle(s); muscle(s) innervated by facial nerve, unilateral (e.g., for blepharospasm or hemifacial spasm)
64615  Chemodenervation of muscle(s); muscle(s) innervated by facial, trigeminal, cervical spinal and accessory nerves, bilateral (e.g., for chronic migraine)
64616  Chemodenervation of muscle(s); neck muscle(s), excluding muscles of the larynx, unilateral (e.g., for cervical dystonia, spasmodic torticollis
64617  Chemodenervation of muscle(s); larynx, unilateral, percutaneous (e.g., for spasmodic dysphonia), includes guidance by needle electromyography, when performed
64642  Chemodenervation of one extremity; 1-4 muscle(s)
64643  Chemodenervation of one extremity; each additional extremity, 1-4 muscle(s) (List separately in addition to code for primary procedure)
64644  Chemodenervation of one extremity; 5 or more muscle(s)
64645  Chemodenervation of one extremity; each additional extremity, 5 or more muscle(s) (List separately in addition to code for primary procedure)
64646  Chemodenervation of trunk muscle(s); 1-5 muscle(s)
64647  Chemodenervation of trunk muscle(s); 6 or more muscle(s)
67345  Chemodenervation of extraocular muscle
J0585  Injection, onabotulinumtoxinA, 1 unit
J0586  Injection, abobotulinumtoxinA, 5 units
J0587  Injection, rimabotulinumtoxinB, 100 units
J0588  Injection, incobotulinum A, 1 unit

- In 2014, CPT established new chemodenervation codes for neck, larynx, extremity and trunk muscles: 64616, 64617, 64642, 64643, 64644, 64645, 64646, 64647.
- In 2013, CPT established specific codes for chemodenervation of the bladder and chemodenervation associated with treatment of chronic migraine: 52287, 64615.
- In 2011, CPT established a code for chemodenervation of parotid and submandibular salivary glands such as that to treat sialorrhea: 64611
• If fewer than 4 salivary glands are injected, code 64611 is to be reported with a modifier -52 to signify reduced service.
• In 2003, CPT established 2 codes (43201 and 43236) for upper gastrointestinal endoscopy procedures with submucosal injection, any substance. These codes could apply to the use of botulinum toxin for the treatment of achalasia.

**ICD-9 Diagnoses**

378.00- Strabismus and other disorders of binocular eye movements (code range)
378.9
333.6 Genetic torsion dystonia
333.71 Athetoid cerebral palsy
333.79 Other acquired torsion dystonia
333.81 Blepharospasm
333.82 Orofacial dyskinesia
333.83 Spasmodic Torticollis
333.84 Organic writer’s cramp
334.1 Hereditary spastic paraplegia
340 Multiple Sclerosis
341.0 Neuromyelitis optica
341.1 Schilder’s disease
342.10 Spastic hemiplegia, affecting unspecified side
342.11 Spastic hemiplegia, affecting dominant side
342.12 Spastic hemiplegia, affecting nondominant side
343.0 Infantile cerebral palsy, diplegic
343.1 Infantile cerebral palsy, hemiplegic
343.2 Infantile cerebral palsy, quadriplegic
343.3 Infantile cerebral palsy, monoplegic
343.4 Infantile cerebral palsy, infantile hemiplegia
343.8 Infantile cerebral palsy, other specified infantile cerebral palsy
343.9 Infantile cerebral palsy, unspecified
346.01 Migraine with aura; with intractable migraine, so stated without mention of status migrainosus
346.03 Migraine with aura; with intractable migraine, so stated, with status migrainosus
346.11 Migraine without aura; with intractable migraine, so stated without mention of status migrainosus
346.21 Variants of migraine, not elsewhere classified; with intractable migraine, so stated without mention of status migrainosus
346.23 Variants of migraine, not elsewhere classified; with intractable migraine, so stated, with status migrainosus
346.51 Persistent migraine aura without cerebral infarction; with intractable migraine, so stated without mention of status migrainosus
346.53 Persistent migraine aura without cerebral infarction; with intractable migraine, so stated, with status migrainosus
346.71 Chronic migraine without aura; with intractable migraine, so stated without mention of status migrainosus
346.73 Chronic migraine without aura; with intractable migraine, so stated, with status migrainosus
346.91  Migraine, unspecified; with intractable migraine, so stated without mention of status migrainosus
346.93  Migraine, unspecified; with intractable migraine, so stated, with status migrainosus
351.0   Facial nerve disorders, Bell's palsy
351.1   Facial nerve disorders, Geniculate ganglionitis
351.8   Facial nerve disorders, other facial nerve disorders
351.9   Facial nerve disorders, other
435.9   Unspecified transient cerebral ischemia
478.75  Laryngeal spasm
478.79  Other diseases of the larynx (spastic dysphonia)
530.0   Achalasia and cardiospasm
565.0   Anal fissure
705.21  Primary focal hyperhidrosis
723.5   Torticollis, unspecified
754.51  Talipes equinovarus
784.49  Voice and resonance disorders; other voice and resonance disorders
788.30- Urinary incontinence (code range)
788.39  

ICD-10 Diagnoses
G11.4   Hereditary spastic paraplegia
G24.09  Other drug induced dystonia
G24.1   Genetic torsion dystonia
G24.2   Idiopathic nonfamilial dystonia
G24.3   Spasmodic torticollis
G24.4   Idiopathic orofacial dystonia
G24.5   Blepharospasm
G35    Multiple sclerosis
G43.019 Migraine without aura, intractable, without status migrainosus
G43.111 Migraine with aura, intractable, with status migrainosus
G43.119 Migraine with aura, intractable, without status migrainosus
G43.511 Persistent migraine aura without cerebral infarction, intractable, with status migrainosus
G43.519 Persistent migraine aura without cerebral infarction, intractable, without status migrainosus
G43.711 Chronic migraine without aura, intractable, with status migrainosus
G43.719 Chronic migraine without aura, intractable, without status migrainosus
G43.811 Other migraine, intractable, with status migrainosus
G43.919 Migraine, unspecified, intractable, without status migrainosus
G43.81  Ophthalmoplegic migraine, intractable
G43.C1  Periodic headache syndromes in child or adult, intractable
G51.0   Bell's palsy
G51.3   Clonic hemifacial spasm
G51.4   Facial myokymia
G51.8   Other disorders of facial nerve
G51.9   Disorder of facial nerve, unspecified
G80.0   Spastic quadriplegic cerebral palsy
G80.1   Spastic diplegic cerebral palsy
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<tr>
<th>Code</th>
<th>Description</th>
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<td>G81.11</td>
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<td>G81.12</td>
<td>Spastic hemiplegia affecting left dominant side</td>
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<tr>
<td>G81.13</td>
<td>Spastic hemiplegia affecting right nondominant side</td>
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<td>G81.14</td>
<td>Spastic hemiplegia affecting left nondominant side</td>
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<td>H49.01</td>
<td>Third [oculomotor] nerve palsy, right eye</td>
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<td>Third [oculomotor] nerve palsy, bilateral</td>
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<td>Fourth [trochlear] nerve palsy, right eye</td>
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<td>Fourth [trochlear] nerve palsy, left eye</td>
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<td>H49.13</td>
<td>Fourth [trochlear] nerve palsy, bilateral</td>
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<td>Sixth [abducent] nerve palsy, right eye</td>
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<td>Total (external) ophthalmoplegia, bilateral</td>
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<td>Progressive external ophthalmoplegia, right eye</td>
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<td>Other paralytic strabismus, right eye</td>
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<td>H49.883</td>
<td>Other paralytic strabismus, bilateral</td>
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<td>Monocular esotropia with V pattern, left eye</td>
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<td>H50.05</td>
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<td>Alternating exotropia with other noncomitancies</td>
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<td>Vertical strabismus, right eye</td>
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<td>Intermittent monocular esotropia, left eye</td>
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<td>Intermittent alternating esotropia</td>
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<td>Intermittent monocular exotropia, right eye</td>
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<td>Intermittent monocular exotropia, left eye</td>
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<td>H50.34</td>
<td>Intermittent alternating exotropia</td>
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<td>H50.40</td>
<td>Unspecified heterotropia</td>
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<tr>
<td>H50.411</td>
<td>Cyclotropia, right eye</td>
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<td>Cyclotropia, left eye</td>
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<td>H50.42</td>
<td>Monofixation syndrome</td>
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<td>Esophoria</td>
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<td>Vertical heterophoria</td>
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<td>H50.54</td>
<td>Cyclophoria</td>
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<td>H50.55</td>
<td>Alternating heterophoria</td>
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<td>H50.611</td>
<td>Brown's sheath syndrome, right eye</td>
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<td>Brown's sheath syndrome, left eye</td>
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<td>H50.69</td>
<td>Other mechanical strabismus</td>
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<td>H50.811</td>
<td>Duane's syndrome, right eye</td>
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<td>Other specified strabismus</td>
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<td>Unspecified strabismus</td>
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<td>H51.0</td>
<td>Palsy (spasm) of conjugate gaze</td>
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<tr>
<td>H51.11</td>
<td>Convergence insufficiency</td>
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<tr>
<td>H51.12</td>
<td>Convergence excess</td>
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<tr>
<td>H51.21</td>
<td>Internuclear ophthalmoplegia, right eye</td>
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<tr>
<td>H51.22</td>
<td>Internuclear ophthalmoplegia, left eye</td>
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<td>H51.23</td>
<td>Internuclear ophthalmoplegia, bilateral</td>
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<td>Unspecified disorder of binocular movement</td>
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<td>J38.5</td>
<td>Laryngeal spasm</td>
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<td>Other diseases of larynx</td>
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<td>K60.0</td>
<td>Acute anal fissure</td>
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<td>K60.1</td>
<td>Chronic anal fissure</td>
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<td>K60.2</td>
<td>Anal fissure, unspecified</td>
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<tr>
<td>L74.510</td>
<td>Primary focal hyperhidrosis, axilla</td>
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<tr>
<td>L74.511</td>
<td>Primary focal hyperhidrosis, face</td>
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<td>L74.512</td>
<td>Primary focal hyperhidrosis, palms</td>
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<td>L74.513</td>
<td>Primary focal hyperhidrosis, soles</td>
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<td>M43.6</td>
<td>Torticollis</td>
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<td>N39.41</td>
<td>Urge incontinence</td>
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<tr>
<td>N39.42</td>
<td>Incontinence without sensory awareness</td>
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<td>N39.44</td>
<td>Nocturnal enuresis</td>
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<td>N39.46</td>
<td>Mixed incontinence</td>
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<td>N39.491</td>
<td>Coital incontinence</td>
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<td>Date</td>
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</tr>
<tr>
<td>10-19-2007</td>
<td>Policy section</td>
</tr>
</tbody>
</table>
| 07-18-2008 | Policy section    | • Added "F. The off-labeled use of botulinum toxin is considered medically necessary in the treatment of incontinence related to detrusor overactivity due to neurogenic causes (i.e. spinal cord injury), when anticholinergic therapy has failed," as an indication."  
• Specified H.13. Overactive bladder by adding "except as specified above." |
| 10-19-2009 | Header            | • Added reference to related policies of: Treatment of Hyperhidrosis and Treatment of Tinnitus |
|            | Description section | Updated Description section.                                                      |
|            | Policy section    | • Updated formatting and wording.                                             |
|            |                   | • Added medically necessary indication C4: "Incontinence due to detrusor overactivity (urge incontinence), either idiopathic or due to neurogenic causes (e.g., spinal cord injury, multiple sclerosis), that is inadequately controlled with anticholinergic therapy." |
|            |                   | • Clarified the list of experimental / investigational indications. This list was previously reflected as "...including, but not limited to...", so the additional indications added do not constitute a policy language change. |
|            |                   | • Revised denial of treatment of wrinkles or other cosmetic indications from "not medically necessary" to "non-covered". |
|            | Coding section    | Added CPT codes: 31513, 31570, 31571, 43201, 43236.                         |
|            |                   | Added Diagnosis coding range for urinary incontinence: 788.30-788.39.      |
| 01-01-2010 | Coding Section    | • Added HCPCS Code: J0586                                                   |
|            |                   | • Updated wording for HCPCS Code: J0585                                     |
| 02-25-2011 | Medical Policy Title | Updated.                                 |
|            |                   | • Removed "(i.e. Botox®, Myobloc ®)" to read "Botulinum Toxin (BT)."         |
|            | Policy Language section | Updated formatting and wording.                                               |
|            |                   | • Added medically necessary indication #11: "Chronic refractory migraine." |
|            |                   | • In the investigational indications section, Item #1, removed "including migraine, chronic daily headache, and tension type headache" and added "other than chronic refractory headache" to read "headaches, other than chronic refractory headaches." |
|            | Documentation section | Removed "There must be a stated goal of treatment." |
|            | Rationale section | Updated.                                                                     |
|            | Coding section    | • Added CPT code: 64611 (2011 Coding updates)                               |
|            |                   | • Added Diagnosis codes: 346.01, 376.03, 346.11, 346.13, .346.21, 346.23, 346.51, 346.53, 346.71, 346.73, 346.91, 346.93. |
Reference section updated.

<table>
<thead>
<tr>
<th>Date</th>
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<tbody>
<tr>
<td>05-13-2011</td>
<td>In Coding section, added HCPCS code Q2040.</td>
</tr>
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</table>
| 12-09-2011 | Updated Description section. In the Policy section:  
|            | • In Item A, #11, inserted “headaches” to read “Chronic refractory migraine headaches”  
|            | • In Item B, #9, inserted “(see separate policy on Treatment of Tinnitus)”  
|            | • In Item B, added the following indications:  
|            |   o #21. Prevention of pain associated with breast reconstruction after mastectomy  
|            |   o #22. Hirschsprung's disease”  
|            | Removed the Documentation section.  
|            | Removed the Utilization section.  
|            | Added Policy Guidelines section.  
|            | In Coding section:  
|            |   • Added the following CPT/HCPCS codes: 46505, C9278  
|            |   • Added the following Diagnosis codes: 333.71, 333.79, 333.81, 333.82, 333.83, 333.84, 340, 351.0, 351.1, 351.9, 435.9, 705.21, 754.51, 784.49  
|            | Updated the Rationale section.  
|            | Updated the Reference section. |
| 01-01-2012 | In the Policy section:  
|            | • In Item A, #6, removed “in patients who have not responded to dilation therapy or who are considered poor surgical candidates” to read “Esophageal achalasia”  
|            | In the Coding section:  
|            |   • Removed HCPCS codes: C9278, Q2040  
|            |   • Added HCPCS code: J0588  
|            |   • Added Diagnosis codes: 333.71, 333.79, 333.81, 333.82, 333.83, 333.84 (Diagnosis code, 333.7 was replaced with the appropriate codes for the policy.)  
| 01-15-2013 | In the Coding section:  
|            | • Added CPT code: 52287 and 64615 (Effective 01-01-2013)  
|            | • Updated CPT code 64612 nomenclature (Effective 01-01-2013)  
| 01-30-2014 | Updated Description section. In Policy section:  
|            | • In Item A, #9, replaced "(urge incontinence), either idiopathic or due to" with "associated with" to read "Incontinence due to detrusor overreactivity associated with neurogenic causes..."  
|            | • In Item A, added #12, "overactive bladder in adults that is inadequately controlled with anticholinergics."  
|            | • In Item B, added #23, "Facial wound healing."  
|            | • In Item B, added #24, "Internal anal sphincter (IAS) achalasia".  
|            | Moved the "Policy Guidelines" to the "Coding" section.  
|            | Updated Rationale section.  
|            | In Coding section:  
|            |   • Removed CPT codes: 64613 and 64614 (Deleted codes, effective December 31, 2013)  
|            |   • Added CPT codes: 64616, 64617, 64642, 64643, 64644, 64645, 64646, 64647 (New codes, effective January 1, 2014)  
|            |   • Added ICD-10 Diagnosis codes (Effective October 1,2014)  
|            | Updated Reference section. |
| 04-15-2014 | In Policy section:  
|            | • In Item B 1 removed the parenthesis around "(migraine)" to read, "headaches other than chronic refractory migraine headaches"  
|            | In Policy Guidelines:  
|            | • Added information pertaining to cervical dystonia and chronic migraine. |

*Contains Public Information*
<table>
<thead>
<tr>
<th>Date</th>
<th>Section</th>
<th>Updates</th>
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<tbody>
<tr>
<td>01-01-2015</td>
<td>Coding section</td>
<td>Updated coding instructions.</td>
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<tr>
<td>02-19-2016</td>
<td>Coding section</td>
<td>Revised CPT Codes: 43201, 43236 (Effective January 1, 2015)</td>
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<td></td>
<td>Policy section</td>
<td>Updated Description section.</td>
</tr>
<tr>
<td></td>
<td>Policy section</td>
<td>In Item A 6, added &quot;in patients who have not responded to dilation therapy or who are considered poor surgical candidates&quot; to read, &quot;Esophageal achalasia in patients who have not responded to dilation therapy or who are considered poor surgical candidates&quot;</td>
</tr>
<tr>
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<td>Policy section</td>
<td>In Item A 9, added &quot;Urinary&quot; to read, &quot;Urinary incontinence due to detrusor overactivity associated with neurogenic causes (e.g., spinal cord injury, multiple sclerosis), that is inadequately controlled with anticholinergics&quot;</td>
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<td></td>
<td>Policy section</td>
<td>Deleted previous Item A 10.</td>
</tr>
<tr>
<td></td>
<td>Policy section</td>
<td>In current Item A 10, added &quot;Prevention (treatment of) and &quot;in the following situations:&quot; and removed &quot;refractory&quot; to read, &quot;Prevention (treatment of) chronic migraine headaches in the following situations:&quot; and added bulleted criteria &quot;Meeting International Classification of Headache Disorders (ICHD-2) diagnostic criteria for chronic migraine headache (key criteria include migraine headaches lasting at least 4 hours on at least 15 days per month; migraine headaches for at least 3 months; absence of medication overuse); 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 (e.g., antidepressants, antihypertensives, antiepileptics). Patients who have contraindications to present medications are not required to undergo a trial of these agents.&quot;</td>
</tr>
<tr>
<td></td>
<td>Policy section</td>
<td>In current Item A 11, added &quot;unresponsive to or intolerant of&quot; and removed “that is inadequately controlled with&quot; to read, &quot;Overactive bladder in adults unresponsive to or intolerant of anticholinergics&quot;</td>
</tr>
<tr>
<td></td>
<td>Policy section</td>
<td>In Item B 1, added &quot;except as noted above for prevention (treatment) of and removed &quot;other than&quot; and &quot;refractory&quot; to read, &quot;Headaches, except as noted above for prevention (treatment) of chronic migraine headaches&quot;</td>
</tr>
<tr>
<td></td>
<td>Policy section</td>
<td>In Item B 6, added &quot;/ fibromyalgia / fibromyositis&quot; to read, &quot;Myofascial pain syndrome / fibromyalgia / fibromyositis.&quot;</td>
</tr>
<tr>
<td></td>
<td>Policy section</td>
<td>In Item B 11, added &quot;ICD-10 F95.1&quot; and &quot;ICD-10 F95.2&quot;, and removed &quot;ICD-9 307.22&quot; and &quot;ICD-9-9 307.23&quot; to read, &quot;Chronic motor tic disorder (ICD-10 F95.1), and tics associated with Tourette syndrome (motor tics) (ICD-10 F95.2).&quot;</td>
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<tr>
<td></td>
<td>Policy section</td>
<td>Removed previous Items B 17, 19, and 20.</td>
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<tr>
<td></td>
<td>Policy section</td>
<td>Added current Items B 21-23.</td>
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<td>Rationale section</td>
<td>Updated Rationale section.</td>
</tr>
<tr>
<td>07-01-2016</td>
<td>Coding section</td>
<td>Removed CPT codes: 64650 and 64653.</td>
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<tr>
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<td>References section</td>
<td>Updated References section.</td>
</tr>
<tr>
<td>10-01-2016</td>
<td>Coding section</td>
<td>Added ICD-10 codes effective 10-01-2016: N39.491, N39.492</td>
</tr>
</tbody>
</table>
03-29-2017

In Policy section:
- In Item C, removed "may be considered not medically necessary" and added "is noncovered" to read, "The use of botulinum toxin as a treatment of wrinkles or other cosmetic indications is noncovered."

REFERENCES


Contains Public Information


Other References
1. Blue Cross and Blue Shield of Kansas Urology Liaison Committee meeting, August 24, 2005 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report. MAC-03-05).
2. Blue Cross and Blue Shield of Kansas Medical Advisory Committee meeting, November 3, 2005 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report. MAC-03-05).
5. Blue Cross and Blue Shield of Kansas Surgery Liaison Committee, August 2010.