



Name of Policy:
Botulinum Toxin

Policy #: 074
Category: Medical/Pharmacy

Latest Review Date: September 2013
Policy Grade: A

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

- 1. The technology must have final approval from the appropriate government regulatory bodies;*
- 2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
- 3. The technology must improve the net health outcome;*
- 4. The technology must be as beneficial as any established alternatives;*
- 5. The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

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

Description of Procedure or Service:

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

There are seven distinct serotypes designated as type A, B, C-1, D, E, F, and G. In the U.S., four preparations of botulinum are commercially available, three using type A serotype and one using type B. The drug names of the botulinum toxin products were changed in 2009; trade names and product formulations did not change. The three formulations of botulinum toxin type A are currently called onabotulinumtoxinA (Botox®), abobotulinumtoxinA (Dysport®), and incobotulinumtoxinA (Xeomin®). 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 four years. Myobloc® contains botulinum toxin type B; the current name of this drug is rimabotulinumtoxinB.

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

Among the botulinum toxin products, onabotulinumtoxinA (Botox) is FDA-approved for the largest number of indications. Other than the indications mentioned above, this includes 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 four hours in duration) that occur on at least 15 days per month for more than three 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.

The newest product, Xeomin, is approved for treating blepharospasm.

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

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

Policy:

Botulinum toxin A (onabotulinumtoxinA) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the following FDA-approved indications:

- Blepharospasm
- Cervical dystonia
- Hemifacial spasm (facial nerve VII disorders)
- Strabismus and other disorders of binocular eye movements
- Increased muscle stiffness in the elbow, wrist and fingers in adults with upper limb spasticity (**effective 03/10/2010**)
- Overactive bladder (**effective 01/18/2013**)
- Treatment or Prevention of chronic migraine headache in adult patients in the following situations:
 - Initial 6-month trial when **all** of the following criteria is met: (**effective 03/26/2011**)
 - Migraine headaches occur ≥ 15 days per month for at least three months, provided there is no medication over use. (ICHD-2 criteria)
 - Migraine headaches last four or more hours per day and interfere with activities of daily living. (ICHD-2 criteria)
 - Symptoms persist despite trial of at least 2 agents used to prevent or reduce migraine frequency representing different classes of these medications. (Patients who have contraindication to preventive medications are not required to undergo a trial of these agents.)
 - Maximum units to be injected cannot exceed 155 units.
 - Continuing treatment beyond 6-months when one of the following criteria is met: (**effective 11/18/2013**)
 - Migraine headache frequency reduced by a least 7 days per month compared to pre-treatment level; **or**
 - Migraine headache duration reduced at least 100 hours per month compared to pre-treatment level.

Botulinum toxin B (rimabotulinumtoxinB) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the following FDA-approved indications:

- Cervical dystonia

Botulinum toxin A and B meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the following **off-label uses**:

- Achalasia and cardiospasm
- Anal/rectal fissures
- Anal spasm
- Congenital torticollis
- Fragments of torsion dystonia, other
- Hereditary spastic paraplegia
- Hyperhidrosis (excessive sweating) (**refer to Treatment of Hyperhidrosis policy for coverage criteria**)
- Idiopathic toe walking

- when used with serial casting and physical therapy; **and**
- the etiology of persistent toe walking is unknown (no other neuromuscular disorders present); **and**
- must be at least 4 years of age
- Idiopathic torsion dystonia
- Infantile cerebral palsy
- Laryngeal dystonia
- Multiple sclerosis
- Organic writer's cramp
- Orofacial dyskinesia
- Other demyelinating diseases of CNS
- Other facial nerve disorders
- Other paralytic syndromes
- Sialorrhea (drooling) associated with Parkinson disease
- Spasmodic dysphonia
- Spasmodic torticollis
- Spastic hemiplegia
- Strabismus and other disorders of binocular eye movements
- Symptomatic torsion dystonia
- Torticollis, unspecified
- Trigeminal neuralgia, other trigeminal nerve disorder, unspecified
- Urinary incontinence due to detrusor overactivity associated with neurogenic causes (e.g., spinal cord injury, multiple sclerosis), that is inadequately controlled with anticholinergics

Effective for dates of service on or after October 15, 2010 through March 25, 2011:

- Prophylaxis of headaches in adult patients with Chronic Migraine (≥ 15 days per month with headache lasting 4 hours a day or longer and interferes with the activities of daily living not to exceed 155 units) (ICD-9 code: 346.00-346.93)

Abobotulinumtoxin A (Dysport™) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for treatment of the following FDA-approved indications:

- cervical dystonia (**effective 04/29/2009**)

Abobotulinumtoxin A (Dysport™) does not meet Blue Cross and Blue Shield of Alabama's medical criteria for the **treatment of glabellar lines as this is considered cosmetic** and contract exclusion.

IncobotulinumtoxinA (Xeomin) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the treatment of adults for the following FDA-approved indications:

- cervical dystonia (**effective 08/02/2010**)
- blepharospasm (**effective 08/02/2010**)

Ultrasound guidance and/or diagnostic ultrasound prior to or concurrent with injection of Botulinum Toxin does not meet Blue Cross and Blue Shield of Alabama criteria for coverage. If guidance is required to isolate a muscle group, it should be done using EMG.

Botulinum toxin does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** for the following, but not limited to, indications:

- Benign prostatic hyperplasia
- Detrusor sphincteric dyssynergia (after spinal cord injury)
- Gastroparesis
- Headaches, except as noted above for prevention (treatment) of chronic migraine headache
- Hirschsprung's disease
- Interstitial cystitis
- Joint pain
- Lateral epicondylitis
- Low-back pain
- Mechanical neck disorders
- Myofascial pain (trigger points included)
- Neuropathic pain after neck dissection
- Pain after hemorrhoidectomy or lumpectomy (breast)
- Prevention of pain associated with breast reconstruction after mastectomy
- Sialorrhea (drooling) except that associated with Parkinson disease
- Tinnitus
- Tremors such as essential tremor, chronic motor tic disorder and tics associated with Tourette syndrome

Botulinum toxin does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **cosmetic** when used for the treatment of **wrinkles or other cosmetic indications**.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

In December 1989, the United States Food and Drug Administration (FDA) approved a commercial preparation of botulinum toxin A (Botox) for therapeutic use in patients with strabismus, certain movement disorders (blepharospasm), and cranial nerve VII nerve disorders (e.g., hemifacial spasm). In December 2000, additional approval for Botox was given for cervical dystonia. In April 2002 approval was granted for Botox for the indication of glabellar lines (wrinkles). Botulinum toxin B (Myobloc) was approved in December 2000 for the treatment of patients with cervical dystonia. Human disease is caused by types A, B, E, and (rarely) F.

The mechanism of action for botulinum toxins is injection into hyperactive muscles inducing a reversible cholinergic blockade at the neuromuscular junction, thus reducing muscle contractions. This produces a localized chemical removal of the nerve supply to a tissue or denervation. Although the denervation with botulinum toxin is reversible, the effect is long lasting. Periodic dosing, however, is required to maintain efficacy. After repeated use of high doses, antibodies can develop in some individuals, making further treatment ineffective indefinitely.

Most clinical trials reported in the literature are using botulinum-A (Botox) and it is anticipated that botulinum-B (Myobloc) will be used for the same range of off-label uses. Numerous off-label indications that have been included in studies and have shown to be safe are: laryngeal dystonia, various spastic disorders, oromandibular dystonia, writer's cramp, achalasia, chronic anal fissures, hyperhidrosis, and extreme spasticity or in spastic foot drop after stroke.

Dystonia/Spasticity

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

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

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

In addition, the AAN assessments summarized the evidence and 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 focal limb dystonia but insufficient for lower focal limb dystonia, and was rated level B for adductor laryngeal dystonia but insufficient for abductor laryngeal dystonia. The bulk of the literature is based on trials using onabotulinumtoxinA (i.e., Botox).

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

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

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

In 2013, Foley and colleagues identified 16 randomized controlled trials (RCTs) comparing injection of botulinum toxin to placebo injections or a non-pharmacologic treatment of moderate to severe upper-extremity spasticity following stroke. 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 to comparison interventions (standardized mean difference [SMD]: 0.54, 95% confidence interval [CI]: 0.35 to 0.71, $p < 0.001$). The largest RCT was published in 2011 by

Shaw and colleagues included 333 patients with post-stroke upper limb spasticity to physical therapy plus Dysport (n=170) or physical therapy alone (n=163). The primary outcome, improved function at one 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 three or 12 months. Change in muscle tone according to median change in the MAS significantly favored the Dysport group over the placebo group at one month (mean change= -0.6 and -0.1, respectively, $p<0.001$), but not at three and 12 months.

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

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

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

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

Strabismus

Strabismus is a condition in which the eyes are not in proper alignment with one another. In 2012, a Cochrane review was published by Rowe and colleagues evaluating the literature on botulinum toxin for strabismus. The investigators identified four RCTs, all of which were published in the 1990s. Three trials compared botulinum toxin injection to surgery, and one compared botulinum toxin injection to a non-invasive treatment control group. Among the trials that used surgery as a comparison intervention, two studies found no statistically significant

differences in outcomes between the two groups, and one found a higher rate of a satisfactory outcome in the surgery group. The study comparing botulinum toxin to no intervention did not find a significant difference in outcomes in the two groups. Complications after botulinum toxin included transient ptosis and vertical deviation; combined complication rates ranged from 24% to 56% in the studies.

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

Section summary:

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, because this treatment is a non-invasive alternative to surgery, it may be considered medically necessary.

Blepharospasm

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

Esophageal Achalasia

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

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

Anal Fissure

Chronic anal fissure is a tear in the lower half of the anal canal that is maintained by contraction of the internal anal sphincter and is treated surgically with an internal sphincterotomy. Since the anal sphincter contraction could be characterized as a dystonia, botulinum toxin is a logical medical approach. In 1998, Maria and colleagues randomly assigned 30 patients with chronic anal fissure to receive either two injections of 20 units of botulinum toxin, on either side of the fissure, or two injections of saline. After two months, 11 patients in the treatment group reported healing, compared to only two in the control group. The four patients who still had fissures after two months underwent retreatment with botulinum toxin; two of these four patients reported healing scars and symptomatic relief. These results are consistent with earlier case series that reported a healing rate of 80%. Nitroglycerin ointment has also been used to successfully treat anal fissure. In 1999, Brisinda and colleagues in Italy compared the results of nitroglycerin ointment and botulinum toxin in a randomized trial of 50 patients. After two months, 96% of the fissures were healed in the botulinum group compared with 60% in the nitroglycerin group. Brisinda and colleagues conducted a second, similar trial in 2007 with 92% versus 70%, respectively, healing rates for botulinum toxin A-treated versus nitroglycerin ointment-treated patients ($p < 0.001$). Another trial by Brisinda and colleagues 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 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 two RCTs comparing botulinum toxin with placebo, one RCT comparing botulinum toxin with lidocaine pomme, five RCTs comparing botulinum toxin with nitrates, and eight RCTs comparing botulinum toxin with surgery. A meta-analysis was not performed due to heterogeneity among studies. The author noted that the studies tended to be small and of short duration, and superiority of botulinum toxin over surgery has not been demonstrated. However, due to the fact that it is a minimally invasive option that can be repeated, it is a reasonable option prior to surgery.

Section summary:

Due to evidence of effectiveness in numerous small RCTs, combined with being a less invasive option than the gold standard of surgery, botulinum toxin is considered medically necessary for treatment of anal fissure.

Urologic Applications

Detrusor overactivity/overactive bladder

In 2011, Duthie and colleagues published a Cochrane review of RCTs evaluating botulinum toxin injections for treating adults with overactive bladder syndrome. The authors identified 19 trials that compare treatment with botulinum toxin to placebo or another intervention in patients with idiopathic or neurogenic overactive bladder. Two studies included botulinum toxin B; the

remainder included botulinum toxin A. The outcomes reported varied, which made it difficult for the authors to pool study findings. A pooled analysis of three studies reporting change in urinary frequency episodes at four to six weeks reported a significantly better outcome with botulinum toxin injection compared to placebo (pooled mean difference: -6.50; 95% CI: -8.92 to -4.07). A pooled analysis of three studies on change in incontinence episodes at four to six weeks also found a significantly greater improvement with botulinum toxin (mean difference: -1.58; 95% CI: -2.16 to -1.01). The findings were similar when two studies that reported outcomes at 12 weeks were pooled. It was noted by the authors that additional data are needed on long-term outcomes and optimal dose of botulinum toxin. This review suggests that botulinum toxin injections are an effective treatment for refractory overactive bladder symptoms.

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

In 2005, Ghei and colleagues conducted a double-blind placebo-controlled crossover trial with 20 patients who had detrusor overactivity unresponsive to oral antimuscarinic agents. Patients received botulinum toxin B or placebo in random order, with six weeks between treatments. There was significantly greater reduction in incontinence episodes and improvement in quality of life with active botulinum toxin injection. In addition, in 2011, Hershorn and colleagues published a double-blind trial that included 57 patients with neurogenic detrusor inactivity. Botulinum toxin A injections were compared to placebo. At weeks six, 24 and 36, the mean daily frequency of incontinence episodes was significantly lower in the botulinum toxin group than the placebo group. At six weeks, there were an average of 1.31 incontinence episodes in the botulinum toxin group compared to 4.75 with placebo, $p < 0.001$.

Representative large, double-blind RCTs are described below:

In 2013, Nitti and colleagues published data from an industry-supported study that included 557 patients with overactive bladder and urinary incontinence inadequately controlled by anticholinergics. Patients were randomized to receive an intradetrusor injection of onabotulinumtoxinA 100U or placebo. At the 12-week follow-up, there was a statistically significantly greater decrease 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 endpoint 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, urinary tract infections occurred in 43 of 278 patients (15.5%) in the botulinum toxin group and 16 of 272 patients (5.9%) in the placebo group. Urinary retention was reported by 15 patients (5.4%) in the A 2012 industry-supported RCT by Ginsberg and colleagues included 416 patients with neurogenic detrusor activity associated with multiple sclerosis or spinal cord injury. Patients were randomized to receive injections with 200U onabotulinumtoxinA, 300U onabotulinumtoxinA or placebo. Decrease in the mean number of weekly incontinence episodes at week six, the primary endpoint, was significantly greater in both active treatment groups (-21 in the 200U group and -23 in the 300U 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 200U group, 42% in the 300 U group and 10% on placebo initiated catheterization. A total of 329 of 416 patients (79%) completed the 52 week study, however outcomes such as the number of weekly incontinence episodes were not reported at 52 weeks.

Section summary:

Numerous RCTs as well as observational data report improvements in outcomes following botulinum toxin treatment in patients with neurogenic detrusor overactivity or overactive bladder who are unresponsive anticholinergic medication. However, intradetrusor injection of botulinum toxin may increase the risk of adverse events including urinary retention and urinary tract infection.

Detrusor sphincter dyssynergia

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

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

studies were the same ones included in the Mehta systematic review. Authors of both systematic reviews noted that, while most of the available studies have reported improvements with botulinum toxin injections, there are few published studies, and studies included small numbers of patients. There is insufficient evidence from RCTs on the impact of botulinum toxin on health outcomes for patients with detrusor sphincter dyssynergia; therefore, this indication is considered investigational.

Benign prostatic hyperplasia (BPH)

The rationale for botulinum treatment is based on the theory that symptoms of benign prostatic hyperplasia are in part due to a static component related to prostate size and a dynamic component related to the contraction of smooth muscle within the gland. Botulinum therapy addresses this latter component. In 2012, Marchal and colleagues published a systematic review of the literature on use of botulinum toxin in treating benign prostatic hyperplasia. The authors identified 25 studies on this topic, including controlled and uncontrolled studies and abstracts published in journal supplements. There were six RCTs, three published as full articles and three as abstracts. Two of the three published RCTs were considered to be of sufficient quality for meta-analysis. The authors reported that pre- and post-treatment mean post-voiding residue did not differ significantly; pooled results were not reported for between-group outcomes. One of the RCTs was published by Maria and colleagues in 2003. The investigators reported on 30 patients with BPH randomly assigned to receive either intraprostatic botulinum toxin A or saline injection. Inclusion criteria for this trial included moderate-to-severe symptoms of BPH based on the American Urological Association (AUA) score and a mean peak urinary flow rate of no more than 15 mL per second with a voided volume of 150 mL or less. After two months, the AUA symptom score decreased by 65% among those receiving botulinum toxin compared to no significant change in the control group. The mean peak urinary flow rate was significantly increased in the treatment group.

Section summary:

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

Interstitial cystitis

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

Section summary:

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

Tremor

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

Sialorrhea (Drooling)

A number of RCTs have evaluated botulinum toxin injection compared with placebo injection to control sialorrhea in patients with neurologic diseases (e.g., Parkinson, cerebral palsy, amyotrophic lateral sclerosis [ALS]). The largest amount of evidence is available on botulinum toxin for treating Parkinson disease. For example, in 2006, Lagalla et al randomly assigned 32 patients with Parkinson disease to placebo or 50 U botulinum toxin A; evaluation at one month post-injection resulted in significant improvements compared with placebo, in drooling frequency, saliva output, and in familial and social embarrassment. Dysphagia scores were not significantly improved. Moreover, Ondo and colleagues randomly assigned 16 patients with Parkinson disease to receive placebo or 2,500 U of botulinum toxin B (Myobloc). The botulinum toxin group had significantly better outcome than the placebo group at one month on four drooling outcomes. Groups did not differ on salivary gland imaging and a dysphagia scale. Mancini and colleagues assigned 20 patients with Parkinson disease to injections of either a saline placebo or 450 U of Dysport. The treatment group was significantly better than placebo on a drooling scale at one week; the effect disappeared by three months.

Cerebral Palsy

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

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

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

Section summary:

While some questions remain, studies on those with Parkinson disease provide consistent findings related to impact on sialorrhea. 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.

Chronic Low Back Pain

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

Headache

Botulinum toxin for treatment of pain from migraine and from chronic tension-type headaches was addressed in a TEC Assessment that was completed in 2002 and updated in 2004. Both TEC 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, among other characteristics, 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 five attacks per month meeting other diagnostic criteria. Chronic migraine is defined as attacks on at least 15 days per month for more than three months, in the absence of medication overuse.

Several RCTs and systematic reviews of RCTs have been published. Most recently, in 2013, the Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review on preventive pharmacological treatments for migraine in adults. The investigators identified 15 double-blind RCTs evaluating botulinum toxin for migraine prevention; 13 used onabotulinumtoxin A and two used abobotulinumtoxin A. In a meta-analysis of three RCTs, onabotulinumtoxin A 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, onabotulinumtoxin A 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 onabotulinumtoxin A and another medication (topiramate or divalproex sodium). Findings were not pooled but for the most part there were not statistically significant differences in outcomes between the two drugs.

In 2012, Jackson and colleagues conducted a meta-analysis of RCTs on botulinum toxin A for the prophylactic treatment of headache in adults; the analysis addressed migraines, as well as other types of headache. The investigators included RCTs that were at least four weeks in duration, had reduction in headache frequency or severity as an outcome, and used patient-reported outcomes. The investigators reviewed study eligibility criteria and categorized them as addressing episodic (<15 headaches per month) or chronic headache (at least 15 days per month). A total of 10 trials on episodic migraine and seven trials on chronic migraine were identified. All of the trials on episodic migraine and five of seven trials on chronic migraine were placebo-controlled; the other two trials compared botulinum toxin injections to oral medication. A pooled analysis of the studies on chronic migraine found a statistically significantly greater reduction in the frequency of headaches per month with botulinum toxin versus a control intervention (difference: -2.30, 95% CI: -3.66 to -0.94, 5 trials). In contrast, in a pooled analysis of studies on episodic migraine, there was not a statistically significant difference between groups in the change in monthly headache frequency (difference: -0.05, 95% CI: -0.25 to 0.36, nine trials).

Previously, in 2009, Shuhendler and colleagues published a systematic review and meta-analysis of trials on botulinum toxin for treating episodic migraines. The investigators identified eight 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 standardized mean difference (SMD) was -0.06 (95% confidence interval [CI]: -0.14 to 0.03, $p=0.18$). After 90 days, the SMD was -0.05 (95% CI: -0.13 to 0.04, $p=0.28$). A subgroup analysis that separately examined trials using low-dose botulinum toxin A

(less than 100 units) separately from trials using high-dose botulinum toxin A (100 units or more) did not find a statistically significant effect of botulinum toxin A compared to placebo in either strata.

A pair of multicenter RCTs that evaluated onabotulinumtoxinA (Botox) for chronic migraine was published in 2010. The trials reported findings from the double-blind portions of the industry-sponsored PREEMPT (Phase II Research Evaluating Migraine Prophylaxis Therapy) studies 1 and 2. Study designs were similar. Both studies 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 four 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 three months or exclude patients who overused pain medication, two of the ICHD-2 criteria for chronic migraine. Eligible patients were randomly assigned to receive two cycles of injections of Botox 155 U or placebo, with 12 weeks between cycles. Randomization was stratified based on the frequency of acute headache pain medication during baseline and whether or not they overused acute headache pain medication. (Medication overuse was defined as baseline intake of simple analgesics on at least 15 days or other medications for at least 10 days and medication use at least two days per week.) The primary endpoint in PREEMPT 1 was mean change from baseline in frequency of headache episodes for 28 days ending with week 24. A headache episode was defined as a headache with a start and stop time indicating that pain lasted at least four hours. Prespecified secondary outcomes included, among others, change in frequency of headache days (calendar days in which pain lasted at least four hours), migraine days (calendar days in which a migraine lasted at least four hours), and migraine episodes (migraine with a start and stop time indicating that pain lasted at least four hours). Based on availability of data from PREEMPT 1 and other factors, the protocol of the PREEMPT 2 trial was amended (after study initiation but before unmasking) to make frequency of headache days the primary endpoint of this study. The authors noted that, to control for potential Type-1 error related to changes to the outcome measures, a more conservative p value, 0.01 instead of 0.05, was used. Several quality-of-life measures were also included in the trials. This includes the six-item Headache Impact Test (HIT-6) and the Migraine Specific Quality of Life Questionnaire (MSQ v.2). Key findings of the two 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 one prophylactic medication and approximately 68% overused headache pain medication during baseline. A total of 296/341 (87%) in the Botox group and 295/338 (87%) in the placebo group completed the 24-week double-blind phase. The primary outcome, change from baseline in frequency of headache episodes over a 28-day period, did not differ significantly between groups. The number of headache episodes decreased by a mean of 5.2 in the Botox group and 5.3 in the placebo group ($p=0.344$). Similarly, the number of migraine episodes did not differ significantly. There was a decrease of 4.8 migraine episodes in the Botox group and 4.9 in the placebo group, $p=0.206$. In contrast, there was a significantly greater decrease in the number of headache days and the number of migraine days in the Botox

group compared to the placebo group. The decrease in frequency of headache days was 7.8 in the Botox group and 6.4 in the placebo group, a difference of 1.4 headache days per 28 days, $p=0.006$. Corresponding numbers for migraine days were 7.6 and 6.1, respectively, $p=0.002$. There was significantly greater improvement in quality of life in the Botox versus the placebo group. The proportion of patients with severe impact of headaches (i.e., HIT-6 score at least 60) in the Botox group decreased from 94% at baseline to 69% at 24 weeks and in the placebo group decreased from 95% at baseline to 80%. There was a between-group difference of 11%, $p=0.001$. The authors did not report scores on the Migraine Specific Quality (MSQ) of Life Questionnaire but stated that there was statistically significant greater improvement in the 3 MSQ role function domains at week 24, restrictive ($p<0.01$), preventive ($p=0.05$), and emotional ($p<0.002$). Adverse events were experienced by 203 patients (60%) in the Botox group and 156 patients (47%) in the placebo group. Eighteen patients (5%) in the Botox group and eight (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. The mean number of migraine days during baseline period was 19.2 in the Botox group and 18.7 in the placebo group. The mean number of headache episodes during the 28-day baseline period was 12.0 in the Botox group and 12.7 in the placebo group. Approximately 65% of patients had previously used at least one prophylactic medication and approximately 63% overused headache pain medication during baseline. A total of 311/347 (90%) in the Botox group and 334/358 (93%) in the placebo group completed the 24-week double-blind phase. The primary outcome, change from baseline frequency of headache days over a 28-day period (a different primary outcome than PREEMPT 1) differed significantly between groups and favored Botox treatment. The number of headache days decreased by a mean of 9.0 in the Botox group and 6.7 in the placebo group, a difference of 2.3 days per 28 days ($p<0.001$). The number of migraine days also decreased significantly, more in the Botox compared to the placebo groups, a mean of 8.7 versus 6.3 ($p<0.001$). In contrast to PREEMPT 1, there was a significantly greater decrease in headache episodes in the Botox group than the placebo group, 5.3 versus 4.6, $p=0.003$. Change in frequency of migraine episodes was not reported.

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

Also published in 2010 was a pooled analysis of findings from the PREEMPT 1 and PREEMPT 2 studies; this analysis was also industry-sponsored. There were 688 patients in the Botox group and 696 in the placebo group in the pooled analysis of outcomes at week 24. In the combined analyses, there was a significantly greater reduction in change from baseline in frequency of

headache days, migraine days, headache episodes and migraine episodes in the Botox compared to placebo groups. For example, the pooled change in frequency of headache days was a mean of 8.4 in the Botox group and 6.6 in the placebo group, $p < 0.001$. The mean difference in number of headache days over a 28-day data collection period was 1.8 (95% CI: 1.13 to 2.52). The pooled change in frequency of headache episodes was 5.2 in the Botox group and 4.9 in the placebo group, a relative difference of 0.3 episodes (95% CI: 0.17 to 1.17, $p = 0.009$). Between-group differences, though statistically significant, were relatively small and may not be clinically significant. In the pooled analysis, the authors also reported the proportion of patients with at least a 50% decrease from baseline in the frequency of headache days at each time point (every four weeks from week four 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 eight. The article did not report the proportion of participants who experienced at least a 50% reduction in migraine days or migraine episodes. The pooled analysis had statistically significant findings for the change in proportion of patients with severe headache impact according to the HIT-6 and change in MSQ questionnaire domains.

There are several issues worth noting regarding the methodology and findings of the PREEMPT studies. There was a statistically significant difference in headache episodes in PREEMPT 2 but not PREEMPT 1 (for which it was the primary outcome); the primary outcome was changed after initiation of PREEMPT 1. Moreover, 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 these were presented as secondary efficacy outcomes.

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

Another example of an RCT on botulinum toxin for treating chronic migraine was published by Cady and colleagues. 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 endpoint, Physician Global Assessment at week 12, physicians noted improvement in 19 of 24 (79%) in the Botox group and 17 of 24 (71%) in the topiramate group; nine patients (15%) were not available for this analysis.

Tension headache

The 2012 meta-analysis by Jackson and colleagues, discussed above, identified seven RCTs evaluating botulinum toxin for treating chronic tension-type headaches; all were placebo-controlled. A pooled analysis of these seven 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 was published by Silberstein and colleagues in 2006. This study included 300 patients randomized to one of four doses of botulinum toxin or placebo. Overall, there was not a 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 this category is not recognized in the International Classification of Headache Disorders, it is commonly defined to include different kinds of chronic headache such as chronic or transformed migraine and daily persistent headache and may also include chronic tension-type headache, addressed separately here. The 2012 meta-analysis by Jackson and colleagues identified three RCTs comparing botulinum toxin A to placebo in patients with at least 15 headaches per month. A pooled analysis of data from these three trials found a significantly greater reduction in the number of headaches per month in the botulinum toxin versus the placebo group (difference: -2.06, 95% CI: -3.56 to -0.56). Individually, only one of the three trials, published by Ondo and colleagues in 2004, found a statistically significant benefit with botulinum toxin treatment. This study included 60 patients and included patients with chronic migraines, as well as chronic tension-type headache. The Ondo study found significantly greater reduction in the number of headache-free days over weeks eight to 12 in the botulinum toxin versus placebo group ($p < 0.05$), but there was not a statistically significant between-group difference in reduction in headache-free days over the entire 12-week study period ($p = 0.07$). The other two studies had much larger sample sizes; 355 patients in a study by Mathew and colleagues and 702 patients in a study by Silberstein and colleagues. Neither found a statistically significant difference in the reduction in the number of headache days per month with botulinum toxin versus placebo. The available evidence from RCTs is conflicting and insufficient for conclusions; thus chronic daily headache remains an investigational indication.

Cluster headache

No controlled trials have been reported on this type of headache. Thus, botulinum toxin is considered investigational for this indication.

Cervicogenic Headache

In 2011, Linde and colleagues published a double-blind placebo-controlled crossover study that included 28 patients with treatment-resistant cervicogenic headache. Patients were randomized to treatment with botulinum toxin A and placebo, in random order; there was at least an eight-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, randomly assigned patients with chronic headache related to whiplash injury to botulinum toxin A treatment or placebo. One trial reported trends toward improvement with treatment for various outcomes; most were not statistically significant. Another reported no significant differences in any of several pain-related

outcomes. One trial reported a significant improvement in pain with treatment while the placebo group reported no improvement, but the study design was flawed in that the placebo group reported less pain at baseline. A Cochrane review of treatment of mechanical neck disorders, published in 2007, included six RCTs (total N=273) of botulinum toxin compared to placebo for chronic neck disorders with or without radicular findings or headache. A meta-analysis of four studies (total N=139) for pain outcomes gave a nonsignificant result. The authors concluded that a range of doses have not shown significant differences compared to placebo or to each other.

Section summary:

For patients with migraine headache, the published evidence does not suggest that botulinum toxin improves net health outcome for patients with an episodic pattern (i.e., fewer than 15 episodes per month); thus, it is considered investigational. There are several published RCTs on botulinum toxin for chronic migraine including the PREEMPT 1 and 2 trials, which had a number of statistically significant findings but the clinical significance of these results were unclear. The 2012 meta-analysis by Jackson et al found that botulinum toxin reduced the frequency of headaches per month compared to placebo or medication. Based on the published data, U.S. Food and Drug Administration (FDA)-approval, and clinical input obtained in 2010, botulinum toxin is considered medically necessary for the prevention of chronic migraine in certain situations, i.e., patients diagnosed with chronic migraine who failed trials of other medications.

For tension headache, RCTs and systematic reviews have been performed. These do not indicate that botulinum toxin improves outcomes. For other headache types, the evidence is scant and insufficient to form conclusions about efficacy.

Myofascial Pain Syndrome

Painful muscles with increased tone and stiffness containing trigger points characterize myofascial pain syndrome. Patients are often treated with injections of the trigger points with saline, dilute anesthetics, or dry needling. These trigger-point injections, while considered established therapy, have been controversial, since it is unclear whether any treatment effect is due to the injection, dry needling of the trigger point, or a placebo effect. The optimal study to evaluate the efficacy of botulinum toxin injection for treating myofascial pain syndrome would be double-blind to minimize the placebo effect and would compare injections of botulinum toxin to dry needling and to anesthetic injection. A 2013 systematic review of evidence on botulinum toxin for treating myofascial pain syndrome searched for studies that were double-blind and compared botulinum toxin injection to an alternate intervention. Seven RCTs were identified that met the review's inclusion criteria; all seven included placebo-control groups. Duration of follow-up in the studies varied from two to six months. Five of seven RCTs reported no significant difference between groups in all or nearly all outcomes. In one of the five, more adverse events were reported by the botulinum toxin group than the saline group. A sixth study reported no significant difference between groups on pain outcomes, but significantly greater improvement in electromyography (EMG) outcomes. The seventh study found significantly greater improvement in pain outcomes with botulinum toxin injection compared to placebo. This positive study, by Gobel and colleagues, received the highest score on the methodological quality instrument used by the review authors. The Gobel study was the only RCT identified to

control for co-interventions by not permitting other treatments e.g., NSAIDS or opioids. The 2013 systematic review did not pool study findings.

A 2011 meta-analysis by Langevin and colleagues of four trials comparing botulinum toxin to placebo for chronic myofascial neck pain did not find a statistically significant short-term difference between groups. The pooled standard mean difference (SMD) was -0.21 (95% CI=-0.50 to 0.70). These four trials were considered by the authors to have high validity; that is they scored at least six on a 12-point risk of bias instrument used by the Cochrane collaboration.

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

Section summary:

Numerous RCTs have been performed for treatment of myofascial pain syndrome. The majority of these trials do not report benefit for botulinum toxin.

Pain Control after Hemorrhoidectomy

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

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 either botulinum toxin A or placebo. Pain scores were reduced for both groups, but there were no significant differences between groups. The trial likely was underpowered to detect clinically significant differences in outcomes

between groups. Other studies include a small, open-label trial from 2006 that tested botulinum toxin A injections in painful vulvar tissue to alleviate provoked vestibulodynia (n=19). Patients receiving either of two doses had significantly reduced pain compared to baseline for eight (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 to baseline, there were nonsignificant reductions in pelvic pain and nonsignificant improvements in quality of life. The evidence is insufficient for this indication.

Neuropathic Pain after Neck Dissection

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

Lateral Epicondylitis and Other Joint Pain

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

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

Tinnitus

In 2005, Stidham and colleagues explored the use of botulinum toxin A injections for tinnitus treatment under the theory that blocking the autonomic pathways could reduce the perception of tinnitus. In this study, 30 patients were randomly assigned in a double-blind study to receive either three subcutaneous injections of botulinum toxin A around the ear followed by placebo

injections four months later, or placebo injections first, followed by botulinum toxin A. The authors reported that seven patients had reduced tinnitus after the botulinum toxin A injections, which was statistically significant when compared to the placebo groups in which only two patients reported reduced tinnitus ($p < 0.005$). The tinnitus handicap inventory scores were also significantly decreased between pretreatment and four months post-botulinum toxin A injections. However, no other significant differences were noted when comparing the two treatments at one and four months after injections. The authors noted larger studies are needed. Also, study limitations, including size and lack of intention-to-treat analysis limit interpretation of results. Due to insufficient evidence from large randomized trials, botulinum toxin for tinnitus is considered investigational.

Antibody Testing for Botulinum Toxin Resistance

Rare patients have no response to initial administration of botulinum toxin (primary resistance) and a small percentage of adult patients develop secondary resistance after long-term treatment. Reasons for resistance include injection of incorrect muscles, unrealistic expectations of a complete cure, and interference from associated disorders that interfere with perception of response. 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 two 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 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, as neutralizing antibodies may re-develop 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 (ELISA). However, unless only the protein sequences that specifically react with neutralizing antibodies are employed, these formats detect both neutralizing and non-neutralizing antibodies and would therefore result in significant numbers of false-positive results. Thus, the currently available testing approach is considered investigational. An option for some patients might be to inject toxin into the frontal muscle above one eyebrow;

a toxin-responsive patient would have asymmetry of the forehead on attempted frowning, whereas, a nonresponsive patient would not.

Chronic Pain after Lumpectomy

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

Pain associated with breast reconstruction after mastectomy

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

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

Hirschsprung's Disease

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

A 2011 series by Patrus and colleagues retrospectively reviewed outcomes in 22 patients with Hirschsprung's disease treated over 10 years who had received a median of two (range 1 to 23) botulinum toxin injections for post-surgical obstructive symptoms. The formulation of botulinum toxin was not specified. Median follow-up (time from first injection to time of chart review) was 5.0 years (range 0 to 10 years). At the time of chart review, two of 22 patients (9%) had persistent symptoms. Eighty percent of children had a "good response" to the initial treatment (not defined) and 69% had additional injections. The authors reported that the number of

hospitalizations for obstructive symptoms decreased significantly after botulinum toxin injection (median=0) compared to pre-injection (median=1.5), $p=0.003$. The authors did not report whether or not patients received other treatments during the follow-up period in either case series. A limitation of the case series study design is that it lacks a control group. Due to the lack of controlled studies showing benefit, this indication is considered investigational.

Section summary:

There are no controlled trials of botulinum toxin for treatment of Hirschsprung's disease, therefore the evidence is insufficient to form conclusions on efficacy.

Gastroparesis

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

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

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

Section summary:

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

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

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

Practice Guidelines and Position Statements

In 2012, the American Urological Association 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 post-void retention.

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

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.”

Key Words:

Botulinum toxin, Botulinum toxin-A, Botulinum toxin-B, Botox, Myobloc, cervical dystonia, strabismus, blepharospasm, facial nerve disorders, torticollis, idiopathic toe walking, ITW,

Dysport™, onabotulinumtoxinA, rimabotulinumtoxinB, abobotulinumtoxinA, incobotulinumtoxinA, Xeomin

Approved by Governing Bodies:

December 1989, botulinum toxin-A (Botox) was approved by the FDA for the use of strabismus, blepharospasm, and facial nerve (VII) disorders. December 2000, FDA approval for botulinum toxin-A was given for the treatment of cervical dystonia.

December 2000, botulinum toxin-B (Myobloc) was approved by the FDA for the treatment of cervical dystonia

April 29, 2009, abobotulinumtoxinA (Dysport™) was approved for cervical dystonia and glabellar lines

March 10, 2010, onabotulinumtoxinA, (Botox) was approved for increased muscle stiffness in the elbow, wrist and fingers

July 30, 2010, incobotulinumtoxinA, (Xeomin) was approved for the treatment of cervical dystonia and blepharospasm.

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 three months, in the absence of medication overuse.

January 18, 2013, the FDA approved onabotulinumtoxinA (Botox) injection for overactive bladder

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply

FEP contracts: FEP does not consider investigational if FDA approved and will be reviewed for medical necessity. Special benefit consideration may apply. Refer to member's benefit plan.

Pre-certification/Pre-determination requirements: Not applicable

Current Coding:

CPT Codes:

20550	Injection (s); tendon sheath, ligament
46505	Chemodenervation of internal anal sphincter
52287	Cystourethroscopy, with injection(s) for chemo-denervation of the bladder (effective 01/01/2013)
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, hemifacial pain)

- 64615** Chemo-denervation of muscle(s); muscle(s) innervated by facial, trigeminal, cervical spinal and accessory nerves, bilateral (e.g. for chronic migraine) (**effective 01/01/2013**)
- 64616** Chemodenervation of muscle(s); neck muscle(s), excluding muscles of the larynx, unilateral (e.g., for cervical dystonia, spasmodic torticollis) (**Effective 01/01/2014**)
- 64617** Chemodenervation of muscle(s); larynx, unilateral, percutaneous (e.g., for spasmodic dysphonia), includes guidance by needle electromyography, when performed (**Effective 01/01/2014**)
- 64640** Destruction by neurolytic agent; other peripheral nerve or branch
- 64642** Chemodenervation of one extremity; 1-4 muscle(s) (**Effective 01/01/2014**)
- 64643** Chemodenervation of one extremity; each additional extremity, 1-4 muscle(s) (list separately in addition to code for primary procedure) (**Effective 01/01/2014**)
- 64644** Chemodenervation of one extremity; 5 or more muscle(s) (**Effective 01/01/2014**)
- 64645** Chemodenervation of one extremity; each additional extremity, 5 or more muscle(s) (list separately in addition to code for primary procedure) (**Effective 01/01/2014**)
- 64646** Chemodenervation of trunk muscle(s); 1-5 muscle(s) (**Effective 01/01/2014**)
- 64647** Chemodenervation of trunk muscle(s); 6 or more muscle(s) (**Effective 01/01/2014**)
- 64650** Chemodenervation of eccrine glands; both axillae
- 64653** Chemodenervation of eccrine glands; other area(s) (e.g., scalp, face, neck), per day
- 67345** Chemodenervation of extraocular muscle
- 95873** Electrical stimulation for guidance in conjunction with chemodenervation (List separately in addition to code for primary procedure)
- 95874** Needle electromyography for guidance in conjunction with chemodenervation (List separately in addition to code for primary procedure)

HCPCS Codes:

- J0585** Injection, Onabotulinumtoxina, 1 unit
- J0586** Injection, Abobotulinumtoxina, 5 units
- J0587** Injection, Rimabotulinumtoxinb, 100 units
- J0588** Injection, Incobotulinumtoxin A, 1 unit (**effective 01/01/2012**)

Units of toxins are not interchangeable.

Previous Coding:

CPT Codes:

- 64613** Chemodenervation of muscle(s); neck muscle(s) (e.g., for spasmodic torticollis, spasmodic dysphonia) **(Deleted 01/01/2014)**
- 64614** Chemodenervation of muscle(s); extremity(s) and /or trunk muscle(s) (e.g., for dystonia, cerebral palsy, multiple sclerosis) **(Deleted 01/01/2014)**

HCPCS Codes:

- J3590** Unclassified biologics (**effective through 12/31/2009**)
- Q2040** Injection, IncobotulinumtoxinA, 1 unit (**effective 04/01/2011 through 12/31/2011**)

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Policy History:

Medical Policy Group, December 2002
 Medical Policy Administration Committee, January 2003
 Available for comment February 6-March 24, 2003
 Medical Policy Administration Committee, March 2004
 Available for comment March 22-May 5, 2004
 Medical Policy Group, December 2005 (4)
 Medical Policy Administration Committee, January 2006
 Medical Policy Group, May 2006 (3)
 Medical Policy Administration Committee, May 2006

Available for comment May 19-July 3, 2006
 Medical Policy Group, December 2007 **(1)**
 Medical Policy Administration Committee, January 2008
 Available for comment January 5-February 20, 2008
 Medical Policy Group, June 2009 **(1)**
 Medical Policy Administration Committee, June 2009
 Available for comment June 5-July 20, 2009
 Medical Policy Group, March 2010 **(1)**: Added new FDA approved indication, Key Points updated
 Medical Policy Administration Committee, April 2010
 Available for comment April 8-May 23, 2010
 Medical Policy Group, August, 2010 **(1)**: Added new FDA approved product (Xeomin) for coverage per FDA labeled indications, Key Points updated
 Medical Policy Administration Committee August 2010
 Available for comment August 6-September 18, 2010
 Medical Policy Group, September 2010 **(1)**: Updated statement regarding units of toxin are not interchangeable, no policy statement change
 Medical Policy Group, October 2010 **(1)**: Added coverage for onabotulinumtoxinA (Botox A) for the prophylaxis of chronic migraine
 Medical Policy Administration Committee November 2010
 Available for comment November 4 – December 20, 2010
 Medical Policy Group, December 2010 – added CPT Code effective Jan 1, 2011
 Medical Policy Group, January 2010
 Medical Policy Group, February 2011
 Medical Policy Administration Committee, February 2011
 Available for comment February 9 – March 25, 2011
 Medical Policy Group March 2011 **(1)**
 Medical Policy Administration Committee March 2011
 Available for comment April 4 – May 18, 2011
 Medical Policy Group, September 2011 **(1)**: Update to Policy, Key Points, and References related to Pain with Breast Reconstruction after Mastectomy, Hirschsprung's Disease and Gastroparesis (all investigational); Update to Policy related to use of Ultrasound prior to and concurrent with injections; Update to Codes with addition of Q2040 (Xeomin); Entire policy reformatted.
 Medical Policy Administration Committee October 2011
 Available for comment October 19 through December 5, 2011
 Medical Policy Group, December 2011 **(1)**: Update to Coding with new 2012 code J0588 for Xeomin
 Medical Policy Panel, September, 2012
 Medical Policy Group, November 2012: 2013 Coding Update – Added Codes 52287 & 64615 and made verbiage change to code 64612, effective 1/1/2013
 Medical Policy Group, January 2013 **(1)**: Update to Policy, Key Points, Governing Bodies and References for onabotulinumtoxinA with addition of FDA approved coverage for overactive bladder effective January 18, 2013
 Medical Policy Administration Committee, February 2013
 Available for comment February 6 through March 22, 2013

Medical Policy Panel, September 2013

Medical Policy Group, September 2013 **(1)**: Continuation criteria added for migraine headache, urge incontinence and idiopathic removed from urinary incontinence criteria, removed information regarding billing of Botox waste, added “but not limited to” to investigational verbiage; update to Descriptions, Key Points and References

Medical Policy Administration Committee, October 2013

Available for comment October 1 through November 18, 2013

Medical Policy Group, December 2013 **(1)**: 2014 Coding Update: added new codes 64616, 64617 and range 64642-64647, effective 01/01/2014; moved deleted codes 64613 and 64614 to previous coding section, effective 01/01/2014

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.