

Medical Policy



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Title: Botulinum Toxin (BT) (i.e. Botox®, Myobloc®)

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

Professional

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DESCRIPTION

Botulinum is a family of toxins produced by the anaerobic organism *Clostridia botulinum*. There are 7 distinct serotypes designated as type A, B, C-1, D, E, F, and G. In this country, 2 preparations of botulinum are available, produced by 2 different strains of bacteria: type A (Botox) and type B (Myobloc). When administered intramuscularly, all botulinum toxins reduce muscle tone by interfering with the release of acetylcholine from nerve endings.

The label for Botox approved by the U.S. Food and Drug Administration (FDA) states that it is indicated for the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients older than 12 years. The FDA-approved label for Myobloc states that it is indicated for the treatment of cervical dystonia to reduce the severity of abnormal head position and neck pain. On January 31, 2008, Ipsen Limited (UK) announced that the FDA accepted the filing of its biologics license application (BLA) for Dysport (botulinum A) to treat patients with cervical dystonia.

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. Since its FDA approval in 1991, Botox has been used for a wide variety of off-label indications, ranging from achalasia, spasticity after strokes, cerebral palsy, and anal fissures. In addition to widening indications, Botox has also been used in children under 12, particularly for the treatment of cerebral palsy. It is anticipated that Myobloc will be used for the same range of off-label indications as Botox.

After successful extended use of botulinum toxin (usually A), some initial responders become nonresponders. Such secondary nonresponse may occur for a variety of reasons; one cause in a small percentage of patients is the development of antibodies that neutralize the activity of the administered botulinum toxin. These patients are likely to respond to another botulinum toxin type. A clinically useful assay for toxin-reactive antibodies would detect only neutralizing antibodies, as non-neutralizing antibodies can be present in the serum of patients who have not developed resistance to treatment. Assay formats best suited to the clinical laboratory, such as immunoprecipitation, western blot, or enzyme-linked immunosorbent assay, typically do not discriminate between neutralizing and non-neutralizing antibodies and would thus generate false-positive results in some patients (e.g., Athena Diagnostics' Botulinum Toxin Type A Antibody Test uses the western blot format; the assay detects both neutralizing and non-neutralizing antibodies per communication with Client Services July 14, 2008).

POLICY

- A. The use of botulinum toxin may be considered **medically necessary** for the FDA-labeled indications of:
1. Strabismus
 2. Blepharospasm
 3. Facial nerve (VII) disorders (including hemifacial spasm)
 4. Cervical dystonia (spasmodic torticollis; applicable whether congenital, due to child birth injury, or traumatic injury). For this use, cervical dystonia must be associated with sustained head tilt or abnormal posturing with limited range of motion in the neck AND a history of recurrent involuntary contraction of one or more of the muscles of the neck, e.g., sternocleidomastoid, splenius, trapezius, or posterior cervical muscles.
 5. Hyperhidrosis (*see separate policy on Treatment of Hyperhidrosis*)
- B. The use of botulinum toxin may be considered **medically necessary** for the off-label indications of dystonia / spasticity resulting in functional impairment (interference with joint function, mobility, communication, nutritional intake) and/or pain in patients with any of the following:
1. Focal dystonias
 - a. Focal upper limb dystonia (e.g., organic writer's cramp)
 - b. Oromandibular dystonia (orofacial dyskinesia, Meige syndrome)
 - c. Laryngeal dystonia (adductor spasmodic dysphonia)

- d. Idiopathic (primary or genetic) torsion dystonia
 - e. Symptomatic (acquired) torsion dystonia
 - f. Spasmodic Torticollis
2. Spastic conditions
 - a. Equinus foot
 - b. Cerebral palsy
 - c. Spasticity related to stroke
 - d. Acquired spinal cord or brain injury
 - e. Hereditary spastic paraparesis
 - f. Spastic hemiplegia
 - g. Neuromyelitis optica
 - h. Multiple sclerosis or Schilder's disease
- C. The use of botulinum toxin may be considered **medically necessary** for the following off-label indications:
1. Esophageal achalasia in patients who have not responded to dilation therapy or who are considered poor surgical candidates;
 2. Sialorrhea (drooling) associated with Parkinson disease;
 3. Chronic anal fissure;
 4. Incontinence due to detrusor overreactivity (urge incontinence), either idiopathic or due to neurogenic causes (e.g., spinal cord injury, multiple sclerosis), that is inadequately controlled with anticholinergic therapy.
- D. The use of botulinum toxin is considered **experimental / investigational** for other indications, including but not limited to:
1. headaches, including migraine, chronic daily headache, and tension-type headache
 2. chronic low back pain
 3. joint pain
 4. mechanical neck disorders
 5. neuropathic pain after neck dissection
 6. myofascial pain syndrome
 7. pain after hemorrhoidectomy or lumpectomy
 8. tremors such as benign essential tremor (upper extremity)
 9. tinnitus
 10. sialorrhea (drooling) except that associated with Parkinson disease
 11. chronic motor tic disorder and tics associated with Tourette syndrome (motor tics)
 12. lateral epicondylitis
 13. benign prostatic hyperplasia
 14. interstitial cystitis
 15. Treatment of the sphincter in detrusor sphincteric dyssynergia (after spinal cord injury)

16. anismus
 17. fibromyalgia / fibromyositis
 18. gastroparesis
 19. Parkinson's disease
 20. Tourette's Syndrome
 21. tremors
- E. The use of assays to detect antibodies to botulinum toxin is considered **experimental / investigational**.
- F. The use of botulinum toxin may be considered cosmetic and therefore **non-covered** as a treatment of wrinkles or other cosmetic indications.

DOCUMENTATION

Guidelines for Botulinum toxin use for Spasticity:

1. There must be documented central mediated neurological based spasticity
2. There must be a stated goal of treatment
3. History and physical examination
4. Statement of medical necessity

UTILIZATION

1. Repeat injection would be approved only if improvement was documented from first injection. If no improvement, the injection should NOT be repeated.
2. If it is felt that perhaps a therapeutic level was not obtained initially a booster may be given.
3. Improvement should be noted within four to seven days.
4. Administration -- one to three vials may be used in one treatment. This is dependent on how many muscles are to be injected and the size of the muscles. Any claim using more than three vials or injecting more than three limbs at one time should be reviewed. More muscles than that can be injected at one time, but it needs to be investigated before approving.
5. There is no age limit. It has been found that pre-school children do require a lesser dose. School age children; however, often take an adult dose. This would be clinical judgment.
6. If there is DOCUMENTED IMPROVEMENT with initial treatment then Botulinum toxin may be given every three months. It may be given sooner with individual consideration.
7. May give indefinitely when there is improvement.

RATIONALE

This section discusses the evidence for off-label uses of botulinum toxin. The literature review focuses primarily on randomized placebo-controlled clinical trials. While the bulk of the literature is based on trials using botulinum A (i.e., Botox), it is anticipated that botulinum B (Myobloc) will be used for the same range of off-label indications as botulinum A. There is a relative lack of head-to-head comparisons of these 2 drugs, but cross-study comparisons have resulted in relative dose equivalents of 1:50 to 100 for Botox:Myobloc and 1:3 to 4 for Botox:Dysport. (1) As part of the FDA-approval process, 2 randomized studies were performed, using as control groups those with cervical dystonia who had an ongoing positive response to botulinum A and those whose initial good response to botulinum A had been secondarily lost. (2) Patients in both trials reported significant improvement, suggesting either of the drugs may be used initially, with a switch to the other drug if resistance develops to the original drug used.

Dystonia/Spasticity

This policy section is based on a 1996 TEC Assessment that focused on the use of botulinum toxin for the treatment of focal dystonia or spasticity (3), the American Academy of Neurology (AAN) assessments of movement disorders and spasticity (1, 4), and additional controlled trials identified by MEDLINE® literature searches and hand searches of reference lists of reviews or other publications.

Based on the evidence, the TEC Assessment concluded that Botulinum A toxin 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. (1, 4)

Spasticity related to stroke may be a significant functional problem. Plantar flexion spasticity may impede walking. Kirazli and colleagues compared the effects of phenol block (standard treatment) and botulinum toxin in a randomized trial of 20 patients with spastic foot after stroke. (5) Both injections were associated with significant improvements, with botulinum toxin outperforming phenol injections after the first month of treatment, with equal treatment effects at 2 and 3 months. A possible advantage of the botulinum toxin is the relative ease of the procedure (15 to

30 minutes), while it may take up to 2 hours to target the motor nerve for phenol injection. Smith and colleagues investigated the use of botulinum toxin in a trial that randomized 21 patients with upper limb spasticity related to stroke or head injury. (6) There was a significant reduction in spasticity in the wrist and fingers in the botulinum group.

Additionally, a National Institutes of Health (NIH) Consensus 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. (7, 8) According to information provided by the NIH National Center 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 (9)

It should be noted that in generalized dystonias botulinum toxin therapy is indicated only for the treatment of particularly severe focal abnormalities, as injection of multiple muscle groups would require unacceptably high doses of toxin. (7, 8)

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 (10) reported a trial that randomized 42 patients with achalasia to receive either 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 Cochrane systematic review and meta-analysis of 178 patients treated with either botulinum toxin or pneumatic dilation. (11)

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. Maria and colleagues randomized 30 patients with chronic anal fissure to receive either 2 injections of 20 units of botulinum toxin, on either side of the fissure, or 2 injections of saline. (12) After 2 months, 11 patients in the treatment group reported healing, compared to only 2 in the control group. The 4 patients who still had fissures after 2 months underwent retreatment with botulinum toxin; 2 of these 4 patients reported healing scars and symptomatic relief. These results are consistent with earlier case series that reported a healing rate of 80%. (13) Nitroglycerin ointment has also been used to successfully treat anal fissure. Brisinda and colleagues compared the results of nitroglycerin ointment and botulinum toxin in a randomized trial of 50 patients. (14) After 2 months, 96% of the fissures were healed in the botulinum group compared with 60% in the nitroglycerin group. The same group conducted a second, similar trial with 92% vs. 70% healing rates for botulinum toxin-treated vs. nitroglycerin ointment-treated patients ($p < 0.001$). (15) Others have reported both supportive (16) and contradictory (17) data from randomized trials comparing the same treatments. Randomized, controlled trials of botulinum toxin vs. sphincterotomy have reported significantly better results

with sphincterotomy but authors concluded that botulinum toxin was a viable first option for patients who are not good surgical candidates. (18) A systematic review concluded that no single treatment was the best for all patients. (19, 20)

Urologic Applications

Detrusor overactivity. Two small blinded, randomized, controlled trials randomized patients with detrusor overactivity (urge incontinence) due to neurogenic origin that was inadequately controlled with anticholinergic therapy to receive either botulinum toxin or placebo injection into the detrusor muscle. Both studies reported significant improvements in urodynamic measures, voiding function, and quality of life favoring botulinum toxin treatment. (21, 22) Benefits of botulinum toxin treatment are supported by several open-label trials, summarized in a review by Sinha and colleagues. (23) Karsenty et al. conducted a systematic review of studies of botulinum toxin intradetrusor injections in adults with neurogenic detrusor overactivity refractory to anticholinergics and concluded that botulinum toxin treatment results in a clinically significant improvement. (24)

Two small blinded, randomized controlled trials randomized patients with idiopathic detrusor overactivity refractory to anticholinergics to botulinum toxin or placebo injected intravesically. For each trial, authors reported significant improvements in maximum capacity, frequency, urgency, and quality of life with botulinum toxin treatment. (25, 26) Results of open-label trials are consistent with these conclusions. (27)

Detrusor sphincter dyssynergia. DeSeze and colleagues studied 13 patients with chronic urinary retention due to detrusor sphincter dyssynergia from spinal cord disease (traumatic injury, multiple sclerosis, congenital malformations), randomized to receive perineal botulinum toxin or lidocaine injections into the external urethral sphincter. (28) 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.

Karsenty and colleagues (29) reviewed trials of botulinum toxin injected into the urethral sphincter to treat different types of lower urinary tract dysfunction, grouped into neurogenic detrusor-sphincter dyssynergia and nonneurogenic obstructive sphincter dysfunction. In the former group, the authors cite 10 small studies (N ranged from 3 to 53; 3 studies included patients in both categories). Most patients were quadriplegic men unable to perform self-catheterization or patients (of both genders) with multiple sclerosis. All except 2 studies were case reports or case series. The previously cited study by DeSeze et al. (28) was included; the other randomized controlled trial enrolled only 5 patients. While most studies report significant improvements, small patient numbers, different causes of dysfunction, and different outcome measures, together with lack of control arms make it difficult to draw conclusions regarding this application.

Benign prostatic hyperplasia. The rationale for botulinum treatment is based on the theory that symptoms of BPH are in part due to a static component related to prostate size and a dynamic component related to the contraction of smooth muscle within the gland. Botulinum therapy addresses this latter component. Maria and colleagues reported on 30 patients with benign prostatic hyperplasia (BPH), randomized to receive either intraprostatic botulinum or saline injection. (30) Inclusion criteria for this trial included moderate-to-severe symptoms of BPH based on the American Urological Association (AUA) score and a mean peak urinary flow rate of no more

than 15 mL per second with a voided volume of 150 mL or less. After 2 months, the AUA symptom score decreased by 65% among those receiving botulinum toxin, compared to no significant change in the control group. The mean peak urinary flow rate was significantly increased in the treatment group.

Chuang and Chancellor (31) reviewed trials testing the use of botulinum toxin in benign prostatic hyperplasia. With the exception of the previously cited trial by Maria and colleagues (30), all were small, open-label trials (n ranged from 8-52) that generally reported improvement in spontaneous voiding and decreases in post-void residual volume compared to baseline. No additional randomized controlled trials were found in a MEDLINE search through June 2008. Given the prevalence of BPH, larger trials comparing the role of BPH with other medical and surgical therapies are warranted.

Interstitial cystitis. Five case series (n ranged from 10 to 19) of botulinum toxin treatment of patients with interstitial cystitis for alleviation of chronic pain and improving bladder capacity have been published. (32-37) All report subjective improvement in a majority of patients, and statistically significant improvement in various measured parameters such as pain by visual analog scale, frequency, nocturia, and functional bladder capacity. The results suggest efficacy but need confirmation in a larger population and preferably in controlled clinical trials.

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. One randomized controlled trial studied 10 patients with essential head tremor. (38) Patients were randomized to receive either botulinum toxin or placebo injections into the sternocleidomastoid and splenius capitus muscle. Five patients improved in the treatment group compared to 3 in the control group but the difference was not significant. Two randomized, placebo-controlled studies addressed essential hand tremors, enrolling 133 and 25 patients, respectively. (39, 40) 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.

Sialorrhea (Drooling)

Five small (N=16-48) randomized, controlled clinical trials evaluated botulinum toxin injection into parotid/submandibular glands compared with placebo injection to control sialorrhea in patients with neurological diseases (e.g. Parkinson's, cerebral palsy, ALS). Ondo and colleagues (41) randomized 16 Parkinson's patients to receive placebo or 2,500 U of botulinum toxin B. The botulinum toxin group had significantly better outcome than the placebo group at 1 month on 4 drooling outcomes but groups did not differ on salivary gland imaging and a dysphagia scale. Mancini and colleagues (42) assigned 20 patients to injections of either a saline placebo or 450 U of botulinum toxin A. The treatment group was significantly better than placebo on a drooling scale at 1 week, the effect disappeared by 3 months. Lipp and colleagues (43) randomized 32 patients to either placebo or 3 different doses of botulinum toxin A: 37.5 U, 75 U, or 150 U. One outcome was an objective measure of drooling based on weight of dental rolls, which significantly favored botulinum toxin over placebo for only the 75 U dose. The same pattern was observed for

a patient-measured count of sialorrhea-related acts. Loss to follow-up was 21% at 3 months and 44% at 6 months; it was unclear what follow-up period was represented in the statistical analyses. Lagalla randomized 32 patients with Parkinson's disease to placebo or 50 U; evaluation at 1 month post-injection resulted in significant improvements, compared with placebo, in drooling frequency, saliva output, and in familial and social embarrassment. (44) Dysphagia scores were not significantly improved. Reid et al. randomized 48 children with cerebral palsy and other neurological disorders to no treatment or to 25 U botulinum toxin A. (45) Maximal response on the Drooling Impact Scale questionnaire occurred at 1 month but the difference between treatment arms remain statistically significant at 6 months. Sixteen of 24 treated were responders. A systematic review of botulinum toxin for treatment of sialorrhea concluded that the ideal dose, injection location, and technique of injections remain to be determined. (46) While some questions remain, studies on those with Parkinson's disease provide consistent findings related to impact on sialorrhea. Thus, for this specific disease indication, this use of botulinum toxin is considered medically necessary. For sialorrhea associated with other disorders, there is little evidence and additional studies are needed; these indications are considered investigational.

Chronic Low Back Pain

Only 1 randomized controlled study of botulinum toxin A treatment in patients with low back pain has been published. (47) The trial enrolled 31 consecutive patients with chronic low back pain of at least 6 months' duration and more predominant pain on one side. Patients were injected with 40 units of Botox (Allergan, Inc.) at 5 lumbosacral locations for a total of 200 U (treated group) or saline placebo (placebo group). Injections were made on one side of the back only, depending on predominance of pain. At 8 weeks, 60% of treated patients and 12.5% of placebo patients showed improvement in VAS pain scores ($p=0.009$). Perceived functional status (Oswestry scale) at 8 weeks showed that 66.7% of treated patients and 18.8% of placebo patients were responders ($p=0.011$). The population with chronic low back pain is a heterogeneous population, and results in this small group of selected subjects cannot be used to generalize results for the whole population with chronic low back pain. Furthermore, studies should examine the long-term effectiveness of using repeated courses of botulinum toxin to determine the durability of repeated treatments.

Headache

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

Botulinum toxin for treatment of pain from migraine and from chronic tension-type headaches, was addressed in TEC Assessments completed in 2002 (48) and updated in 2004. (2) An AAN assessment of botulinum toxin for treatment of autonomic disorders and pain addressed these indications as well as chronic daily headache. (49) Because of the typically high placebo response rate in patients with headache, assessment of evidence focuses on randomized, placebo-controlled trials. Both TEC Assessments concluded that the evidence was insufficient for either indication. The AAN assessment concluded that botulinum toxin should not be considered for episodic migraine and chronic tension-type headache, and that the evidence was insufficient for treatment of chronic daily headache.

Migraine Headache. Nine randomized controlled trials of botulinum toxin for treatment of migraine have been published. The studies included in the AAN assessment (50, 53, 55, 62) are described in table E-4 of the AAN supplemental information (accessible online at http://www.neurology.org/content/vol70/issue19/images/data/1707/DC1/Tables_e-1_to_4.doc). Other randomized controlled trials in the treatment of migraine include Anand 2006 (52), Vo 2007 (63), Aurora 2007 (54), Relja 2007 (64), and Blumenfeld 2008 (51). All enrolled at least 20 patients per treatment arm (including arms testing different botulinum toxin doses). One publication reported on 3 sequential trials of a large group of patients with re-randomization for each trial. (50) Most trials studied episodic migraine (<15 headaches per month; usually 4-8 on average). One trial enrolled patients with either episodic (76% of patients) or chronic (>15 headaches per month) migraine. (51) One trial compared botulinum toxin to divalproex sodium, approved for migraine prophylaxis (51); all other trials treated the control arm patients with placebo injection. Four trials were rated AAN Class I (50, 52-54; see Table A for definition) and the others were rated Class II. Of all trials, only 1 Class I and 1 Class II trial reported statistically significant improvement in the botulinum toxin treatment arm for the primary outcome. (52, 55) Some trials reported improvements in some secondary outcomes. Most studies reported mild to moderate adverse events primarily in the treatment arms. In contrast to single-arm studies and retrospective studies, the preponderance of randomized clinical trial evidence shows no significant effect of botulinum toxin in reducing frequency of migraine.

Tension Headache. Nine randomized, controlled trials of botulinum toxin for treatment of chronic tension-type headaches have been published. The studies included in the AAN assessment (56, 69, 70, 71) are described in table E-4 of the AAN supplemental information (accessible online at http://www.neurology.org/content/vol70/issue19/images/data/1707/DC1/Tables_e-1_to_4.doc). Other randomized controlled trials in the treatment of tension headache include Smuts 1999 (57), Rollnick 2000 (65), Rollnick 2002 (66), Rollnik 2001 (67), Schmitt 2001 (68) and Straube 2008 (72). Two were rated AAN Class I, 3 Class II, and 4 Class IV. Five trials enrolled fewer than 20 patients per treatment arm. One very small Class III trial reported statistically significant differences favoring treatment in change in mean tenderness and in headache severity (56; no primary outcome identified); another small Class III trial reported a significantly higher percentage of patients with a greater than 50% decrease in headache score. (57) All other trials reported no significant difference between trial arms for the primary outcome. Thus, the higher quality evidence for this indication shows no significant effect for botulinum toxin treatment of chronic tension-type headache.

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. Five randomized, placebo-controlled trials have been published. (68-72) The studies included in the AAN assessment (73, 74, 75, 76) are described in table E-4 of the AAN supplemental information (accessible online at http://www.neurology.org/content/vol70/issue19/images/data/1707/DC1/Tables_e-1_to_4.doc). An additional randomized controlled trial in the treatment of chronic daily headache published since the AAN assessment is Freitag 2008 (77). All were rated AAN Class II, enrolled at least 20 patients per treatment arm, and administered botulinum toxin-A including doses in the range of 100–200 U. Two studies reported significant improvement in primary outcomes, while the other 3 reported no significant differences. The evidence is conflicting and insufficient for conclusions.

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

Cervicogenic Headache. Three randomized controlled trials randomized patients with chronic headache related to whiplash injury to botulinum toxin treatment or placebo. (58-60) One trial reported trends toward improvement with treatment for various outcomes; most were not statistically significant. (60) Another reported no significant differences in any of several pain-related outcomes. (59) 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. (58) The evidence from these trials is conflicting and insufficient for conclusions. A Cochrane Review of treatment of mechanical neck disorders, published in 2007 (61), included 6 randomized controlled trials (total N=273) of botulinum toxin compared to placebo for chronic neck disorders with or without radicular findings or headache. A meta-analysis of 4 studies (total N=139) for pain outcomes gave a nonsignificant result. The authors concluded that a range of doses have not shown significant differences compared to placebo or to each other.

Myofascial Pain Syndrome

Painful muscles with increased tone and stiffness containing trigger points characterize myofascial pain syndrome. Patients are often treated with injections of the trigger points with saline, dilute anesthetics, or dry needling. These trigger-point injections, while considered established therapy, have been controversial, since it is unclear whether any treatment effect is due to the injection, dry needling of the trigger point, or a placebo effect. Seven randomized, blinded, placebo-controlled clinical trials of botulinum toxin vs. placebo for cervicothoracic myofascial pain syndrome have been reported. All trials injected botulinum toxin or placebo into trigger points in the upper back, shoulder, and/or cervical muscles. Total botulinum toxin doses varied considerably across trials as did numbers of patients enrolled (20–132) and methods of pain assessment. Five trials reported no significant differences in response between treatment and placebo. (78-82) One trial, administering high-dose botulinum toxin versus placebo, reported significant differences in pain relief at marginal p values. (83) The last trial reported significant differences in only a few of several outcome measures. (84)

Two randomized, controlled trials compared botulinum toxin to dry needling and to lidocaine or bupivacaine injection. In 1 trial, lidocaine trigger point injection was significantly more effective than dry needling, but significantly less effective than botulinum toxin. (85) In the other, both bupivacaine and botulinum toxin were similarly effective and not significantly different. (86) Three studies addressed another form of myofascial pain, piriformis syndrome, characterized by buttock tenderness and sciatica. One study of 9 patients (87) compared botulinum toxin with placebo, finding that postinjection pain scores were significantly improved in the treatment group for only 1 of 4 pain domains, while none improved in the placebo group. Another study of 36 patients (88) had a high loss to follow-up (23%), and found that the botulinum toxin group had a significantly higher proportion, with 50% or greater reduction in pain on each of the last 2 follow-up visits, compared with placebo. These small and flawed studies do not establish that the effects of botulinum toxin exceed those of placebo. A third study (89), 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.

One randomized controlled trial enrolled patients with myofascial pain related to bruxism; while subjective and objective improvements in several outcomes measures were reported favoring treatment versus placebo; none was significant. (90)

A systematic review (91) selected randomized controlled trials of trigger-point injection; use of the Oxford Pain Validity Scale was also a selection criterion. Five trials were included; 1 trial resulted in a significant effect whereas the other 4 did not. The data were described as "limited and clinically heterogeneous" and the authors concluded that the evidence did not support the use of botulinum toxin injections in trigger points for myofascial pain.

Wound Healing and Pain Control

Three small randomized controlled trials of botulinum toxin intrasphincter injection for controlling pain after hemorrhoidectomy have been published (92 [Davies et al 2003], n=50; 93 [Patti et al 2005], n=30; 94 [Patti et al 2006], n=30). Davies and colleagues (92) showed marginal improvement in pain control at days 6 and 7 by patient visual analogue scores ($p<0.05$); there was no significant difference in morphine or analgesic use. Patti et al (93) randomized 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. Patti and colleagues (94) 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.

Gassner and colleagues (95) conducted a small, randomized, controlled trial of botulinum toxin-induced immobilization of facial lacerations to improve wound healing compared to placebo (n=31). The outcome was determined by blinded assessment of photographs of wound healing at intervals using a visual analogue scale. The authors report enhanced wound healing in the treatment arm (8.9 vs. 7.2, $p=0.003$). These results conflict with the wound-healing outcome after hemorrhoidectomy as reported by Patti and colleagues. (94) Additional studies are necessary to identify indications and confirm improved outcomes.

Pelvic and Genital Pain in Women

One small, open-label trial (96) tested botulinum toxin injections into painful vulvar tissue to alleviate provoked vestibulodynia (n=19). Patients receiving either of 2 doses had significantly reduced pain compared to baseline for 8 (lower dose) to 14 weeks (higher dose). A prospective cohort study tested different doses of botulinum toxin in 12 women with pelvic floor muscle hypertonicity and history of chronic pelvic pain. (97). Compared to baseline, there were nonsignificant reductions in pelvic pain and nonsignificant improvements in quality of life. In a double-blinded, randomized, placebo-controlled trial (98), botulinum toxin was injected into pelvic floor muscles to attempt to alleviate chronic pelvic pain (n=60). Pain scores were reduced for both groups, but there were no significant differences between groups. The placebo response was underestimated, and the trial likely was underpowered for the outcome. 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 injected into the area of complaint. (99, 100) 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.

Chronic Pain after Lumpectomy

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

Lateral Epicondylitis and Other Joint Pain

Wong and colleagues reported on the results of a double-blind, placebo-controlled trial that randomized 60 patients with lateral epicondylitis of at least 3 months' duration to receive either a single intramuscular injection of botulinum toxin or placebo, targeted at the tender spot in the elbow. (101) In the botulinum group, the mean visual analogue score improved from 65.5 mm to 25.3 mm at 4 weeks, compared to a change of 66.2 mm to 50.5 mm in the placebo group, a statistically significant difference. Mild paresis was reported in 4 patients in the botulinum group. In a similarly designed study of 40 patients, Hayton and colleagues reported no treatment effect at 3 months. (102) 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 into the painful origin of the forearm extensor muscles was tested versus placebo. (103) Treated patients were significantly improved overall at weeks 2, 6, 12, and 18. Continuous pain was significantly improved in the treated group only at weeks 6 and 18; maximum pain showed no improvement compared to placebo.

Two case series of patients with chronic joint pain refractory to conservative management studied the effect of botulinum toxin injections into several joints of patients with arthritis, and into the knee joint of patients with chronic knee pain. (104, 105) 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.

Tinnitus

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. (106) In this study, 30 patients were randomized in a double-blind study to receive either 3 subcutaneous injections of botulinum toxin A around the ear followed by placebo injections 4 months later, or placebo injections first followed by botulinum toxin A. The authors reported that 7 patients had reduced tinnitus after the botulinum toxin A injections, which was statistically significant when compared to the placebo groups in which only 2 patients reported reduced tinnitus ($p < 0.005$). The tinnitus handicap inventory scores were also significantly decreased between pretreatment and 4 months post-botulinum toxin A injections. However, no other significant differences were noted when comparing the two treatments at 1 and 4 months after injections. The authors noted larger studies are needed. Also, study limitations including size and lack of intent-to-treat analysis limit interpretation of results.

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. (107) In about 3%–10% of adult patients, true secondary resistance arises due to the development of antibodies that specifically neutralize the activity of botulinum toxin. (108-111) 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. (112) 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. (109, 113) In 2 studies of pediatric patients treated for spasticity, neutralizing antibodies were detected in 28%–32% of patients. (114, 115) Recommendations for avoiding eventual resistance are to use the lowest dose possible to obtain a clinical response, and schedule intervals of 10–12 weeks between injections, if possible. (107)

Patients who develop secondary resistance to botulinum toxin A may stop treatment for several months and then undergo re-treatment with likely success; however, the duration of response is often short, as neutralizing antibodies may re-develop quickly. (109, 116) 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 side effects have occurred at higher frequencies than for botulinum toxin A. (113, 117)

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 (118) or with an in vitro toxin-neutralizing assay based on a mouse diaphragm nerve-muscle preparation. (119) 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 (113, 120, 121) 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. (120)

Physician Specialty Society and Academic Medical Center Input

In response to requests, input was received from 5 physician specialty societies and 3 academic medical centers while this policy was under review. 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. Nearly all reviewers who provided input agreed with the investigational determination for use in headaches and on the investigational role for antibody testing. Among the 4 reviewers who commented on use in sialorrhea, 2 reviewers felt this was medically necessary and 2 disagreed.

CODING

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

CPT/HCPCS

31513	Laryngoscopy, indirect; with vocal cord injection
31570	Laryngoscopy, direct, with injection into vocal cord(s), therapeutic;
31571	Laryngoscopy, direct, with injection into vocal cord(s), therapeutic; with operating microscope or telescope
43201	Esophagoscopy, rigid or flexible; with directed submucosal injection(s), any substance
43236	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with directed submucosal injection(s), any substance
46505	Chemodenervation of internal anal sphincter
64612	Chemodenervation of muscle(s); muscle(s) innervated by facial nerve (e.g., for blepharospasm or hemifacial spasm)
64613	Chemodenervation of muscle(s); cervical spinal muscle(s) (e.g. spasmodic torticollis)
64614	Chemodenervation of muscle(s); extremity(s) and/or trunk muscle(s) (e.g., for dystonia, cerebral palsy, multiple sclerosis)
64650	Chemodenervation of eccrine glands; both axillae
64653	Chemodenervation of eccrine glands; other area(s) (eg. Scalp, face, neck), per day
67345	Chemodenervation of extraocular muscle
J0585	Botulinum toxin type A (Botox®), per unit
J0587	Botulinum toxin type B (Myobloc®), per 100 units

DIAGNOSIS

333.6	Idiopathic torsion dystonia
333.7	Symptomatic torsion dystonia
333.81	Blepharospasm
333.82	Orofacial dyskinesia
333.83	Spasmodic Torticollis
333.84	Organic writer's cramp
333.89	Other torsion dystonia
334.1	Hereditary spastic paraplegia
340	Multiple Sclerosis
341.0	Neuromyelitis optica
341.1	Schilder's disease
342.10	Spastic hemiplegia, affecting unspecified side
342.11	Spastic hemiplegia, affecting dominant side
342.12	Spastic hemiplegia, affecting nondominant side
343.0	Infantile cerebral palsy, diplegic
343.1	Infantile cerebral palsy, hemiplegic

- 343.2 Infantile cerebral palsy, quadriplegic
- 343.3 Infantile cerebral palsy, monoplegic
- 343.4 Infantile cerebral palsy, infantile hemiplegia
- 343.8 Infantile cerebral palsy, other specified infantile cerebral palsy
- 343.9 Infantile cerebral palsy, unspecified
- 351.0 Facial nerve disorders, Bells palsy
- 351.1 Facial nerve disorders, Geniculate ganglionitis
- 351.8 Facial nerve disorders, other facial nerve disorders
- 351.9 Facial nerve disorders, other
- 378.00-378.9 Strabismus and other disorders of binocular eye movements (code range)
- 435.9 Unspecified transient cerebral ischemia
- 478.75 Laryngeal spasm
- 478.79 Other diseases of the larynx (spastic dysphonia)
- 530.0 Achalasia and cardiospasm
- 565.0 Anal fissure
- 705.21 Primary focal hyperhidrosis
- 723.5 Torticollis, unspecified
- 754.51 Talipes equinovarus
- 784.49 Spasmodic dysphonia
- 788.30-788.39 Urinary incontinence

REVISIONS

10-19-2007	In Policy section: <ul style="list-style-type: none"> ▪ B.1 replaced "Cerebral Palsy" with "spasticity".
07-18-2008	In Policy section: <ul style="list-style-type: none"> ▪ Added "F. The off-labeled use of botulinum toxin is considered medically necessary in the treatment of incontinence related to detrusor overactivity due to neurogenic causes (i.e. spinal cord injury), when anticholinergic therapy has failed." as an indication. ▪ Specified H.13. Overactive bladder by adding "except as specified above."
10-19-2009	In Header: <ul style="list-style-type: none"> ▪ Added reference to related policies of: Treatment of Hyperhydrosis and Treatment of Tinnitus
	Updated Description section.
	In Policy section: <ul style="list-style-type: none"> ▪ Updated formatting and wording. ▪ Added medically necessary indication C4: "Incontinence due to detrusor overreactivity (urge incontinence), either idiopathic or due to neurogenic causes (e.g., spinal cord injury, multiple sclerosis), that is inadequately controlled with anticholinergic therapy." ▪ Clarified the list of experimental / investigational indications. This list was previously reflected as "...including, but not limited to...", so the additional indications added do not constitute a policy language change. ▪ Revised denial of treatment of wrinkles or other cosmetic indications from "not medically necessary" to "non-covered".

	Added Rationale section.
	In Coding section: <ul style="list-style-type: none"> ▪ Added CPT codes: 31513, 31570, 31571, 43201, 43236. ▪ Added Diagnosis coding range for urinary incontinence: 788.30-788.39.

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1. Blue Cross and Blue Shield of Kansas Urology Liaison Committee meeting, August 24, 2005 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report. MAC-03-05).
 2. Blue Cross and Blue Shield of Kansas Medical Advisory Committee meeting, November 3, 2005 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report. MAC-03-05).
 3. Blue Cross and Blue Shield of Kansas Urology Liaison Committee, August 2007.
 4. Blue Cross and Blue Shield of Kansas Medical Advisory Committee, November 2007.
 5. Blue Cross and Blue Shield of Kansas Urology Liaison Committee, August 2008.
 6. Blue Cross and Blue Shield of Kansas Urology Liaison Committee, August 2009.