

Medical Policy



Title: Botulinum Toxin (BT)

See also: Treatment of Hyperhidrosis

Professional

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Populations	Interventions	Comparators	Outcomes
Individuals: • With esophageal achalasia who fail initial treatment with medications	Interventions of interest are: • Botulinum toxin injections	Comparators of interest are: • Pneumatic dilation • Laparoscopic myotomy	Relevant outcomes include: • Symptoms • Functional outcomes • Treatment-related morbidity
Individuals: • With chronic anal fissure who fail medical management	Interventions of interest are: • Botulinum toxin injections	Comparators of interest are: • Surgery	Relevant outcomes include: • Symptoms • Health status measures • Treatment-related morbidity
Individuals: • With Hirschprung disease who develop obstructive symptoms after a pull-through operation	Interventions of interest are: • Botulinum toxin injections	Comparators of interest are: • Standard of care	Relevant outcomes include: • Symptoms • Health status measures • Treatment-related morbidity
Individuals: • With other indications (eg, tremors, musculoskeletal pain, neuropathic pain, postsurgical pain)	Interventions of interest are: • Botulinum toxin injections	Comparators of interest are: • Conservative measures • Medication	Relevant outcomes include: • Symptoms • Functional outcomes • Medication use • Treatment-related morbidity

DESCRIPTION

Botulinum toxin (BoNT) is a neurotoxin produced by the bacteria *Clostridium botulinum*. Botulinum toxin is divided into 7 structurally similar neurotoxins (type A, B, C [C1, C2], D, E, F, and G) with varying potencies.

BoNT acts by binding presynaptically on cholinergic nerve terminals and decreasing the release of acetylcholine which causes a neuromuscular blockade. It is thought that recovery occurs by the eventual regeneration of the neuromuscular junction.

Objective

The objective of this policy is to assess whether the use of botulinum toxin in a wide variety of neuromuscular conditions and pain syndromes improves the net health outcome.

Background

Botulinum Toxins

This policy refers to the following botulinum toxin types A and B drug products: abobotulinumtoxinA (Dysport), incobotulinumtoxinA (Xeomin), onabotulinumtoxinA (Botox) and rimabotulinumtoxinB (Myobloc). PrabotulinumtoxinA-xvfs (Jeuveau) was approved by the Food and Drug Administration (FDA) on February 1, 2019 for cosmetic use and is considered out of scope of the review.

Regulatory Status

On December 9, 1991, onabotulinumtoxinA (Botox) was approved by the FDA for treatment of ocular dystonias. Since then, its use has been expanded for multiple indications.

On December 8, 2000, rimabotulinumtoxinB (Myobloc) was approved by the FDA for treatment of cervical dystonias. Since then, its use has also been expanded for multiple indications.

On April 29, 2009, abobotulinumtoxinA (Dysport) was approved by the FDA for treatment of cervical dystonias. Since then, its use has been expanded for multiple indications.

On July 30, 2010, incobotulinumtoxinA (Xeomin) was approved by the FDA for treatment of cervical dystonias and blepharospasm. Since then, its use has been expanded for multiple indications.

The FDA-approved indications for the various botulinum toxin products are summarized in Table 1. The evidence for the FDA approved indication for botulinum toxin is not reviewed.

Table 1. FDA Labeled Indications and Dosage

Agent	FDA Labeled Indications	Dosing and Administration
Botox® (onabotulinum toxin A) Intramuscular, intradetrusor, or intradermal injection	Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication	Overactive Bladder: Recommended total dose 100 Units, as 0.5 mL (5 Units) injections across 20 sites into the detrusor; re-treat every 12 weeks or longer Dose per session should not exceed 100 units Max dosing: The maximum cumulative dose should not exceed 400 units in a 3-month interval in patients being treated for one or more indication.
	Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication	Detrusor Overactivity associated with a Neurologic Condition: Recommended total dose 200 Units, as 1 mL (~6.7 Units) injections across 30 sites into the detrusor; re-treat every 12 weeks or longer Dose per session should not exceed 200 units Max dosing: The maximum cumulative dose should not exceed 400 units in a 3-month interval in patients being treated for one or more indication.
	Prophylaxis of headaches in adult patients with chronic migraine (≥ 15 days per month with headache lasting 4 hours a day or longer) Important Limitations: Safety and effectiveness of BOTOX have not been established for: <ul style="list-style-type: none"> • Prophylaxis of episodic migraine (14 headache days or fewer per month) 	Chronic Migraine: Recommended total dose 155 Units, as 0.1 mL (5 Units) injections per each site divided across 7 head/neck muscles; re-treat every 12 weeks Max dosing: The maximum cumulative dose should not exceed 400 units in a 3-month interval in patients being treated for one or more indication.
	Treatment of upper (elbow flexors [biceps], wrist flexors [flexor carpi radialis and flexor carpi ulnaris], finger flexors [flexor digitorum profundus and flexor digitorum sublimis], and thumb flexors [adductor pollicis and flexor pollicis longus]) and lower (ankle and toe flexors	Upper Limb Spasticity: Select dose based on muscles affected, severity of muscle activity, prior response to treatment, and adverse event history; Electromyographic guidance recommended; Up to 400 Units divided among affected muscles; re-treat every 12 weeks or longer Lower Limb Spasticity: Recommended total dose 300 Units to 400 Units divided among 5 muscles

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Agent	FDA Labeled Indications	Dosing and Administration
	<p>[gastrocnemius, soleus, tibialis posterior, flexor hallucis longus, and flexor digitorum longus]) limb spasticity in adult patients</p> <p>Important Limitations:</p> <ul style="list-style-type: none"> • Safety and effectiveness have not been established for treatment of other upper or lower limb muscle groups • Improve upper extremity functional abilities or range of motion at a joint affected by a fixed contracture • Not intended to substitute for usual standard of care rehabilitation regimens 	<p>Max dosing: The maximum cumulative dose should not exceed 400 units in a 3-month interval in patients being treated for one or more indication.</p>
	<p>Treatment of upper limb spasticity, and lower limb spasticity (excluding spasticity due to cerebral palsy), in pediatric patients 2 to 17 years of age</p> <p>Important Limitations: Safety and effectiveness of BOTOX have not been established for:</p> <ul style="list-style-type: none"> • Treatment with Botox is not intended to substitute for usual standard of care rehabilitation regimens in pediatric patients 2 to 17 years of age for upper limb spasticity 	<p>Upper Limb Spasticity: 3 to 6 units/kg divided among the different muscles. Max of 6 units/kg or 200 units, whichever is lower, per treatment.</p> <p>Lower Limb Spasticity: 4 to 8 units/kg divided among the affected muscles. Max of 8 units/kg or 300 units, whichever is lower, per treatment.</p> <p>Max dose when treating both upper and lower limb in combination: total dose should not exceed the lower of 10 units/kg or 340 units, in a 3-month interval.</p> <p>Max cumulative dosing: should not exceed the lower of 8 units/kg or 300 units in a 3-month interval in patients being treated for one or more indication.</p>
	<p>Treatment of cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain</p>	<p>Cervical Dystonia: Base dosing on the patient's head and neck position, localization of pain, muscle hypertrophy, patient response, and adverse event history; use lower initial dose in botulinum toxin naïve patients</p> <p>No more than 50 Units per site up to a total dose of 400 units divided among affected muscles</p> <p>Max dosing: Adults: The maximum cumulative dose should not exceed 400 units in a 3-month interval in patients being treated for one or more indication.</p>
	<p>Treatment of severe primary axillary hyperhidrosis that is inadequately managed by topical agents</p> <p>Important Limitations: Safety and effectiveness of BOTOX have not been established for:</p> <ul style="list-style-type: none"> • Treatment of hyperhidrosis in body areas other than axillary • Safety and effectiveness of Botox have not been established for the treatment of axillary hyperhidrosis in pediatric patients under age 18 	<p>Axillary Hyperhidrosis: 50 Units per axilla</p> <p>Max dosing: The maximum cumulative dose should not exceed 400 units in a 3-month interval in patients being treated for one or more indication.</p>

Agent	FDA Labeled Indications	Dosing and Administration
	Treatment of blepharospasm associated with dystonia in patients ≥12 years of age	<p>Blepharospasm: 1.25 Units-2.5 Units into each of 3 sites per affected eye</p> <p>Max cumulative dose for blepharospasm in a 30-day period should not exceed 200 Units</p> <p>Max dosing: Adults: The maximum cumulative dose should not exceed 400 units in a 3-month interval in patients being treated for one or more indication. Pediatrics: The maximum cumulative dose should not exceed the lower of 8 units/KG or 300 unites in a 3-month interval in patients being treated for one or more indication.</p>
	Treatment of strabismus in patients ≥12 years of age	<p>Strabismus: The dose is based on prism diopter correction or previous response to treatment with BOTOX; Initial doses range from 1.25 Units to 5 Units per muscle, subsequent doses have a maximum recommended dose of 25 Units per muscle</p> <p>Max dosing: Adults: The maximum cumulative dose should not exceed 400 units in a 3-month interval in patients being treated for one or more indication. Pediatrics: The maximum cumulative dose should not exceed the lower of 8 units/KG or 300 unites in a 3-month interval in patients being treated for one or more indication.</p>
	<p>In adult patients, temporary improvement in the appearance of:</p> <ul style="list-style-type: none"> • Moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity • Moderate to severe lateral canthal lines associated with orbicularis oculi activity • Moderate to severe forehead lines associated with frontalis muscle activity 	<p>Glabellar lines: Total dose of 20 units divided among 5 sites, may repeat in 3 months</p> <p>Lateral lines: Total dose of 24 units divided among 3 sites on each side of the face, may repeat in 3 months</p> <p>Forehead lines: Total dose of 20 units divided among 5 sites, may repeat in 3 months</p> <p>Max dosing: The maximum cumulative dose should not exceed 400 units in a 3-month interval in patients being treated for one or more indication.</p>
<p>Dysport® (abobotulinum toxin A)</p> <p>Intramuscular injection</p>	Treatment of adults with cervical dystonia	<p>Cervical dystonia: initial dose 500 units IM divided among affected muscles; re-treat every 12 weeks or longer</p>
	Temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients <65 years of age	<p>Glabellar lines: total dose of 50 units IM no more than every 3 months</p>
	Treatment of spasticity in adults	<p>Upper limb spasticity: 500 Units to 1000 Units divided among affected muscles</p> <p>Lower limb spasticity: up to 1500 Units divided among affected muscles</p> <p>Re-treat every 12 weeks or longer</p>

Agent	FDA Labeled Indications	Dosing and Administration
	Treatment of upper limb spasticity (excluding spasticity due to cerebral palsy), and lower limb spasticity in pediatric patients 2 to 17 years of age	<p>Upper limb spasticity: 8-16 Units/kg per limb (not to exceed 640 Units); re-treat every 12 weeks</p> <p>Lower limb spasticity: 10–15 Units/kg per limb; re-treat every 12 weeks or longer</p>
<p>Myobloc® (rimabotulinum toxin B)</p> <p>Intramuscular injection</p>	Treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia	<p>Cervical dystonia: Patients previously tolerating botulinum toxin injections: 2,500 to 5,000 units divided among affected muscles</p> <p>Botulinum toxin naïve: lower initial dosage</p> <p>Retreatment should be no more frequent than every 12 weeks</p>
	Treatment of chronic sialorrhea in adults	<p>Chronic sialorrhea: 1,500 units to 3,500 units divided among the parotid and submandibular glands. Retreatment should be no more frequent than every 12 weeks</p>
<p>Xeomin® (incobotulinum toxin A)</p> <p>Intramuscular or intraglandular injection</p>	Treatment of adult patients with chronic sialorrhea	<p>Chronic sialorrhea: recommended total dose per treatment session is 100 Units, repeat no sooner than ever 16 weeks</p> <p>Max Dosing: The maximum cumulative dose for any indication should not exceed 400 units in a treatment session</p>
	Treatment of adult patients with upper limb spasticity	<p>Upper Limb Spasticity: recommended total dose is up to 400 Units, repeat no sooner than every 12 weeks</p> <p>Max Dosing: The maximum cumulative dose for any indication should not exceed 400 units in a treatment session</p>
	Treatment of adult patients with cervical dystonia	<p>Cervical Dystonia: recommended initial total dose is 120 Units per treatment session, repeat no sooner than every 12 weeks</p> <p>Max Dosing: The maximum cumulative dose for any indication should not exceed 400 units in a treatment session</p>
	Treatment of adult patients with blepharospasm	<p>Blepharospasm: Previously treated with botulinum toxin: past dose, response, duration of effect, and adverse event history should be considered when determining dose</p> <p>Treatment naïve: 50 units (25 units per eye)</p> <p>Dose per session should not exceed 100 units (50 units per eye) and repeat no sooner than every 12 weeks</p> <p>Max Dosing: The maximum cumulative dose for any indication should not exceed 400 units in a treatment session</p>
	Temporary improvement in the appearance of moderate to severe glabellar lines with corrugator and/or procerus muscle activity in adult patients	<p>Glabellar Lines: total recommended dose is 20 Units per treatment session; wait a minimum of three months before retreatment</p> <p>Max Dosing: The maximum cumulative dose for any indication should not exceed 400 units in a treatment session</p>

POLICY

- A. Botulinum toxin may be considered **medically necessary** for treatment of the following:
1. Cervical dystonia (spasmodic torticollis; applicable whether congenital, due to childbirth injury, or traumatic injury). For this use, cervical dystonia must be associated with sustained head tilt or abnormal posturing with limited range of motion in the neck AND a history of recurrent involuntary contraction of one or more of the muscles of the neck, eg, sternocleidomastoid, splenius, trapezius, or posterior cervical muscles. (See additional details in Policy Guidelines.)
 2. Dystonia resulting in functional impairment (interference with joint function, mobility, communication, nutritional intake) and/or pain in patients with any of the following:
 - a. Focal upper limb dystonia (eg, 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
 3. Upper and lower limb spasticity as well spastic conditions related to:
 - a. Cerebral palsy
 - b. Stroke
 - c. Acquired spinal cord or brain injury
 - d. Hereditary spastic paraparesis
 - e. Spastic hemiplegia
 - f. Neuromyelitis optica
 - g. Multiple sclerosis or Schilder's disease
 4. Overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication
 5. Urinary incontinence due to detrusor overreactivity associated with a neurogenic condition (eg, spinal cord injury, multiple sclerosis) in adults who have an inadequate response to or are intolerant of an anticholinergic medication
 6. Prophylaxis of chronic migraine headache in the following situations:
 - a. Initial 6-month trial. Adults who:
 - 1) Meet International Classification of Headache Disorders (ICHD) diagnostic criteria for chronic migraine headache (see Policy Guidelines); and
 - 2) Have symptoms that persist despite adequate trials of at least 2 agents from different classes of medications used in the treatment of chronic migraine headaches (eg, antidepressants, antihypertensives, antiepileptics). Patients who have contraindications to preventive medications are not required to undergo a trial of these agents.

- b. Continuing treatment beyond 6 months:
 - 1) Migraine headache frequency reduced by at least 7 days per month compared with pretreatment level, or
 - 2) Migraine headache duration reduced at least 100 hours per month compared with pretreatment level.
 - 7. Blepharospasm associated with dystonia or facial nerve (VII) disorders (including hemifacial spasm).
 - 8. Strabismus
 - 9. Chronic sialorrhea (drooling) associated with amyotrophic lateral sclerosis or atypical parkinsonian disorders or cerebral palsy or Parkinson's disease or stroke or traumatic brain injury AND has experienced excessive salivation for 3 or more months AND refractory to at least 2 months of continuous treatment with at least one oral pharmacotherapy (e.g., anticholinergics).
 - 10. Esophageal achalasia in patients who have not responded to dilation therapy or who are considered poor surgical candidates.
 - 11. Chronic anal fissure in patients with a history of failure, contraindication, or intolerance to one of the following conventional therapies:
 - a. Topical nitrates
 - b. Topical calcium channel blockers (e.g., diltiazem, nifedipine).
 - 12. Treatment of patients with Hirschsprung disease who develop obstructive symptoms after a pull-through operation.
- B. With the exception of cosmetic indications, the use of botulinum toxin is considered **experimental / investigational** for all other indications not specifically mentioned above, including, but not limited to:
- 1. Neurological indications such as:
 - a. Headaches, except as noted above for prevention (treatment) of chronic migraine headache
 - b. Essential tremor
 - c. Tinnitus (see separate policy, *Treatment of Tinnitus*)
 - d. Chronic motor tic disorder and tics associated with Tourette's syndrome (motor tics)
 - 2. Urological indications such as:
 - a. Benign prostatic hyperplasia
 - b. Interstitial cystitis
 - c. Detrusor sphincteric dyssynergia (after spinal cord injury)
 - 3. Pain due to multiple etiologies such as:
 - a. Chronic low back pain
 - b. Joint pain
 - c. Mechanical neck disorders
 - d. Neuropathic pain after neck dissection
 - e. Myofascial pain syndrome
 - f. Temporomandibular joint disorders
 - g. Trigeminal neuralgia

- h. Pain after hemorrhoidectomy or lumpectomy
 - i. Lateral epicondylitis
 - j. Prevention of pain associated with breast reconstruction after mastectomy
 - 4. Ano-rectal conditions such as:
 - a. Internal anal sphincter (IAS) achalasia
 - b. Anismus
 - 5. Other miscellaneous conditions such as:
 - a. Gastroparesis
 - b. Facial wound healing
 - c. Depression
- C. The use of botulinum toxin as a treatment of wrinkles or other cosmetic indications is **noncovered**.
- D. The use of assays to detect antibodies to botulinum toxin is considered **experimental / investigational**.

Policy Guidelines

1. Dystonia is a general term describing a state of abnormal or disordered tonicity of muscle. As an example, 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.
2. International Classification of Headache Disorders (ICHD-3) diagnostic criteria for chronic migraine headache include the following:
 - a. Headaches at least 15 days per month for more than 3 months; have features of migraine headache on at least 8 days.
 - b. Features of migraine headache:
 - 1) Lasts 4 to 72 hours
 - 2) Has at least 2 of the following 4 characteristics:
 - a) Unilateral
 - b) Pulsating
 - c) Moderate or severe pain intensity
 - d) Aggravates or causes avoidance of routine physical activity
 - 3) Associated with:
 - a) Nausea and/or vomiting
 - b) Photophobia and photophobia

(In ICHD-2, absence of medication overuse was one of the diagnostic criteria for chronic migraine. In the ICHD-3, this criterion was removed from the chronic migraine diagnosis and "medication overuse headache" is now a separate diagnostic category.)
3. Continuing treatment with botulinum toxin beyond 6 months for chronic migraine: The policy includes the requirement that migraine headache frequency be reduced

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

4. The safety and efficacy of combination therapy with botulinum toxin and calcitonin gene related peptide (CGRP) when used for prophylaxis has not been studied in the treatment of migraine headache.

RATIONALE

This evidence review has been updated with searches of the MEDLINE database. The most recent literature update was performed through July 29, 2019. In this section, evidence was only reviewed for clinical indications for which none of the four commercially available Food and Drug Administration approved botulinum toxin products are available in the U. S.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Esophageal Achalasia

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

Clinical Context and Therapy Purpose

The purpose of botulinum toxin in patients with esophageal achalasia is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does use of commercially available botulinum toxin products improve the net health outcome in patients with esophageal achalasia?

The following PICO's were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with esophageal achalasia who are not candidates for PD, surgical myotomy, or peroral endoscopic myotomy.

Interventions

The therapy being considered is commercially available botulinum toxin products and is generally prescribed by general physicians, surgeons, and gastroenterologist. It is injected directly using endoscopic ultrasound techniques to facilitate localization in the lower esophageal sphincter region in an outpatient setting.

Comparators

The following therapies are currently being used to treat esophageal achalasia: medications (ie, zolpidem), PD, surgical myotomy, or peroral endoscopic myotomy.

Outcomes

The general outcomes of interest are symptoms, functional outcomes, and treatment-related morbidity. Follow-up ranges from six months to a year to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Evidence Review**Systematic Reviews**

A Cochrane review by Leyden et al (2014) identified 7 RCTs (total n=178 participants) that compared onabotulinumtoxinA with endoscopic PD.¹ Outcomes reported was symptom remission rate at 1, 6 and 12 months. Study characteristics and results are summarized in Tables 2 and 3 respectively. The meta-analysis of RCTs showed no difference in relative risk (RR) of symptom remission at one month between PD vs onabotulinumtoxinA. (RR=1.11, 95% confidence interval [CI]: 0.97 to 1.27). However, at 6 and 12 months, PD resulted in higher symptom remission rates and the difference was statistically significant (RR=1.57, p<0.005; RR=1.88, p= <0.005). No serious adverse events were reported after onabotulinumtoxinA injection; however, there were three cases of perforation after PD. Authors concluded that PD resulted in superior long-term

efficacy compared with onabotulinumtoxinA (at 6 and 12 months). While the overall methodological quality of the individual RCTs was reported to be good, the risk of bias was high. In particular, only one RCT was double blind, five RCTs were potentially at a risk of selection, performance or detection bias due to inappropriate allocation of concealment, blinding of participants and personnel, and outcome assessment.

Wang et al (2009) conducted a meta-analysis of RCTs that compared the efficacy of different treatments for primary achalasia.² Five RCTs compared botulinum toxin A injection with PD in patients with untreated achalasia, and also examined both subjective and objective parameters of esophageal improvement in all patients over 12 months. Authors reported that symptom remission rate was significantly higher in patients treated with PD vs botulinum toxin A injection (65.8% vs 36% respectively). Proportion of patients who relapsed within a year was 16.7% with PD vs 50% with botulinum toxin injection. Moreover, relapse time of botulinum toxin injection was shorter than that of PD after first therapy. Two RCTs compared efficacy of laparoscopic myotomy with botulinum toxin A injection in patients with untreated achalasia. Authors reported that the symptom remission rate of botulinum toxin injection rapidly decreased and nearly 50% of patients were symptomatic again after 1 year of treatment. Laparoscopic myotomy had superior efficacy to botulinum toxin injection (laparoscopic myotomy 83.3% vs botulinum toxin injection 64.9%, RR 1.28; 95% CI 1.02–1.59; P=0.03). Patients treated with onabotulinumtoxinA had more frequent relapse and shorter time to relapse than those treated with laparoscopic myotomy. Some limitations of this meta-analysis include small number of cohorts in each trial, poor randomization techniques, and inadequate follow-up.

While the evidence is suggestive that PD and surgical myotomy are definitive therapies for esophageal achalasia and associated with superior long-term outcomes compared with botulinum toxin A, in patients who are not good candidates for PD and/or surgical myotomy, botulinum toxin A may be a reasonable option. Further, botulinum toxin injection has the advantage of being less invasive as compared with surgery, can be easily performed during routine endoscopy. Initial success rates with botulinum toxin are comparable to PD and surgical myotomy.² However, patients treated with botulinum toxin have more frequent relapses and a shorter time to relapse.² Greater than 50% of patients with achalasia treated with botulinum toxin A require retreatment within 6 to 12 months. Repeated botulinum toxin injections may also make a subsequent Heller myotomy more challenging.³

Table 2. Systematic Review/Meta-Analysis Characteristics

Study (Year)	Dates	Trials	Participants	N (Range)	Design	Duration
Leyden et al (2014) ¹	1955-2008	7	Individuals with primary achalasia with the aim to compare endoscopic pneumatic dilation vs botulinum toxin A	178 (NR)	RCT	7 trials followed up patients ranging from 1 to 12 months
Wang et al (2009) ²	1989-2007	17	Individuals with primary achalasia who received botulinum toxin injection, pneumatic dilation, laparoscopic myotomy, surgical intervention, or nifedipine	761 (NR)	RCT	17 trials followed up patients ranging from 8 to 68 months

NR: not reported; RCT: randomized controlled trial.

Table 3. Systematic Review/Meta-Analysis Results

Study (Year)	Symptom Remission at 1 Month	Symptom Remission at 6 Months	Symptom Remission at 12 Months
Leyden et al (2014) ¹ : Endoscopic pneumatic dilation vs botulinum toxin A (onabotulinumtoxinA)			
Total N	189 (5 RCTs)	113 (3 RCTs)	147 (4 RCTs)
Pooled effect (95% CI); p-value	RR = 1.11 (0.97 to 1.27); P value = NR	RR = 1.57 (1.19 to 2.08); P value = 0.0015	RR = 1.88 (1.35 to 2.61); P value = 0.0002
I ² (p)	0.0%	79%	42%
Wang et al (2009) ² : Remission Rate Over 12 Months			
Endoscopic pneumatic dilation vs botulinum toxin A			
Total N	154 (5 RCTs)	154 (5 RCTs)	
Pooled effect (95% CI); p-value	65.8% vs 36%; RR= 2.20 (95% CI: 1.51 to 3.20, P<0.0001)	16.7% vs 50%; RR=0.36 (95% CI 0.22 to 0.58)	
Laparoscopic Myotomy vs botulinum toxin A			
Total N	117 (2 RCTs)	Not reported	
Pooled effect (95% CI); p-value	83.3% vs 64.9%, RR 1.28 (95% CI 1.02 to 1.59; P = 0.03).	Not reported	

CI: confidence interval; NR: not reported; RCT: randomized controlled trial; RR: relative risk.

Section Summary: Esophageal Achalasia

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

Chronic anal fissure

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

Clinical Context and Therapy Purpose

The purpose of botulinum toxin in patients with chronic anal fissure is to provide a treatment option

that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does use of commercially available botulinum toxin products improve the net health outcome in patients with chronic anal fissure?

The following PICO's were used to select literature to inform this review.

Patients

The relevant populations of interest are individuals with chronic anal fissure who fail medical management and are at a high-risk of incontinence.

Interventions

The therapy being considered is commercially available botulinum toxin products and is generally prescribed by general physicians, surgeons, and gastroenterologist. It is injected intrasphincteric in an outpatient setting.

Comparators

The following therapies are currently being used for individuals with chronic anal fissure who failed medical management: fissurectomy, anal advancement flap and lateral internal sphincterotomy.

Outcomes

The general outcomes of interest are symptoms, health status measures, and treatment-related morbidity. Follow-up ranges from six months to a year to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using similar criteria mentioned previously.

evidence review

Systematic Reviews

Chen et al (2014) compared outcomes of onabotulinumtoxinA injection with lateral internal sphincterotomy based on 7 RCTs.⁴ The study characteristics and results are summarized in Table 4 and 5. Treatment with botulinum toxin injection was associated with lower healing rate and a higher recurrence rate compared with lateral internal sphincterotomy. Sphincterotomy also resulted in higher complication rates but the difference was not statistically significant (p-value=0.35). The meta-analysis suggests that internal sphincterotomy is more effective to treat anal fissure but onabotulinumtoxinA injection was associated with lower rates of incontinence. Authors reported multiple limitations in the evidence pooled for the meta-analysis including various dose of onabotulinumtoxinA used in different trials, inconsistent definition of chronic anal fissure used in the RCTs and none of the included RCTs were blinded. In addition, results of included studies were not consistent. The total complication rate varied from 0 to 64 % among the trials, while the incontinence rate varied from 0 to 48%. Nelson et al (2012) published a Cochrane review that compared multiple treatment options for chronic anal fissure.⁵ Reported results for comparison of botulinum toxin injection with sphincterotomy are consistent with those reported by Chen et al (2014). Botulinum toxin A injection is therefore preferably used for patients who are at a high-risk of developing fecal incontinence (eg, multiparous women or older patients).

Table 4. Systematic Review/Meta-Analysis Characteristics

Study (Year)	Dates	Trials	Participants	N (Range)	Design	Duration
Chen et al (2014) ⁴	2003-2012	7	Individuals with chronic anal fissure	489 (NR)	RCT	7 trials followed up patients ranging from 18 weeks to 3 years

NR: not reported; RCT: randomized controlled trial.

Table 5. Systematic Review/Meta-Analysis Results

Study (Year)	Healing	Complications	Incontinence	Recurrence Rate
Chen et al (2014) ⁴ : Botulinum A toxin injection vs lateral internal sphincterotomy				
Total N	409 (6 RCTs)	451 (6 RCTs)	489 (7 RCTs)	489 (7 RCTs)
Pooled effect (95% CI); p-value	OR = 0.15 (0.08 to 0.27); P < 0.001	OR = 0.55 (0.15 to 1.94); P=0.35	OR = 0.12 (0.05 to 0.26); P < 0.001	OR = 5.97 (3.51 to 10.17); P < 0.001
I ² (p)	0% (0.5)	75% (0.001)	0% (0.53)	4% (0.39)
Nelson et al (2012) ⁵ : Botulinum A toxin injection vs sphincterotomy				
Total N	365 (5 RCTs)	Not reported	321 (4 RCTs)	Not reported
Pooled effect (95% CI); p-value	7.20 ^a (3.97 to 13.07); P < 0.001	Not reported	0.11 (0.02 to 0.46); p < 0.001	Not reported
I ² (p)	47%	Not reported	0	Not reported

^a Comparison indicates that sphincterotomy was 7.2 times more likely to heal than botulinum toxin injection

NR = Not reported; CI: Confidence interval; OR: odds ratio; RCT: randomized controlled trial.

Section Summary: Anal Fissure

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

Hirschsprung Disease

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

Clinical Context and Therapy Purpose

The purpose of botulinum toxin in patients with Hirschsprung disease is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does use of commercially available botulinum toxin products improve the net health outcome in patients with Hirschsprung disease?

The following PICO were used to select literature to inform this review.

Patients

The relevant populations of interest are individuals with Hirschsprung disease who develop obstructive symptoms after a pull-through operation.

Interventions

The therapy being considered is commercially available botulinum toxin products and is generally used by surgeons. It is injected intrasphincteric in an inpatient setting.

Comparators

The mainstay of treatment is surgery. The goals are to resect the affected segment of the colon, bring the normal ganglionic bowel down close to the anus, and preserve internal anal sphincter function. Many surgical techniques have been developed. The choice among them usually is based upon surgeon preference since the overall complication rates and long-term results are similar

Outcomes

The general outcomes of interest are symptoms, health status measures, and treatment-related morbidity. Follow-up ranges from six months to five years to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using similar criteria mentioned previously.

evidence review

The published literature on use of onabotulinumtoxinA to treat Hirschsprung disease consists of case series summarized in Table 6 and 7.^{6,7,8,}

A retrospective case series by Han-Geurts et al (2014), included 33 children with surgically treated Hirschsprung disease treated with intrasphincteric botulinum toxin A injections for obstructive symptoms was analyzed with a retrospective chart review between 2002 and 2013 in the Netherlands.⁹ The mean age at time of botulinum toxin A treatment was 3.6 years and median follow-up was 7.3 years (range 1 to 24). A median of two (range 1–5) injections were given. Initial short-term improvement was achieved in 76%, with a median duration of 4.1 months (range 1.7 to 58.8). Proportion of children hospitalized for enterocolitis decreased after treatment from 19 to 7. More than half (51%) of patients reported good or excellent long-term outcomes after a median follow-up of 126 months. Two children experienced complications: transient pelvic muscle paresis with impairment of walking. In both children symptoms resolved within four months without treatment.

A prospective case series by Minkes and Langer (2000), included 18 children (median age, 4 years) with persistent obstructive symptoms after surgery for Hirschsprung disease.⁷ Patients received injections of onabotulinumtoxinA into four quadrants of the sphincter. The total dose of onabotulinumtoxinA during the initial series of injections was 15 to 60 U. Twelve (67%) of 18 patients improved for more than 1 month and the remaining 6 (33%) either showed no improvement or improved for less than 1 month. Ten children had one to five additional injections due to either treatment failure or recurrence of symptoms; retreatment was not based on a standardized protocol.

A retrospective case series by Patrus et al (2011) reviewed outcomes in 22 patients with Hirschsprung disease treated over 10 years; subject had received a median of 2 (range, 1-23)

onabotulinumtoxinA injections for postsurgical obstructive symptoms.⁸ Median follow-up (time from first injection to time of chart review) was five years (range, 0-10 years). At chart review, 2 (9%) of 22 patients had persistent symptoms. Eighteen (80%) children had a “good response” to the initial treatment (not defined), and 15 (68%) had additional injections. The authors reported that the number of hospitalizations for obstructive symptoms decreased significantly after onabotulinumtoxinA injection (median, 0) compared with preinjection (median, 1.5; $p=0.003$). The authors did not report whether patients received other treatments during the follow-up period in either case series.

Table 6. Summary of Key Nonrandomized Trials OR Observational Comparative Study Characteristics

Author (Year)	Study Type	Country/ Institution	Dates	Participants	Treatment1	Follow-Up
Minkes et al (2000) ⁷ ,	Prospective	U.S./ University of Washington	NR	Children with Hirschsprung’s disease who have persistent obstructive symptoms after operation	OnabotulinumtoxinA (Botox) N = 18	4 years
Patrus et al (2010) ⁸ ,	Retrospective	Canada/ Hospital for Sick Children	1998-2008	Children with Hirschsprung’s disease who have persistent obstructive symptoms after operation	OnabotulinumtoxinA (Botox) N = 22	10 years
Han-Geurts et al (2014) ⁹ ,	Retrospective	Netherlands/ University Medical Centers of Maastricht and Nijmegen	2002-2013	Children with Hirschsprung’s disease who have persistent obstructive symptoms after operation	OnabotulinumtoxinA (Botox) N = 33	7.3 years

NR: not reported.

Table 7. Summary of Key Nonrandomized Trials OR Observational Comparative Study Results

Study (Year)	Outcomes (Efficacy)
Minkes et al (2000) ⁷ ,	
Total N	18
OnabotulinumtoxinA	Clinical response after 1 month 67% (12/18)
Patrus et al (2010) ⁸ ,	
Total N	22
OnabotulinumtoxinA injection	Median number of hospitalization for obstructive symptoms: Prior to treatment: 1.5 (IQR: 1 to 3) Post treatment: 0 Clinical Response After 1 st dose: 80%
p-value	$P < 0.05$
Han-Geurts et al (2014) ⁹ ,	
Total N	33
OnabotulinumtoxinA	Short-term improvement 76% (25/33) Long-term improvement Poor = 19% (6) Fair = 30% (10) Good = 27% (9) Excellent = 24% (8)
Difference (95% CI); p-value	NR

CI: confidence interval; IQR = interquartile range; NR: not reported.

Section Summary: Hirschsprung Disease

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

Miscellaneous Conditions

Clinical Context and Therapy Purpose

The purpose of botulinum toxin in patients with miscellaneous conditions listed below is to provide a treatment option that is an alternative to or an improvement on existing therapies. In general, many treatment options are available for treatment of these indications. Commercially available botulinum toxin products have been evaluated in the setting when patients have failed the standard of care or in whom standard of care interventions are contraindicated.

The question addressed in this evidence review is: Does use of various type of commercially available botulinum toxin products improve the net health outcome in patients with miscellaneous conditions listed below?

Table 8. List of Miscellaneous Clinical Conditions Where Botulinum Toxin Has Been Evaluated as a Potential Treatment

Indication Category	Clinical Indication	Description
Neurological indications	Non-migraine Headaches	Tension-type headache is the most common type of headache. Depending on the frequency, there are infrequent episodic (less than 1 day of headache per month), frequent episodic (1 to 14 days of headache per month) and chronic (15 days or more per month). ¹⁰ It is postulated that botulinum toxin A affects the neuronal signaling pathways activated during a headache and also has a blocking action on the parasympathetic nervous system and might inhibit the release of other neurotransmitters or affect the transmission of afferent neuronal impulses. ¹¹ Cervicogenic headache is head pain caused by a disorder of the cervical spine and its component bone, disc and/or soft tissue elements. There is ongoing debate regarding the existence of cervicogenic headache as a distinct clinical disorder, as well as its underlying pathophysiology and source of pain. ¹² Botulinum toxin A has been evaluated as a potential treatment given its efficacy in migraine.
	Essential tremor	Essential tremor is the most common cause of action tremor in adults. It classically involves the hands and is brought out by arm movement and sustained antigravity postures, affecting common daily activities such as writing, drinking from a glass, and handling eating utensils. Essential tremor is slowly progressive and can involve the head, voice, and rarely the legs, in addition to the upper limbs. Disability from the tremor can be significant, and a variety of symptomatic therapies are available.
	Tinnitus	Tinnitus is a perception of sound in proximity to the head in the absence of an external source. In patients with myoclonus of the palatal muscles or middle ear structures, botulinum toxin injections into the palate or sectioning of the tendons with the middle ear has been evaluated for symptomatic relief.
Urological	Benign prostatic	Benign prostatic hyperplasia is an enlargement of prostate gland in men. The

Indication Category	Clinical Indication	Description
indications	hyperplasia	enlargement of prostate presses causes narrowing of the urethra and losing the inability to empty the bladder completely. The symptoms include urinary frequency, urinary urgency, nocturia, urinary retention, and urinary incontinence. Transperineal or transurethral (via cystoscope) injection of botulinum toxin A into the prostate has been evaluated for reduction in symptoms associated with benign prostatic hyperplasia.
	Interstitial cystitis	Interstitial cystitis is a chronic condition characterized by pain, urgency, and frequent urination of small volumes. Intravesical injection of botulinum toxin A has been evaluated in patients with interstitial cystitis/bladder pain syndrome for patients with symptoms that significantly affect quality of life, who have failed other measures, and who are aware of and willing to accept the risk of adverse effects. ¹³ .
Pain	Multiple etiologies	This category include chronic low back pain, joint pain, mechanical neck disorders, neuropathic pain after neck dissection, myofascial pain syndrome, temporomandibular joint disorders, trigeminal neuralgia, pain after hemorrhoidectomy or lumpectomy, lateral epicondylitis and prevention of pain associated with breast reconstruction after mastectomy
Ano-rectal conditions	Internal anal sphincter achalasia	Internal anal sphincter achalasia is a clinical condition with presentation similar to Hirschsprung's disease, but with the presence of ganglion cells on rectal suction biopsy. The diagnosis is made by anorectal manometry, which demonstrates the absence of the rectosphincteric reflex on rectal balloon inflation.
	Anismus	Anismus is the failure of the normal relaxation of pelvic floor muscles during attempted defecation. Symptoms include tenesmus (the sensation of incomplete emptying of the rectum after defecation has occurred) and constipation. Retention of stool may result in fecal loading (retention of a mass of stool of any consistency) or fecal impaction (retention of a mass of hard stool). This mass may stretch the walls of the rectum and colon, causing megarectum and/or megacolon.
Others	Gastroparesis	Gastroparesis is a syndrome of objectively delayed gastric emptying in the absence of a mechanical obstruction and cardinal symptoms of nausea, vomiting, early satiety, belching, bloating, and/or upper abdominal pain.
	Depression	Depression is common that affects US population and is also the leading cause of disability. It is postulated that treating the frown muscles of depressed patients with botulinum toxin A may improve depressive symptoms as it is hypothesized that facial expression influences emotional perception; producing an expression that is characteristic of a particular emotion can lead to experiencing that emotion (eg, smiling can lead to happiness, scowling can lead to anger). Inhibiting the muscles responsible for expressions of anguish and sadness, one may decrease the patient's experience of these feelings.

The following PICO's were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with miscellaneous conditions listed above who have failed standard of care or in whom standard of care interventions are contraindicated.

Interventions

The therapy being considered is commercially available botulinum toxin products.

Comparators

The following therapies are currently being used to treat miscellaneous conditions listed above.

Table 9. Current Treatment Options for Miscellaneous Indications

Indication Category	Clinical Indication	Current Treatment Options
Neurological indications	Non-migraine Headaches	The acute or abortive (symptomatic) therapy of tension-type headache ranges from nonpharmacologic therapies to simple and combination analgesic medications. Chronic tension-type headache is often associated with comorbid stress, anxiety, and depression. In this setting, simple analgesics are usually of little or no benefit. When acute treatment of tension-type headache is ineffective, other possible causes should be considered. There is no proven effective treatment for cervicogenic headache. However, a number of different treatment modalities are available. Physical therapy is the preferred initial treatment because it is noninvasive. The available evidence suggests that pharmacologic therapy and botulinum toxin injections are not beneficial.
	Essential tremor	The initial approach to treatment is conservative measures such as pharmacotherapy with first-line treatment with propranolol and/or primidone. In case of inadequate response, second line agents include benzodiazepines, gabapentin, topiramate.
	Tinnitus	Treatment for tinnitus includes correcting identified comorbidities as well as directly addressing the effects of tinnitus on quality of life. Several treatment modalities including behavioral treatments and medications have been studied but the benefit for most of these interventions has not been conclusively demonstrated in randomized trials.
Urological indications	Benign prostatic hyperplasia	Medications commonly used to treat lower urinary tract symptoms associated with benign prostatic hyperplasia include alpha-1-adrenergic antagonists, 5-alpha-reductase inhibitors, anticholinergic agents and phosphodiesterase-5 inhibitors.
	Interstitial cystitis	There are numerous treatments and management approaches are organized in the order of increasing risk. For most patients, it is reasonable to move from one level (eg, first-line to second-line) when less risky approaches have failed. Less invasive treatments include self-care practices and behavior modifications, physical therapy, oral medications such as amitriptyline, pentosan polysulfate sodium antihistaminic agents. More invasive treatments include, bladder hydrodistention, resection, electrical cauterization, or injection of Hunner lesions with a corticosteroid and intravesical instillation of glycosaminoglycans or dimethyl sulfoxide.
Pain	Multiple etiologies	Treatment of pain depends on the cause and nature of the pain. Generally, the initial approach is conservative and includes use of non-invasive pharmacotherapy including non-steroidal anti-inflammatory drugs, anticonvulsants, antidepressants, and opioids. Patients who fail to respond to first-line agents are candidates for second- or third line agents or more invasive treatments.
Ano-rectal conditions	Internal anal sphincter achalasia	The recommended treatment of choice is posterior internal anal sphincter myectomy.
	Anismus	Anismus is usually treated with dietary adjustments, such as dietary fiber supplementation. Biofeedback therapy, during which a sensor probe is inserted into the person's anal canal in order to record the pressures exerted by the pelvic floor muscles and pressure readings are visually relayed to the patient via a monitor who has also been used.
Others	Gastroparesis	Initial management of gastroparesis consists of dietary modification, optimization of glycemic control and hydration, and in patients with continued symptoms, pharmacologic therapy with prokinetic and antiemetics.
	Depression	The goal of initial treatment for depression is symptom remission and restoring baseline functioning

Outcomes

The general outcomes of interest are symptoms, medication use, and treatment-related morbidity.

Study Selection Criteria

Methodologically credible studies were selected using similar criteria mentioned previously.

Neurological indications

Tension and Cervicogenic Headache

The meta-analysis by Jackson et al (2012) identified 8 RCTs evaluating onabotulinumtoxinA (6 trials) and abobotulinumtoxinA (2 trials) for treating chronic tension-type headaches; all were placebo-controlled.¹⁴ A pooled analysis of these 8 studies did not find a statistically significant difference in change in the monthly number of headache days in the botulinum toxin group vs the placebo group (difference=-1.43; 95% CI, -3.13 to 0.27; p-value=0.02). Silberstein et al (2006)¹⁵, randomized 300 patients to onabotulinumtoxinA (5 different doses) or placebo for the prophylaxis of chronic tension-type headache. The trial failed to demonstrate statistically significant difference between the onabotulinumtoxinA groups and the placebo group in the number of headache free days per month.

Multiple RCT's^{16,17,18,19}, with smaller sample size (<50) have evaluated the efficacy of onabotulinumtoxinA in patients with cervicogenic headache but either reported a lack of treatment benefit^{16,17,19}, or were methodological flawed (pain scores imbalanced at baseline) to derive meaningful conclusions.¹⁸

Essential Tremor

Botulinum toxin type A (BoNT-A) have been shown to provide benefit for limb tremor associated with essential tremor but have been associated with dose-dependent hand weakness. A systematic review published in 2011²⁰, concluded that botulinum toxin A is possibly effective for the treatment of essential hand tremor, with a beneficial effect that was modest at best. The conclusion was drawn on the basis of 2 double-blind, placebo-controlled, parallel-design trials of botulinum toxin type A- one enrolled 25 patients and the other enrolled 133 patients. In the first trial, 11 of 12 treated patients reported mild (50%) or moderate (42%) wrist or finger weakness.²¹ In the second trial, symptomatic hand weakness occurred in 30% of the low-dose group and 70% of the high-dose group. Neither the investigators nor the patients reported any subjective benefit, and there was minimal (0.5 points) change at six weeks.²² Subsequent to this systematic review, Mittal et al (2017) published the results of a small randomized trial of 30 patients with essential tremor and Parkinson disease tremor to incobotulinumtoxinA in a crossover design.²³ Statistically significant improvements in clinical rating scores of rest tremor and tremor severity at four and eight weeks were reported in the treated patients and of action/postural tremor at eight weeks; however, there was no statistically significant difference in grip strength at four weeks between the two groups. The clinical significance of small benefits observed in trials that were offset by frequent adverse effects (hand weakness) do not permit conclusions about net health benefit. A larger trial with longer term follow-up is required to replicate these findings and provide long-term follow-up to mitigate the risk of developing hand weakness over the course of time.

Tinnitus

Slengerik-Hansen et al (2016) reported the findings of a systematic review that included 22 studies, mainly case reports and case series with a total of 51 treated patients treated with onabotulinumtoxinA for the treatment of tinnitus.²⁴ A small (n=30) cross over prospective study by Stidham et al (2005) reported statistical significant decrease in tinnitus handicap inventory scores between pretreatment and 4 month postbotulinum toxin A injection. Multiple other outcomes

studies showed no difference.²⁵ Well-conducted RCTs with sufficiently large sample sizes are needed.

Trigeminal Neuralgia

Evidence for the efficacy and safety of botulinum toxin A for trigeminal neuralgia is limited and was summarized by Morral et al (2016) in a systematic review that included 4 RCTs (total n=178 patients).²⁶ The largest trial randomly assigned 80 patients to either botulinum toxin A or placebo.²⁶ While the meta-analysis reported significant reductions in mean pain scores and attack frequency in the botulinum toxin A compared with the placebo group, there are concerns about small patient numbers, limited durability and quality of evidence.

Urological Indications

Benign Prostatic Hyperplasia

Marchal et al (2012) reported the results of a systematic review on use of onabotulinumtoxinA and abobotulinumtoxinA to treat benign prostatic hyperplasia.²⁷ Two clinical trials with sufficient quality were selected for meta-analysis reported no difference in pre- and post-treatment of maximum flow, prostate volume, International Prostate Symptom Score and prostate-specific antigen post-voiding residue.

Interstitial Cystitis

The mechanism of the effect of Intradetrusor botulinum toxin therapy for interstitial cystitis is likely the ability of botulinum toxin to modulate sensory neurotransmission. While botulinum toxin has been shown to alleviate symptoms in multiple studies^{28,29,30}, mostly conducted outside of the U. S., there is a risk of urinary retention²⁹, which may be particularly devastating for a patient with a painful bladder and therefore any patient considering this treatment must be willing and able to perform intermittent self-catheterization.

A network meta-analysis of 16 trials including 905 patients published in 2016 indicated that botulinum toxin-A treatment had the highest probability of being the best treatment course based on global response assessment and significantly ameliorates bladder capacity in patients with interstitial cystitis.³¹ However, botulinum toxin A showed no treatment advantages with regard to pain, urinary frequency, and urgency results. Wang et al (2016) who reported the findings of a systematic review that included 7 RCTs and a retrospective study on onabotulinumtoxinA and abobotulinumtoxinA rated only 1 of the 7 RCTs as high-quality (ie, low-risk of bias) while 5 were rated as moderate, and the other was rated as a high-risk of bias.³² Kuo et al (2016) reported the results of an RCT that included 60 Taiwanese patients (52 women, 8 men) with IC/painful bladder syndrome who had failed at least 6 months of conventional therapy.²⁹ In this trial, at a higher dose (200 units of botulinum toxin A), adverse reactions occurred in 9 of 15 patients (4 patients had acute or chronic urinary retention, 7 had severe dysuria).²⁹ Later, the dose was decreased to 100 units that resulted in reduction of adverse events but they still occurred more frequent than hydrodistention alone.

Pain due to multiple etiologies

Lateral Epicondylitis

Although the mechanism for action for botulinum toxin in epicondylitis is not clearly understood, it is thought to be as "proinflammatory". Botulinum toxin has been evaluated as a treatment for epicondylitis in a number of RCTs as summarized in a number of systematic reviews.^{33,34,35} In the systematic review and meta-analysis published by Lin et al (2019), authors included 6 RCTs

(n=321) that comparing onabotulinumtoxinA or abobotulinumtoxinA with placebo or corticosteroid injections in patients with lateral epicondylitis.³³ Four of the 6 trials enrolled less than 30 participants per treatment arm and allocation concealment was unclear in 4 out of 6 trials. Results were reported as standardized mean differences and a negative number implied a favorable effect of botulinum toxin on pain reduction.

Compared with placebo, botulinum toxin injection significantly reduced pain at all 3 time points (2 to 4 weeks, 8 to 12 weeks and at 16 weeks or more; standardized mean difference -0.73 (-1.29 to -0.17), -0.45 (-0.74 to -0.15) and -0.54 (-0.99 to -0.11) respectively. In contrast, botulinum toxin was significantly less effective than corticosteroid 2 to 4 weeks following injection; standardized mean difference 1.15 (0.57 to 1.34) with no difference at 8-12 weeks or 16 weeks or more time point. While the systematic reviews generally report pain relief in individual trials of botulinum toxin vs the comparator, treatment with botulinum toxin was associated with temporary paresis of finger extension.

Myofascial Pain Syndrome

Several systematic reviews of RCTs have evaluated onabotulinumtoxinA and abobotulinumtoxinA for myofascial pain syndrome. The Cochrane systematic review by Soares et al (2014) identified 4 placebo-controlled, double-blind RCTs that included 233 participants with myofascial pain syndrome excluding neck and head muscles.³⁶ Due to heterogeneity among studies, reviewers did not pool analyses. The primary outcomes were change in pain as assessed by validated instruments. Three of the four studies found that botulinum toxin did not significantly reduce pain intensity. Major limitations included high-risk of bias due to study size in three of the four studies and selective reporting in one study. Two other systematic reviews that focused on myofascial pain syndrome involving head and neck muscles reported similar findings. Systematic review by Desai et al (2014) included 7 trials that evaluated the efficacy of botulinum toxin type A in cervico-thoracic myofascial pain syndrome.³⁷ Majority of studies found negative results and except for one, six identified trials had significant failings due to deficiencies in one or more major quality criteria.

Low Back Pain

Foster et al (2001) reported the findings of an RCT in which 31 consecutive patients with chronic low back pain of at least 6 months in duration were randomized to onabotulinumtoxinA or saline.³⁸ Botulinum toxin A was superior to placebo injection for pain relief and improved function at 3 and 8 weeks (50 % pain relief at 3 weeks 73.3 vs 25%; at 8 weeks 60 vs 16%, respectively). However, in most patients, benefits were no longer present after three to four months. These results should be considered preliminary, and further data from randomized trials are needed to confirm findings in a larger number of patients over a longer duration and to evaluate benefits and harms of repeated injections before this treatment can be recommended.

Temporomandibular Joint Disorders

Chen et al (2015) summarized the evidence assessing the efficacy of botulinum toxin A for treatment of temporomandibular joint disorders in a systematic review that included 5 RCTs.³⁹ Sample size in majority of trials was 30 or less except for 1. Three of the five studies were judged to be at high-risk of bias. All studies administered a single injection of onabotulinumtoxinA or abobotulinumtoxinA and followed patients up at least one month later. Four studies used a placebo (normal saline) control group and the fifth used abobotulinumtoxinA to fascial manipulation. Data were not pooled due to heterogeneity among trials. In a qualitative review of the studies, two of

the five trials found a significant short-term (1-2 months) benefit of onabotulinumtoxinA compared with control on pain reduction.

Post Hemorrhoidectomy Pain

Several small RCTs of botulinum toxin intrasphincter injection for controlling pain after hemorrhoidectomy have been published. A trial by Patti et al (2005) randomized 30 patients to onabotulinumtoxinA 20 U or saline injection and reported a significantly shorter duration of postoperative pain at rest and during defecation in the treated group.⁴⁰ A trial by Patti et al (2006), which also included 30 patients, found significant differences in postoperative maximum resting pressure change from baseline with onabotulinumtoxinA vs topical glyceryl trinitrate ($p < 0.001$).⁴¹ In addition, there was a significant reduction in postoperative pain at rest ($p = 0.01$) but not during defecation. There was no difference in healing.

Pelvic and Genital Pain in Women

One double-blind, randomized, placebo-controlled trial by Abbott et al (2006) evaluated 60 women with chronic pelvic pain and pelvic floor spasm.⁴² Patients received injections of onabotulinumtoxinA 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.

Ano-Rectal Conditions

Internal Anal Sphincter Achalasia

Friedmacher and Puri (2012) reported results of a meta-analysis that included 395 patients from 2 prospective and 14 retrospective case series that compared internal anal sphincter myectomy ($n = 229$) with botulinum A injection ($n = 166$).⁴³ Regular bowel movements (odds ratio [OR]=0.53; 95% CI 0.29 to 0.99, $p = 0.04$), short-improvements (OR=0.56; 95% CI 0.32 to 0.97, $p = 0.04$) and long-term improvement (OR=0.25; 95% CI 0.15 to 0.41, $p < 0.0001$) favored myectomy compared with botulinum toxin A injection. Further, rate of transient fecal incontinence (OR=0.07, 95% CI 0.01 to 0.54; $p < 0.01$), rate of non-response (OR 0.52, [95 % CI 0.27-0.99]; $p = 0.04$) and subsequent surgical treatment (OR 0.18, [95 % CI 0.07-0.44]; $p < 0.0001$) was significantly higher with botulinum A injection compared with myectomy. There was no significant difference in continued use of laxatives or rectal enemas, overall complication rates, constipation and soiling between the two procedures. Authors concluded that myectomy was more effective treatment option compared with intrasphincteric botulinum toxin A injection.

Anismus

Emile et al (2016) reported on the results of a systematic review that assessed 7 studies comprising 189 patients with a follow-up period greater than 6 months in each study.⁴⁴ Of the seven studies, two were RCTs and the others comparative and observational studies. Both RCTs were single-site from the same author group and conducted in Egypt, enrolling 15 and 24 patients, respectively.^{45,46} Improvement was defined as patients returning to their normal habits. The first RCT used biofeedback and the other used surgery as the comparator. In the first RCT, 50% of individuals in the biofeedback group reported improvement initially at 1 month but it dropped down to 25% by the end of year. The respective proportions of patients in the botulinum toxin arm were 70.8% and 33.3%. In the second RCT, surgery improved outcomes in all patients at 1 month but that percentage dropped to 66.6% at 1 year. The respective proportions of patients in the botulinum toxin arm were 87% and 40%, respectively. While these results would suggest temporary

improvement, methodologic limitations, including small sample size and lack of blinded assessment, limit the interpretation of these RCTs.

Others

Gastroparesis

A systematic review by Bai et al (2010) identified 15 studies on onabotulinumtoxinA to treat gastroparesis.⁴⁷ Two studies were RCTs; the remainder was case series or open-label observational studies. Reviewers stated that, while the nonrandomized studies generally found improvements in subjective symptoms and gastric emptying after onabotulinumtoxinA injections, the RCTs^{48,49} did not report treatment benefit with onabotulinumtoxinA for treating gastroparesis. The 2 RCTs were inadequately powered RCTs; one included 23 patients and the other included 32 patients. Additional adequately powered RCTs are needed.

Depression

Magid et al (2015) published a pooled analysis⁵⁰ of individual patient data from 3 randomized trials^{51,52,53}, evaluating injections of onabotulinumtoxinA in the glabellar region (forehead) for treating unipolar major depressive disorder as an adjunctive treatment. The response rate (defined as $\geq 50\%$ improvement from baseline scores in the depression score) was higher in the onabotulinumtoxinA group compared with placebo (54.2% vs 10.7%; OR=11.1; 95% CI 4.3 to 28.8). The respective remission rate (defined as score ≤ 7 for the Hamilton Depression Rating scales, ≤ 10 for the Montgomery-Asberg Depression Rating Scale) was 30.5% vs 6.7% (7.3; 95% CI, 2.4 to 22.5). While the effect size of the treatment observed in the pooled analysis and individual RCTs is clinically meaningful and large, there are multiple limitations that preclude drawing meaningful conclusions about net health benefit. Limitations in study design and conduct include potential of unblinding due to changes in cosmetic appearance, small sample size, lack of power analysis,⁵² short duration of follow-up in two out of three RCTs,^{52,51} lack of clarity on allocation concealment^{51,52,53}, and lack of intention-to-treat analysis. More importantly, patients with a history of major depressive disorder presenting with acute depression episode prior to enrollment in the trial were evaluated, it is unclear if botulinum toxin A treatment is intended to be used as a short-term treatment of a depressive episode or as a maintenance treatment for depression. Further, a large trial (NCT02116361) with 258 patients to evaluate the efficacy of OnabotulinumtoxinA as treatment for major depressive disorder in adult females was completed in 2016 but has not been published which raises concerns about potential for publication bias.

Facial Wound Healing

Ziade et al (2013) reported results of an RCT in which 30 adults presenting to the emergency department with facial wounds without tissue loss were assigned to single an injection of onabotulinumtoxinA (n=11) or no injection (n=13) within 72 hours of the suturing of the wounds.⁵⁴ Scars were assessed at a one-year follow-up visit by patients, an independent evaluator as well as board of six experienced medical specialists. There were no significant differences between the two groups in multiple outcomes that were assessed. Limitations of the study included relatively small sample size, lost to follow-up of 20% patients and lack of patients blinding. Gassner et al (2006) reported the results of another RCT that randomized 31 patients to onabotulinumtoxinA- or placebo-induced immobilization of facial lacerations to improve wound healing.⁵⁵ Blinded assessment of standardized photographs by experienced facial plastic surgeons using a 10-cm visual analog scale at six months served as the main outcome measure. The difference in visual scores was 8.9 in the treatment arm vs 7.2 in the placebo arm (p=0.003). Limitations of the study

included a single-institution study, relatively small sample size, lack of clarity on number screened/randomized/excluded from the final analysis.

Section Summary: miscellaneous conditions

Botulinum toxin has been evaluated as a treatment option for multiple neurological, urological, pain, ano-rectal and miscellaneous clinical indications. Generally botulinum toxin has been evaluated in clinical settings where patients have failed the standard of care or in whom standard of care interventions are contraindicated. However, in multiple indications with high prevalence rates such as benign prostate hyperplasia, low back pain, depression, tinnitus etc. where multiple effective treatments supported by adequate quality evidence base are available, studies using a placebo comparator that lack scientific rigor do not permit conclusions about net health benefit of botulinum toxin. Future studies in these clinical indications should use appropriate comparators in adequately powered prospective studies using standardized dose of treatment and adequate follow-up.

Summary of Evidence

For individuals who have esophageal achalasia who fail initial treatment with medications who receive botulinum toxin injections, the evidence includes two meta-analyses that included RCTs comparing endoscopic PD or laparoscopic myotomy with botulinum toxin. The relevant outcomes are symptoms, functional outcomes, and treatment-related morbidity. The systematic review reported that PD as well as laparoscopic myotomy afforded higher and statistically significant greater symptom remission rates. OnabotulinumtoxinA was not associated with any serious adverse events while PD resulted in perforation in a few cases. While the evidence was suggestive that PD and surgical myotomy are definitive therapies for esophageal achalasia and are associated with superior long-term outcomes compared with botulinum toxin A, in patients who are not good candidates for PD and/or surgical myotomy, botulinum toxin A may be a reasonable option. Further, botulinum toxin injection has the advantage of being less invasive as compared with surgery and can be easily performed during routine endoscopy. Initial success rates with botulinum toxin are comparable to PD and surgical myotomy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with chronic anal fissure who fail medical treatment who receive botulinum toxin injections, the evidence includes two meta-analyses. The relevant outcomes are symptoms, health status measures, and treatment-related morbidity. Results of two meta-analyses suggest that sphincterotomy is a more effective treatment option for chronic anal fissure compared with botulinum toxin A and is associated with a significantly higher healing rate as well as a lower recurrence rate. However, these meta-analyses report higher fecal incontinence rates with surgical procedures. Since botulinum toxin A injections are less invasive and do not require the internal sphincter muscle to be divided and, thereby, reduce the risk of fecal incontinence, they are preferred for patients who are not good surgical candidates or who want to minimize the likelihood of incontinence. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with Hirschsprung disease who develop obstructive symptoms after a pull-through operation who receive botulinum toxin injections, the evidence includes three case series. The relevant outcomes are symptoms, health status measures, and treatment-related morbidity. The 3 case series included a total of 73 patients with median follow-up of more than 7 years. In 2 out of the 3 published case series consistent short-term responses were reported in more than 75% of

patients. Long- term follow-up is suggestive of durability of response. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have other indications such as neurological indications (non-migraine headaches, essential tremor, tinnitus), urological indications (benign prostatic hyperplasia, interstitial cystitis), pain due to multiple etiologies, other ano-rectal conditions (internal anal sphincter achalasia, anismus) and miscellaneous other conditions (gastroparesis, depression and facial wound healing) who receive botulinum toxin injections, evidence includes case series and RCTs. The relevant outcomes are symptoms, functional outcomes, medication use, and treatment-related morbidity. Generally, botulinum toxin has been evaluated in clinical settings where patients have failed the standard of care or in whom standard of care interventions are contraindicated. However, in multiple indications with high prevalence rates such as benign prostate hyperplasia, low back pain, depression, tinnitus, etc. where multiple effective treatments supported by adequate quality evidence base are available, studies using a placebo comparator that lack scientific rigor do not permit conclusions about net health benefit of botulinum toxin. Future studies in these clinical indications should use appropriate comparators in adequately powered prospective studies using standardized dose of treatment and adequate follow-up. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2011 Input

Input was received only on botulinum toxin for migraine from 4 academic medical centers and 4 physician specialty societies (7 reviews) while this policy was under review in 2011. Most reviewers agreed with the investigational indication for episodic migraine. Several reviewers indicated that botulinum toxin was medically necessary in patients with disabling and/or frequent episodic migraines refractory to other treatments. Input was more divergent on the use of botulinum toxin for chronic migraine; some agreed that use was investigational and others did not. Reviewers who considered botulinum toxin medically necessary for patients with chronic migraines generally thought its use should be limited to patients unresponsive to other treatments.

2008 Input

Input was received on a number of indications from 3 academic medical centers and 5 physician specialty societies while this policy was under review in 2008. Nearly all reviewers 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.

Practice Guidelines and Position Statements

American Urological Association

The American Urological Association guideline (2019) on non-neurogenic overactive bladder states, "clinicians may offer intradetrusor onabotulinumtoxinA (100U) as third-line treatment in the carefully-selected and thoroughly-counseled patient who has been refractory to first- and second-line overactive bladder treatments. The patient must be able and willing to return for frequent post-

void residual evaluation and able and willing to perform self-catheterization if necessary. Standard (Evidence Strength Grade B).^{56,}

The American Urological Association

n (2014) guideline on diagnosis and treatment of interstitial cystitis/bladder pain syndrome states, "intradetrusor botulinum toxin A may be administered if other treatments have not provided adequate symptom control and quality of life or if the clinician and patient agree that symptoms require this approach. Patients must be willing to accept the possibility that post-treatment intermittent self- catheterization may be necessary. Option (Evidence Strength C)".^{13,}

American Academy of Neurology

The American Academy of Neurology (2016) updated its practice guidelines on use of botulinum toxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and chronic headache.^{57,} Recommendations are summarized in Table 10.

Table 10. Recommendations for Use of Botulinum Toxin to Treat Various Disorders

Recommendation	LOR
Blepharospasm	
<ul style="list-style-type: none"> OnabotulinumtoxinA and incobotulinumtoxinA injections should be considered AbobotulinumtoxinA may be considered 	B C
Cervical dystonia	
<ul style="list-style-type: none"> AbobotulinumtoxinA and rimabotulinumtoxin B should be offered OnabotulinumtoxinA and incobotulinumtoxinA should be considered 	A B
Focal manifestations of adult spasticity involving the upper limb	
<ul style="list-style-type: none"> AbobotulinumtoxinA, incobotulinumtoxin A, and onabotulinumtoxin A should be offered RimabotulinumtoxinB should be considered as treatment options. OnabotulinumtoxinA should be considered as a treatment option before tizanidine for treating adult upper-extremity spasticity 	A B B
For focal manifestations of adult spasticity involving the lower limb	
<ul style="list-style-type: none"> OnabotulinumtoxinA and abobotulinumtoxin A should be offered as treatment options. There is insufficient evidence to support or refute a benefit of incobotulinumtoxin A or rimabotulinumtoxin B for treatment of adult lower-limb spasticity 	A
Headache	
<ul style="list-style-type: none"> To increase the number of headache-free days, onabotulinumtoxin A should be offered as a treatment option to patients with chronic headaches Onabotulinumtoxin A should be considered to reduce headache impact on health-related quality of life. Chronic migraine refers to migraine attacks occurring 15 days or more monthly for at least 3 months, with attacks lasting 4 hours or more. OnabotulinumtoxinA should not be offered as a treatment for episodic migraines. Episodic migraine refers to migraine with a lesser frequency of attack. 	A B A

LOR: level of recommendation.

In 2011 (reaffirmed in 2014), the American Academy of Neurology updated its evidence-based guidelines that conclude botulinum toxin A is "possibly effective (Level C)" for treatment of essential tremor.^{58,}

American Society of Colon and Rectal Surgeon

The revision of a practice parameter on the treatment of anal fissures by the American Society of Colon and Rectal Surgeons (2017) states, "Botulinum toxin has similar results compared with topical therapies as first-line therapy for chronic anal fissures, and modest improvement in healing rates as second-line therapy following treatment with topical therapies. Grade of Recommendation: Strong recommendation based on low- and very-low-quality evidence."^{59,}

American Pediatric Surgical Association

The American Pediatric Surgical Association (2017) published guidelines based on group discussions, literature review and expert consensus for the management of postoperative obstructive symptoms in children with Hirschsprung disease. These guidelines recommend that if there is no mechanical obstruction and rectal biopsy is normal, botulinum toxin injection into the internal anal sphincter should be tried. If a patient shows significant improvement, the patient can receive botulinum toxin injection every 3–6 months as many times as necessary depending on symptoms. In most cases, the symptoms will gradually improve with age.⁶⁰

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force recommendations for botulinum toxin have been identified.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 11.

Table 11. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02270736	Clinical Study to Investigate the Efficacy and Safety of NT 201 Compared to Placebo in the Treatment of Chronic Troublesome Drooling Associated With Neurological Disorders and/or Intellectual Disability	249	Apr 2019
NCT02414425	Effect and Tolerance of Botulinum A Toxin Rectal Injections on Fecal Incontinence (FI_TOXIN)	200	Jul 2019
Unpublished			
NCT02555982 ^a	Evaluation of Botulinum Toxin Injection Efficacy in the Treatment of Head Essential Tremor	120	Dec 2017 (unknown)

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

CODING

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

CPT/HCPCS

- 31513 Laryngoscopy, indirect; with vocal cord injection
- 31570 Laryngoscopy, direct, with injection into vocal cord(s), therapeutic;
- 31571 Laryngoscopy, direct, with injection into vocal cord(s), therapeutic; with operating microscope or telescope
- 43201 Esophagoscopy, flexible, transoral; with directed submucosal injection(s), any substance
- 43236 Esophagogastroduodenoscopy, flexible, transoral; with directed submucosal injection(s), any substance
- 46505 Chemodenervation of internal anal sphincter

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- 52287 Cystourethroscopy, with injection (s) for chemodenervation of the bladder
- 64611 Chemodenervation of parotid and submandibular salivary glands, bilateral
- 64612 Chemodenervation of muscle(s); muscle(s) innervated by facial nerve, unilateral (eg, for blepharospasm, hemifacial spasm)
- 64615 Chemodenervation of muscles(s); muscles(s) innervated by facial, trigeminal, cervical spinal and accessory nerves, bilateral (eg, for chronic migraine)
- 64616 Chemodenervation of muscle(s); neck muscle(s), excluding muscles of the larynx, unilateral (eg, for cervical dystonia, spasmodic torticollis)
- 64617 Chemodenervation of muscle(s); larynx, unilateral, percutaneous (eg, for spasmodic dysphonia), includes guidance by needle electromyography, when performed
- 64642 Chemodenervation of one extremity; 1-4 muscle(s)
- 64643 Chemodenervation of one extremity; each additional extremity, 1-4 muscle(s) (List separately in addition to code for primary procedure)
- 64644 Chemodenervation of one extremity; 5 or more muscle(s)
- 64645 Chemodenervation of one extremity; each additional extremity, 5 or more muscle(s) (List separately in addition to code for primary procedure)
- 64646 Chemodenervation of trunk muscle(s); 1-5 muscle(s)
- 64647 Chemodenervation of trunk muscle(s); 6 or more muscle(s)
- 67345 Chemodenervation of extraocular muscle
- J0585 Injection, onabotulinumtoxinA, 1 unit
- J0586 Injection, abobotulinumtoxinA, 5 units
- J0587 Injection, rimabotulinumtoxinB, 100 units
- J0588 Injection, incobotulinum A, 1 unit

ICD-10 Diagnoses

- G11.4 Hereditary spastic paraplegia
- G24.09 Other drug induced dystonia
- G24.1 Genetic torsion dystonia
- G24.2 Idiopathic nonfamilial dystonia
- G24.3 Spasmodic torticollis
- G24.4 Idiopathic orofacial dystonia
- G24.5 Blepharospasm
- G35 Multiple sclerosis
- G43.019 Migraine without aura, intractable, without status migrainosus
- G43.111 Migraine with aura, intractable, with status migrainosus
- G43.119 Migraine with aura, intractable, without status migrainosus
- G43.511 Persistent migraine aura without cerebral infarction, intractable, with status migrainosus
- G43.519 Persistent migraine aura without cerebral infarction, intractable, without status migrainosus
- G43.711 Chronic migraine without aura, intractable, with status migrainosus
- G43.719 Chronic migraine without aura, intractable, without status migrainosus
- G43.811 Other migraine, intractable, with status migrainosus
- G43.919 Migraine, unspecified, intractable, without status migrainosus
- G43.B1 Ophthalmoplegic migraine, intractable
- G43.C1 Periodic headache syndromes in child or adult, intractable
- G51.0 Bell's palsy
- G51.31 Clonic hemifacial spasm, right

G51.32	Clonic hemifacial spasm, left
G51.33	Clonic hemifacial spasm, bilateral
G51.4	Facial myokymia
G51.8	Other disorders of facial nerve
G51.9	Disorder of facial nerve, unspecified
G80.0	Spastic quadriplegic cerebral palsy
G80.1	Spastic diplegic cerebral palsy
G80.2	Spastic hemiplegic cerebral palsy
G81.11	Spastic hemiplegia affecting right dominant side
G81.12	Spastic hemiplegia affecting left dominant side
G81.13	Spastic hemiplegia affecting right nondominant side
G81.14	Spastic hemiplegia affecting left nondominant side
H49.01	Third [oculomotor] nerve palsy, right eye
H49.02	Third [oculomotor] nerve palsy, left eye
H49.03	Third [oculomotor] nerve palsy, bilateral
H49.11	Fourth [trochlear] nerve palsy, right eye
H49.12	Fourth [trochlear] nerve palsy, left eye
H49.13	Fourth [trochlear] nerve palsy, bilateral
H49.21	Sixth [abducent] nerve palsy, right eye
H49.22	Sixth [abducent] nerve palsy, left eye
H49.23	Sixth [abducent] nerve palsy, bilateral
H49.31	Total (external) ophthalmoplegia, right eye
H49.32	Total (external) ophthalmoplegia, left eye
H49.33	Total (external) ophthalmoplegia, bilateral
H49.41	Progressive external ophthalmoplegia, right eye
H49.42	Progressive external ophthalmoplegia, left eye
H49.43	Progressive external ophthalmoplegia, bilateral
H49.881	Other paralytic strabismus, right eye
H49.882	Other paralytic strabismus, left eye
H49.883	Other paralytic strabismus, bilateral
H50.011	Monocular esotropia, right eye
H50.012	Monocular esotropia, left eye
H50.021	Monocular esotropia with A pattern, right eye
H50.022	Monocular esotropia with A pattern, left eye
H50.031	Monocular esotropia with V pattern, right eye
H50.032	Monocular esotropia with V pattern, left eye
H50.041	Monocular esotropia with other noncomitancies, right eye
H50.042	Monocular esotropia with other noncomitancies, left eye
H50.05	Alternating esotropia
H50.06	Alternating esotropia with A pattern
H50.07	Alternating esotropia with V pattern
H50.08	Alternating esotropia with other noncomitancies
H50.111	Monocular exotropia, right eye
H50.112	Monocular exotropia, left eye
H50.121	Monocular exotropia with A pattern, right eye
H50.122	Monocular exotropia with A pattern, left eye
H50.131	Monocular exotropia with V pattern, right eye
H50.132	Monocular exotropia with V pattern, left eye

H50.141	Monocular exotropia with other noncomitancies, right eye
H50.142	Monocular exotropia with other noncomitancies, left eye
H50.15	Alternating exotropia
H50.16	Alternating exotropia with A pattern
H50.17	Alternating exotropia with V pattern
H50.18	Alternating exotropia with other noncomitancies
H50.21	Vertical strabismus, right eye
H50.22	Vertical strabismus, left eye
H50.311	Intermittent monocular esotropia, right eye
H50.312	Intermittent monocular esotropia, left eye
H50.32	Intermittent alternating esotropia
H50.331	Intermittent monocular exotropia, right eye
H50.332	Intermittent monocular exotropia, left eye
H50.34	Intermittent alternating exotropia
H50.40	Unspecified heterotropia
H50.411	Cyclotropia, right eye
H50.412	Cyclotropia, left eye
H50.42	Monofixation syndrome
H50.43	Accommodative component in esotropia
H50.51	Esophoria
H50.52	Exophoria
H50.53	Vertical heterophoria
H50.54	Cyclophoria
H50.55	Alternating heterophoria
H50.611	Brown's sheath syndrome, right eye
H50.612	Brown's sheath syndrome, left eye
H50.69	Other mechanical strabismus
H50.811	Duane's syndrome, right eye
H50.812	Duane's syndrome, left eye
H50.89	Other specified strabismus
H50.9	Unspecified strabismus
H51.0	Palsy (spasm) of conjugate gaze
H51.11	Convergence insufficiency
H51.12	Convergence excess
H51.21	Internuclear ophthalmoplegia, right eye
H51.22	Internuclear ophthalmoplegia, left eye
H51.23	Internuclear ophthalmoplegia, bilateral
H51.8	Other specified disorders of binocular movement
H51.9	Unspecified disorder of binocular movement
J38.5	Laryngeal spasm
J38.7	Other diseases of larynx
K22.0	Achalasia of cardia
K60.0	Acute anal fissure
K60.1	Chronic anal fissure
K60.2	Anal fissure, unspecified
L74.510	Primary focal hyperhidrosis, axilla
L74.511	Primary focal hyperhidrosis, face
L74.512	Primary focal hyperhidrosis, palms

L74.513	Primary focal hyperhidrosis, soles
M43.6	Torticollis
N39.41	Urge incontinence
N39.42	Incontinence without sensory awareness
N39.44	Nocturnal enuresis
N39.46	Mixed incontinence
N39.491	Coital incontinence
N39.492	Postural (urinary) incontinence
N39.498	Other specified urinary incontinence
Q66.01	Congenital talipes equinovarus, right foot
Q66.02	Congenital talipes equinovarus, left foot
R32	Unspecified urinary incontinence
R49.8	Other voice and resonance disorders

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 Hyperhidrosis 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.
01-01-2010	In Coding Section: <ul style="list-style-type: none"> ▪ Added HCPCS Code: J0586 ▪ Updated wording for HCPCS Code: J0585
02-25-2011	Medical Policy Title updated. <ul style="list-style-type: none"> ▪ Removed "(i.e. Botox®, Myobloc ®)" to read "Botulinum Toxin (BT)." In Policy Language section: <ul style="list-style-type: none"> ▪ Updated formatting and wording. ▪ Added medically necessary indication #11: "Chronic refractory migraine." ▪ In the investigational indications section, Item #1, removed "including migraine,

REVISIONS	
	<p>chronic daily headache, and tension type headache" and added "other than chronic refractory headache" to read "headaches, other than chronic refractory headaches."</p> <p>In the Documentation section:</p> <ul style="list-style-type: none"> ▪ Removed "There must be a stated goal of treatment." <p>Rationale section updated.</p> <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Added CPT code: 64611 (2011 Coding updates) ▪ Added Diagnosis codes: 346.01, 376.03, 346.11, 346.13, .346.21, 346.23, 346.51, 346.53, 346.71, 346.73, 346.91, 346.93. <p>Reference section updated.</p>
05-13-2011	In Coding section, added HCPCS code Q2040.
12-09-2011	<p>Updated Description section.</p> <p>In the Policy section:</p> <ul style="list-style-type: none"> • In Item A, #11, inserted "headaches" to read "Chronic refractory migraine headaches" • In Item B, #9, inserted "(see separate policy on Treatment of Tinnitus)" • In Item B, added the following indications: <ul style="list-style-type: none"> ○ "#21. Prevention of pain associated with breast reconstruction after mastectomy ○ #22. Hirschsprung's disease" <p>Removed the Documentation section.</p> <p>Removed the Utilization section.</p> <p>Added Policy Guidelines section.</p> <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Added the following CPT/HCPCS codes: 46505, C9278 ▪ Added the following Diagnosis codes: 333.71, 333.79, 333.81, 333.82, 333.83, 333.84, 340, 351.0, 351.1, 351.9, 435.9, 705.21, 754.51, 784.49 <p>Updated the Rationale section.</p> <p>Updated the Reference section.</p>
01-01-2012	<p>In the Policy section:</p> <ul style="list-style-type: none"> ▪ In Item A, #6, removed "in patients who have not responded to dilation therapy or who are considered poor surgical candidates" to read " Esophageal achalasia" <p>In the Coding section:</p> <ul style="list-style-type: none"> ▪ Removed HCPCS codes: C9278, Q2040 ▪ Added HCPCS code: J0588 ▪ Added Diagnosis codes: 333.71, 333.79, 333.81, 333.82, 333.83, 333.84 (Diagnosis code, 333.7 was replaced with the appropriate codes for the policy.)
01-15-2013	<p>In the Coding section:</p> <ul style="list-style-type: none"> ▪ Added CPT code: 52287 and 64615 (Effective 01-01-2013) ▪ Updated CPT code 64612 nomenclature (Effective 01-01-2013)
01-30-2014	<p>Updated Description section.</p> <p>In Policy section:</p> <ul style="list-style-type: none"> ▪ In Item A, #9, replaced "(urge incontinence), either idiopathic or due to" with "associated with" to read "Incontinence due to detrusor overreactivity associated with neurogenic causes..." ▪ In Item A, added #12, "overactive bladder in adults that is inadequately controlled with anticholinergics." ▪ In Item B, added #23, "Facial wound healing." ▪ In Item B, added #24, "Internal anal sphincter (IAS) achalasia". ▪ Moved the "Policy Guidelines" to the "Coding" section. <p>Updated Rationale section.</p> <p>In Coding section:</p>

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	<ul style="list-style-type: none"> ▪ Removed CPT codes: 64613 and 64614 (<i>Deleted codes, effective December 31, 2013</i>) ▪ Added CPT codes: 64616, 64617, 64642, 64643, 64644, 64645, 64646, 64647 (<i>New codes, effective January 1, 2014</i>) ▪ Added ICD-10 Diagnosis codes (<i>Effective October 1, 2014</i>)
	Updated Reference section.
04-15-2014	<p>In Policy section:</p> <ul style="list-style-type: none"> ▪ In Item B 1 removed the parenthesis around "(migraine)" to read, "headaches other than chronic refractory migraine headaches" <p>In Policy Guidelines:</p> <ul style="list-style-type: none"> ▪ Added information pertaining to cervical dystonia and chronic migraine.
	<p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Updated coding instructions.
01-01-2015	<p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Revised CPT Codes: 43201, 43236 (Effective January 1, 2015)
02-19-2016	<p>Updated Description section.</p> <p>In Policy section:</p> <ul style="list-style-type: none"> ▪ In Item A 6, added "in patients who have not responded to dilation therapy or who are considered poor surgical candidates" to read, "Esophageal achalasia in patients who have not responded to dilation therapy or who are considered poor surgical candidates" ▪ In Item A 9, added "Urinary" to read, "Urinary incontinence due to detrusor overreactivity associated with neurogenic causes (e.g., spinal cord injury, multiple sclerosis), that is inadequately controlled with anticholinergics*." ▪ Deleted previous Item A 10. ▪ In current Item A 10, added "Prevention (treatment of) and "in the following situations:" and removed "refractory" to read, "Prevention (treatment) of chronic migraine headaches in the following situations:" and added bulleted criteria "Meeting Internal Classification of Headache Disorders (ICHD-2) diagnostic criteria for chronic migraine headache (key criteria include migraine headaches lasting at least 4 hours on at least 15 days per month; migraine headaches for at least 3 months; absence of medication overuse); and Have symptoms that persist despite adequate trials of at least 2 agents from different classes of medications used in the treatment of chronic migraine headaches (e.g., antidepressants, antihypertensives, antiepileptics). Patients who have contraindications to present medications are not required to undergo a trial of these agents." ▪ In current Item A 11, added "unresponsive to or intolerant of" and removed "that is inadequately controlled with" to read, "Overactive bladder in adults unresponsive to or intolerant of anticholinergics*" ▪ In Item B 1, added "except as noted above for prevention (treatment) of" and removed "other than" and "refractory" to read, "Headaches, except as noted above for prevention (treatment) of chronic migraine headaches" ▪ In Item B 6, added "/ fibromyalgia / fibromyositis" to read, "Myofascial pain syndrome / fibromyalgia / fibromyositis." ▪ In Item B 11, added "ICD-10 F95.1" and "ICD-10 F95.2", and removed "ICD-9 307.22" and "ICD-9-307.23" to read, "Chronic motor tic disorder (ICD-10 F95.1), and tics associated with Tourette syndrome (motor tics) (ICD-10 F95.2)." ▪ Removed previous Items B 17, 19, and 20. ▪ Added current Items B 21-23.
	Updated Rationale section.
	In Coding section:

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	<ul style="list-style-type: none"> ▪ Removed CPT codes: 64650 and 64653.
	Updated References section.
07-01-2016	Updated Description section.
	In Policy section:
	<ul style="list-style-type: none"> ▪ In Item A 10 a, removed "(key criteria include migraine headaches lasting at least 4 hours on at least 15 days per month; migraine headaches for at least 3 months; absence of medication overuse)" and added "(see Policy Guidelines)" to read "Meet International Classification of Headache Disorders (ICHD) diagnostic criteria for chronic migraine headache; and" ▪ In Policy Guidelines, added Item 2.
	Updated Rationale section.
10-01-2016	In Coding section:
	<ul style="list-style-type: none"> ▪ Added ICD-10 codes effective 10-01-2016: N39.491, N39.492
03-29-2017	In Policy section:
	<ul style="list-style-type: none"> ▪ In Item C, removed "may be considered not medically necessary" and added "is noncovered" to read, "The use of botulinum toxin as a treatment of wrinkles or other cosmetic indications is noncovered."
02-15-2018	Updated Description section.
	In Policy section:
	<ul style="list-style-type: none"> ▪ In Policy Guidelines, added "Indications and Dosage" table.
	Updated Rationale section.
	In Coding section:
	<ul style="list-style-type: none"> ▪ Updated Coding bullets. ▪ ICD-9 codes removed.
	Updated References section.
10-01-2018	In Coding section:
	<ul style="list-style-type: none"> ▪ Added ICD-10 codes: G51.31, G51.32, G51.33. ▪ Removed ICD-10 code: G51.3.
	Updated References section.
11-20-2018	Updated Description section.
	In Policy section:
	<ul style="list-style-type: none"> ▪ In Item A 9, added "in patients unresponsive to or intolerant of" and removed "that is inadequately controlled with" to read, "Urinary incontinence due to detrusor overreactivity associated with neurogenic causes (eg, spinal cord injury, multiple sclerosis) in patients unresponsive to or intolerant of anticholinergics." ▪ In Item B 11, removed "(ICD-10 F95.1)" and "(ICD-10 F95.2)" to read, "Chronic motor tic disorder, and tics associated with Tourette's syndrome (motor tics)."
	Updated Rationale section.
	In Coding section:
	<ul style="list-style-type: none"> ▪ Removed coding bullets.
	Updated References section.
10-11-2019	Policy published 09-11-2019. Policy effective 10-11-2019.
	In Title heading:
	<ul style="list-style-type: none"> ▪ Removed "Treatment of Tinnitus" from the <i>See Also</i> policies.
	In Policy section:
	<ul style="list-style-type: none"> ▪ In Policy Guidelines, added new Item 4, "The safety and efficacy of combination therapy with botulinum toxin and calcitonin gene related peptide (CGRP) has not been studied in the treatment of migraine headache."
	In Coding section:
	<ul style="list-style-type: none"> ▪ Removed ICD10 Code: Q66.0 (Effective 10-01-2019) ▪ Added ICD10 Codes: Q66.01, Q66.02 (Effective 10-01-2019)

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10-18-2020	Policy published 07-xx-2020. Policy effective 08-xx-2020.
	Description section updated
	In Policy section: <ul style="list-style-type: none"> ▪ In Item A added "treatment of" to read "Botulinum toxin may be considered medically necessary for treatment of the following" ▪ In Items 2 and 3 "Focal dystonias" and "Spastic conditions" were separated to read, "2. Dystonia resulting in functional impairment (interference with joint function, mobility, communication, nutritional intake) and/or pain in patients with any of the following: <ol style="list-style-type: none"> a. Focal upper limb dystonia (eg, 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 3. Upper and lower limb spasticity as well spastic conditions related to: <ol style="list-style-type: none"> a. Cerebral palsy b. Stroke c. Acquired spinal cord or brain injury d. Hereditary spastic paraparesis e. Spastic hemiplegia f. Neuromyelitis optica g. Multiple sclerosis or Schilder's disease" ▪ In Item 4 "with symptoms of urge urinary incontinence, urgency, and frequency" and "medication" were added to read "Overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication" ▪ In Items 4 and 5 remove "unresponsive" and added "who have an inadequate response to" to read "...in adults who have an inadequate response to or are intolerant of an anticholinergic medication" ▪ In Item 6 removed "Prevention (treatment)" and added 'Prophylaxis" to read "Prophylaxis of chronic migraine headache..." ▪ In Item 7 added "associated with dystonia" to read "Blepharospasm associated with dystonia..." ▪ In Item 9 revised Sialorrhea (drooling) associated with Parkinson's disease" to be expanded to read "Chronic sialorrhea (drooling) associated with amyotrophic lateral sclerosis or atypical parkinsonian disorders or cerebral palsy or Parkinson's disease or stroke or traumatic brain injury AND has experienced excessive salivation for 3 or more months AND refractory to at least 2 months of continuous treatment with at least one oral pharmacotherapy (e.g., anticholinergics)." ▪ In Item 11 revised Chronic anal fissure to be restricted to "Chronic anal fissure in patients with a history of failure, contraindication, or intolerance to one of the following conventional therapies: <ol style="list-style-type: none"> a. Topical nitrates b. Topical calcium channel blockers (e.g., diltiazem, nifedipine)." ▪ In Item 12 move from E/I to medically necessary "Treatment of patients with Hirschsprung disease who develop obstructive symptoms after a pull-through operation." ▪ In Item B, the E/I section, added the following headers to their respective indications: <ol style="list-style-type: none"> "1. Neurological indications such as: 2. Urological indications such as: 3. Pain due to multiple etiologies such as:

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	4. Ano-rectal conditions such as: 5. Other miscellaneous conditions such as:" <ul style="list-style-type: none"> ▪ In Item B 1 b removed "such as benign essential tremor (upper extremity)" to read Essential tremor" ▪ In Item B 3 e removed "fibromyalgia / fibromyositis" to read "Myofascial pain syndrome" ▪ In Item B removed "Sialorrhea (drooling) except that associated with Parkinson's disease". ▪ Policy Guidelines updated
	Rationale section updated
	References updated

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