

Medical Policy



Title: Botulinum Toxin (BT)

Related Policies:	▪ <i>Treatment of Hyperhidrosis</i>
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Professional	Institutional
Original Effective Date: February 1996	Original Effective Date: June 3, 2004
Revision Date(s): May, 12, 1998; June 1, 1999; January 1, 2001; February 1, 2001; July 20, 2004; December 29, 2004; October 5, 2005; November 3, 2005; December 15, 2005; March 10, 2006; May 31, 2006; July 18, 2006; October 1, 2006; October 19, 2007; July 18, 2008 January 1, 2010; February 25, 2011; May 13, 2011; December 9, 2011; January 1, 2012; January 15, 2013; January 30, 2014; April 15, 2014; January 1, 2015; February 19, 2016; July 1, 2016; October 1, 2016; March 29, 2017; February 15, 2018; October 1, 2018; November 20, 2018; October 11, 2019; October 18, 2020; December 13, 2022	Revision Date(s): July 20, 2004; December 29, 2004; October 5, 2005; November 3, 2005; December 15, 2005; March 10, 2006; May 31, 2006; July 18, 2006; October 1, 2006; October 19, 2007; July 18, 2008 January 1, 2010; February 25, 2011; May 13, 2011; December 9, 2011; January 1, 2012; January 15, 2013; January 30, 2014; April 15, 2014; January 1, 2015; February 19, 2016; July 1, 2016; October 1, 2016; March 29, 2017; February 15, 2018; October 1, 2018; November 20, 2018; October 11, 2019; October 18, 2020; December 13, 2022
Current Effective Date: December 13,2022	Current Effective Date: December 13,2022

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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 Hirschsprung 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 (e.g., 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 is a family of toxins produced by the anaerobic organism *Clostridia botulinum*. Multiple formulations of botulinum toxin have been approved by the U.S. Food and Drug Administration (FDA). Labeled indications of these agents differ. Botulinum toxin products are also used for a range of off-label indications. The scope of the evidence review is limited to off-label use of 4 botulinum toxin agents currently available and approved by the FDA for medical use. These include— onabotulinumtoxinA (Botox), abobotulinumtoxinA (Dysport), incobotulinumtoxinA (Xeomin), and rimabotulinumtoxinB (Myobloc)

OBJECTIVE

The objective of this evidence review 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 U.S. 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, 1989, 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 Indications of Botulinum Toxin Products^a

	FDA Approved Indication^a	Botox	Dysport	Myobloc	Xeomin
1	Overactive bladder	Approved for adults			
2	Urinary incontinence	Approved for adults and pediatric patients ≥ 5 years			
3	Limb spasticity	Approved for ≥ 2 years of age (upper limb and lower limb)	Approved for ≥ 2 years of age (upper limb and lower limb)		Approved for adults (upper limb) Approved for 2 to 17 years of age (upper limb) excluding spasticity caused by cerebral palsy
4	Chronic migraine	Approved for adults			
5	Cervical dystonia	Approved for adults	Approved for adults	Approved for adults	Approved for adults
6	Severe axillary hyperhidrosis	Approved for adults			
7	Blepharospasm	Approved for ≥ 12 years of age			Approved for adults
8	Strabismus	Approved for ≥ 12 years of age			
9	Chronic sialorrhea			Approved for adults	Approved for ≥ 2 years of age

FDA: U.S. Food and Drug Administration.

^a All botulinum toxin products carry black box warnings of the potential for a distant spread of the toxin effect. The warning notes that the risk of symptoms is probably greatest in children treated for spasticity, but symptoms can also occur in adults, particularly in those patients who have an underlying condition that would predispose them to these symptoms.

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, e.g., 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 (e.g., organic writer's cramp)
 - b. Oromandibular dystonia (orofacial dyskinesia, Meige syndrome)
 - c. Laryngeal dystonia (adductor spasmodic dysphonia)
 - d. Idiopathic (primary or genetic) torsion dystonia
 - e. Symptomatic (acquired) torsion dystonia
 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
 4. Multiple sclerosis or Schilder's disease
 5. 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
 6. Urinary incontinence due to detrusor over reactivity associated with a neurogenic condition (e.g., spinal cord injury, multiple sclerosis) in adults who have an inadequate response to or are intolerant of an anticholinergic medication

7. Prophylaxis of chronic migraine headache in the following situations:
 - a. Initial 6-month trial. Adults who:
 - i. Meet International Classification of Headache Disorders (ICHD) diagnostic criteria for chronic migraine headache (see Policy Guidelines); **AND**
 - ii. Have symptoms that persist despite adequate trials of at least 2 agents from different classes of medications used in the treatment of chronic migraine headaches (e.g., antidepressants, antihypertensives, antiepileptics). Patients who have contraindications to preventive medications are not required to undergo a trial of these agents.
 - b. Continuing treatment beyond 6 months:
 - i. Migraine headache frequency reduced by at least 7 days per month compared with pretreatment level, **OR**
 - ii. Migraine headache duration reduced at least 100 hours per month compared with pretreatment level.
 8. Blepharospasm associated with dystonia or facial nerve (VII) disorders (including hemifacial spasm).
 9. Strabismus
 10. 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).
 11. Esophageal achalasia in patients who have not responded to dilation therapy or who are considered poor surgical candidates.
 12. 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).
 13. 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

- A. 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.

- B. International Classification of Headache Disorders (ICHD-3) diagnostic criteria for chronic migraine headache include the following:
1. Headaches at least 15 days per month for more than 3 months; have features of migraine headache on at least 8 days.
 2. Features of migraine headache:
 - a. Lasts 4 to 72 hours
 - b. Has at least 2 of the following 4 characteristics:
 - i. Unilateral
 - ii. Pulsating
 - iii. Moderate or severe pain intensity
 - iv. Aggravates or causes avoidance of routine physical activity
 - c. Associated with:
 - i. Nausea and/or vomiting
 - ii. 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.

- C. 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 (i.e., 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.

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.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through August 17, 2022. In this section, evidence was only reviewed for clinical indications for which none of the 4 commercially available botulinum toxin products are approved 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 a technology, 2 domains are examined: the relevance, and quality and credibility. To be

relevant, studies must represent 1 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. Randomized controlled trials 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 (LES), accompanied by a loss of peristalsis in the distal esophagus. Treatment is aimed at decreasing the resting pressure in the LES to a level at which the sphincter no longer impedes the passage of ingested material. This can be achieved by 2 ways: 1) mechanical disruption of the muscle fibers of the LES through pneumatic dilation (PD), surgical myotomy, or peroral endoscopic myotomy (POEM) and 2) pharmacological reduction in LES pressure (e.g., 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 was used to select literature to inform this review.

Populations

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

Interventions

The therapy being considered is commercially available botulinum toxin products. These are injected directly using endoscopic ultrasound techniques to facilitate localization in the LES region.

Comparators

The following therapies are currently being used to treat esophageal achalasia: medications (i.e., zolpidem), PD, surgical myotomy, or POEM.

Outcomes

The general outcomes of interest are symptoms, functional outcomes, and treatment-related morbidity. Follow-up ranges from 6 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.

REVIEW OF EVIDENCE

Systematic Reviews

A Cochrane review by Leyden et al (2014) identified 7 RCTs (N=178 participants) that compared onabotulinumtoxinA with endoscopic PD.¹ The outcome 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 1 month between PD versus 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, $p < .005$; RR=1.88, $p = < .005$, respectively). No serious adverse events were reported after onabotulinumtoxinA injection; however, there were 3 cases of perforation after PD. The 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 1 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. The authors reported that symptom remission rate was significantly higher in patients treated with PD versus botulinum toxin A injection (65.8% vs. 36%). The proportion of patients who relapsed within a year was 16.7% with PD versus 50% with botulinum toxin injection. Moreover, the relapse time for botulinum toxin injection was shorter than that of PD after first therapy. Two RCTs compared the efficacy of laparoscopic myotomy with botulinum toxin A injection in patients with untreated achalasia. The 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 to 1.59; $p = .03$). Patients treated with onabotulinumtoxinA had more frequent relapse and a shorter time to relapse than those treated with laparoscopic myotomy. Some limitations of this meta-analysis include a 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, it 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, PD, laparoscopic myotomy, surgical intervention, or nifedipine	761 (NR)	RCT	17 trials followed up patients ranging from 8 to 68 months

NR: not reported; PD: pneumatic dilation; 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 PD 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=NR	RR=1.57 (1.19 to 2.08); p=.0015	RR=1.88 (1.35 to 2.61); p=.0002
I ² (p)	0.0%	79%	42%

Study (Year)	Symptom Remission at 1 Month	Symptom Remission at 6 Months	Symptom Remission at 12 Months
Wang et al (2009) ² ,	Remission Rate Over 12 Months	Relapse Rate Over 12 months	-
Endoscopic PD 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<.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)	NR	-
Pooled effect (95% CI); p-value	83.3% vs. 64.9%, RR=1.28 (95% CI 1.02 to 1.59; p=.03).	NR	-

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

Section Summary: Esophageal Achalasia

For the treatment of esophageal achalasia, 2 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 a 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 and 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 (a combination of supportive measures such as a high fiber diet, sitz bath, topical analgesic, and 1 of the topical vasodilators such as nifedipine or nitroglycerin for 1 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 (e.g., 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 was used to select literature to inform this review.

Populations

The relevant population of interest is 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. These products are injected intrasphincteric.

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 6 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.

REVIEW OF EVIDENCE**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 a 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 ($p=.35$). The meta-analysis suggests that internal sphincterotomy is more effective to treat anal fissure, but onabotulinumtoxinA injection was associated with lower rates

of incontinence. The authors reported multiple limitations in the evidence pooled for the meta-analysis including a varying dose of onabotulinumtoxinA used in different trials, inconsistent definition of chronic anal fissure used in the RCTs, and lack of blinding. 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 the 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 (e.g., 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<.001	OR=0.55 (0.15 to 1.94); p=.35	OR=0.12 (0.05 to 0.26); p<.001	OR=5.97 (3.51 to 10.17); p<.001
I ² (p)	0% (.5)	75% (.001)	0% (.53)	4% (.39)
Nelson et al (2012) ⁵ : Botulinum A toxin injection vs. sphincterotomy				
Total N	365 (5 RCTs)	NR	321 (4 RCTs)	NR
Pooled effect (95% CI); p-value	7.20 ^a (3.97 to 13.07); p<.001	NR	0.11 (0.02 to 0.46); p<.001	NR
I ² (p)	47%	NR	0	NR

^a Comparison indicates that sphincterotomy was 7.2 times more likely to heal than botulinum toxin injection. CI: confidence interval; NR: not reported; OR: odds ratio; RCT: randomized controlled trial.

Section Summary: Anal Fissure

Two meta-analyses suggest that sphincterotomy is a more effective treatment option for chronic anal fissure compared with botulinum toxin A and results in a significantly higher healing rate as well as lower recurrence rate. However, these meta-analyses report a 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 thereby reducing the risk of fecal incontinence, these injections 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 a 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 was used to select literature to inform this review.

Populations

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

Interventions

The therapy being considered is commercially available botulinum toxin products. These are injected intrasphincteric.

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 6 months to 5 years 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.

Review of Evidence

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 cohort study by Svetanoff et al (2021) included 40 patients admitted for Hirschsprung-associated enterocolitis (HAEC) from January 2010 to December 2019.⁹ The aim of the study was to determine if botulinum toxin injection during HAEC episodes decreased the number of recurrent HAEC episodes and/or increased the interval between readmissions. In the 40 patients analyzed, a total of 120 episodes of HAEC occurred. Patients who received botulinum toxin during their inpatient HAEC episode had a longer median time between readmissions ($p=.04$) and trended toward an association with fewer readmissions prior to a follow-up clinic visit ($p=.08$). This study provides additional evidence that the use of botulinum injections for Hirschsprung disease among patients hospitalized for HAEC is associated with an increased time between recurrent HAEC episodes and trend toward decreasing recurrent enterocolitis incidence.

A retrospective cohort study of 41 patients consecutively treated for Hirschsprung disease in 2 academic hospitals in Amsterdam with a follow-up duration of ≥ 1 year after corrective surgery were analyzed.¹⁰ All patients had obstructive defecation problems non-responsive to high-dose laxatives or rectal irrigation, 2 patients also had an episode of HAEC. Twenty-five (61%) of 41 patients had clinical improvement after a first injection. In 29 (71%) of the 41 patients, spontaneous defecation or treatment with laxatives only was achieved.

A retrospective case series by Han-Geurts et al (2014), included 33 children with surgically treated Hirschsprung disease administered intrasphincteric botulinum toxin A injections for obstructive symptoms between 2002 and 2013 in the Netherlands.¹¹ 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 2 (range 1 to 5) injections were given. Initial short-term improvement was achieved in 76% of patients, with a median duration of 4.1 months (range 1.7 to 58.8). The 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 4 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 4 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 1 to 5 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 to 23) onabotulinumtoxinA injections for postsurgical obstructive symptoms.⁸The median follow-up (time from first injection to time of chart review) was 5 years (range, 0 to 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 pre-injection (median, 1.5; $p=.003$). 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	Treatment	Follow-Up
Minke et al (2000) ⁷	Prospective	U.S./University of Washington	NR	Children with Hirschsprung's disease who have persistent obstructive symptoms after operation	Onabotulinum toxinA (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	Onabotulinum toxinA (Botox) N=22	10 years
Han-Geurts et al (2014) ¹¹	Retrospective	Netherlands/University Medical Centers of Maastricht and Nijmegen	2002-2013	Children with Hirschsprung's disease who have	Onabotulinum toxinA (Botox) N=33	7.3 years

Author (Year)	Study Type	Country/Institution	Dates	Participants	Treatment	Follow-Up
				persistent obstructive symptoms after operation		
Roorda et al (2021) ^{10,}	Retrospective	Netherlands/Academic Medical Centre and VU Medical Centre	2003-2017	Children with Hirschsprung's disease who have persistent obstructive symptoms after operation	Onabotulinum toxinA (Botox) or abobotulinum toxinA (Dysport) N=41 Note: Botox and Dysport represented 69% and 31% of all injections, respectively	8 years
Svetanoff et al (2021) ^{9,}	Retrospective	U.S./Children's Mercy Hospital	2010-2019	Children with Hirschsprung's disease who required an inpatient Hirschsprung-associated enterocolitis admission	Onabotulinum toxinA (Botox) N=21	NR

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,}	

Study (Year)	Outcomes (Efficacy)
Total N	22
OnabotulinumtoxinA	Median number of hospitalizations for obstructive symptoms: Prior to treatment: 1.5 (IQR: 1 to 3) Post treatment: 0 Clinical Response After 1st dose: 80%
p-value	p<.05
Han-Geurts et al (2014) ¹¹ ,	
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
Roorda et al (2021) ¹⁰ ,	
Total N	N=41 (botulinum toxin) N=90 (no botulinum toxin)
OnabotulinumtoxinA or abobotulinumtoxinA	Clinical improvement after 1st dose: 61% (25/41), p<.001 (significant within-group difference pre-post intervention) Mean duration of improvement after 1st dose: 3.7 months (SD = 3.0) Spontaneous defecation or defecation with laxatives after botulinum toxin injections: 71% (29/41)
Svetanoff et al (2021) ⁹ ,	
Total N	N=21 (botulinum toxin) N=19 (no botulinum toxin)
OnabotulinumtoxinA	Time between HAEC episodes for botulinum toxin vs. non-botulinum toxin injection group 146 days (IQR 100, 326) vs. 68 days (IQR 16, 173), p=.03 Less recurrence of HAEC episodes for botulinum toxin vs. non-botulinum toxin injection group 45% vs. 76%, p=.02 Injection of botulinum toxin was associated with a longer time between recurrent HAEC episodes (p=.04) No difference in the number of recurrent HAEC episodes based on the use of botulinum toxin injections was seen (p=.08)

CI: confidence interval; HAEC: Hirschsprung-associated enterocolitis; IQR: interquartile range; NR: not reported; SD: standard deviation.

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

botulinum toxin to treat Hirschsprung disease consists of case series with a total of 135 patients and a median follow-up of more than 7 years in 3 out of 5 published case series. A consistent short-term response in more than 75% of patients was seen in 2 of the 5 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 the 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 these settings 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 the commercially available botulinum toxin products improve the net health outcome in patients with the miscellaneous conditions listed below (Table 8)?

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) headaches. ¹² It is postulated that botulinum toxin A affects the neuronal signaling pathways activated during a headache, blocks action on the parasympathetic nervous system, and might inhibit the release of other neurotransmitters or affect the transmission of afferent neuronal impulses. ¹³ 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. ¹⁴ 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

Indication Category	Clinical Indication	Description
		injections into the palate or sectioning of the tendons with the middle ear has been evaluated for symptomatic relief.
Urological indications	Benign prostatic hyperplasia	Benign prostatic hyperplasia is an enlargement of the prostate gland in men. The enlargement of the prostate presses causes narrowing of the urethra and loss of 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. ¹⁵
Pain	Multiple etiologies	This category includes 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 a 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 among the 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 (e.g., smiling can lead to

Indication Category	Clinical Indication	Description
		happiness, scowling can lead to anger). Inhibiting the muscles responsible for expressions of anguish and sadness may decrease the patient's experience of these feelings.

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

Populations

The relevant population of interest is individuals with the 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 the 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, and 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,

Indication Category	Clinical Indication	Current Treatment Options
		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 1 level (e.g., first-line to second-line) when less risky approaches have failed. Less invasive treatments include self-care practices and behavior modifications, physical therapy, and oral medications such as amitriptyline, pentosan polysulfate, and 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 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 prokinetics 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, functional outcomes, medication use, and treatment-related morbidity.

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.

REVIEW OF EVIDENCE

NEUROLOGICAL INDICATIONS

Tension and Cervicogenic Headache

A 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.¹⁶ 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 versus the placebo group (difference=-1.43; 95% CI, -3.13 to 0.27; p=.02). Silberstein et al (2006)¹⁷ randomized 300 patients to onabotulinumtoxinA (5 different doses) or placebo for the prophylaxis of chronic tension-type headache. The trial failed to demonstrate a statistically significant difference between the onabotulinumtoxinA group and the placebo group in the number of headache free days per month.

Multiple RCTs^{18,19,20,21}, with a smaller sample size (<50) have evaluated the efficacy of onabotulinumtoxinA in patients with cervicogenic headache, but either reported a lack of treatment benefit^{18,19,21}, or were methodologically flawed (pain scores imbalanced at baseline) to derive meaningful conclusions.²⁰

Essential Tremor

Botulinum toxin type A (BoNT-A) has been shown to provide benefit for limb tremor associated with essential tremor, but has been associated with dose-dependent hand weakness. A systematic review published in 2011²², 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: 1 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.²³ 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 change at 6 weeks.²⁴ 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.²⁵ Statistically significant improvements in clinical rating scores of rest tremor and tremor severity at 4 and 8 weeks were reported in the treated patients and of action/postural tremor at 8 weeks; however, there was no statistically significant difference in grip strength at 4 weeks between the 2 groups. The clinical significance of small benefits observed in trials that were offset by frequent adverse effects (hand weakness) do not permit conclusions about the 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 patients treated with onabotulinumtoxinA for the treatment of tinnitus.²⁶ A small (N=30) cross-over prospective study by Stidham et al (2005) reported a statistically significant decrease in tinnitus handicap inventory scores between pretreatment and 4 months post botulinum toxin A injection. Multiple other outcome studies showed no difference.²⁷ 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 (N=178 patients).²⁸ The largest trial randomly assigned 80 patients to either botulinum toxin A or placebo.²⁸ While the meta-analysis reported a 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.²⁹ Two clinical trials with sufficient quality were selected for the meta-analysis and 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,^{30,31,32} mostly conducted outside of the U.S., there is a risk of urinary retention,³¹ which may be particularly devastating for a patient with a painful bladder. 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.³³ 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 (i.e., low-risk of bias) while 5 were rated as moderate, and the other was rated as a high-risk of bias.³⁴ Kuo et al (2016) reported the results of a RCT that included 60 Taiwanese patients (52 women, 8 men) with interstitial cystitis/painful bladder syndrome who had failed at least 6 months of conventional therapy.³¹ 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).³¹ Later, the dose was decreased to 100 units, resulting in a

reduction of adverse events, but they still occurred more frequently than hydrodistention alone.

PAIN DUE TO MULTIPLE ETIOLOGIES

Lateral Epicondylitis

Although the mechanism of action for botulinum toxin in epicondylitis is not clearly understood, it is thought to be "proinflammatory". Botulinum toxin has been evaluated as a treatment for epicondylitis in a number of RCTs as summarized in a number of systematic reviews.^{35,36,37} In the systematic review and meta-analysis published by Lin et al (2019), authors included 6 RCTs (N=321) comparing onabotulinumtoxinA or abobotulinumtoxinA with placebo or corticosteroid injections in patients with lateral epicondylitis.³⁵ 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 a 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 a corticosteroid 2 to 4 weeks following injection; standardized mean difference 1.15 (0.57 to 1.34) with no difference at the 8 to 12 weeks or 16 weeks or more time points. While the systematic reviews generally report pain relief in individual trials of botulinum toxin versus 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.³⁸ Due to heterogeneity among studies, reviewers did not pool analyses. The primary outcome was change in pain as assessed by validated instruments. Three of the 4 studies found that botulinum toxin did not significantly reduce pain intensity. Major limitations included a high-risk of bias due to study size in 3 of the 4 studies and selective reporting in 1 study. Two other systematic reviews that focused on myofascial pain syndrome involving head and neck muscles reported similar findings. A 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.³⁹ The majority of studies found negative results and 6 identified trials had significant failings due to deficiencies in 1 or more major quality criteria.

Low Back Pain

Foster et al (2001) reported the findings of a RCT in which 31 consecutive patients with chronic low back pain of at least 6 months in duration were randomized to onabotulinumtoxinA or saline.⁴⁰ 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 3 to 4 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.⁴¹ Sample size in majority of trials was 30 or less except for 1. Three of the 5 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 1 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, 2 of the 5 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.⁴² 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 versus topical glyceryl trinitrate ($p < .001$).⁴³ In addition, there was a significant reduction in postoperative pain at rest ($p = .01$), 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.⁴⁴ 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 ($n = 166$).⁴⁵ Regular bowel movements (odds ratio [OR]=0.53; 95% CI 0.29 to 0.99, $p = .04$), short-term improvements (OR=0.56; 95% CI 0.32 to 0.97, $p = .04$) and long-term improvement (OR=0.25; 95% CI 0.15 to 0.41, $p < .0001$) favored myectomy compared with botulinum toxin A injection. Further, the rate of transient fecal incontinence (OR=0.07, 95% CI 0.01 to 0.54; $p < .01$), rate of non-response (OR 0.52, [95 % CI 0.27-0.99]; $p = .04$) and subsequent surgical treatment (OR 0.18, [95 % CI 0.07-0.44]; $p < .0001$) 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 2 procedures. The authors concluded that myectomy was a 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.⁴⁶ Of the 7 studies, 2 were RCTs and the others were comparative and observational studies. Both RCTs were from the same author group and were conducted at a single site in Egypt, enrolling 15 and 24 patients, respectively.^{47,48} 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 a small sample size and lack of blinded assessment, limit the interpretation of these RCTs.

OTHER POPULATIONS

Gastroparesis

A systematic review by Bai et al (2010) identified 15 studies on onabotulinumtoxinA to treat gastroparesis.⁴⁹ Two studies were RCTs; the remainder were 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^{50,51} did not report treatment benefit with onabotulinumtoxinA for treating gastroparesis. The 2 RCTs were inadequately powered ; 1 included 23 patients and the other included 32 patients. Additional adequately powered RCTs are needed.

Depression

Magid et al (2015) published a pooled analysis⁵² of individual patient data from 3 randomized trials^{53,54,55} 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 a score ≤ 7 for the Hamilton Depression Rating scales, ≤ 10 for the Montgomery-Asberg Depression Rating Scale) was 30.5% vs. 6.7% (OR=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 the net health benefit. Limitations in study design and conduct include the potential of unblinding due to changes in cosmetic appearance, small sample size, lack of power analysis,⁵⁴ short duration of follow-up in 2 out of 3 RCTs,^{54,53} lack of clarity on allocation concealment,^{53,54,55} and lack of an intention-to-treat analysis. More importantly, patients with a history of major depressive disorder, presenting with an acute depressive 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 a treatment for major

depressive disorder in adult females was completed in 2016 but has not been published, which raises concerns about the potential for publication bias.

Facial Wound Healing

Ziade et al (2013) reported results of a RCT in which 30 adults presenting to the emergency department with facial wounds without tissue loss were assigned to a single injection of onabotulinumtoxinA (n=11) or no injection (n=13) within 72 hours of wound suturing.⁵⁶ Scars were assessed at a 1 year follow-up visit by patients, an independent evaluator, as well as a board of 6 experienced medical specialists. There were no significant differences between the 2 groups in the multiple outcomes that were assessed. Limitations of the study included a relatively small sample size, loss to follow-up of 20% of patients, and lack of patient 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.⁵⁷ Blinded assessment of standardized photographs by experienced facial plastic surgeons using a 10-cm visual analog scale at 6 months served as the main outcome measure. The difference in visual scores was 8.9 in the treatment arm versus 7.2 in the placebo arm (p=.003). Limitations of the study included its single site nature, relatively small sample size, and 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 (e.g., benign prostatic hyperplasia, low back pain, depression, tinnitus, etc.), where multiple effective treatments supported by an adequate quality evidence base are available, studies using a placebo comparator that lack scientific rigor do not permit conclusions about the net health benefit of botulinum toxin. Future studies in these clinical indications should use appropriate comparators in adequately powered prospective studies with a standardized treatment dose 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 2 meta-analyses that included RCTs comparing endoscopic PD or laparoscopic myotomy with botulinum toxin. Relevant outcomes are symptoms, functional outcomes, and treatment-related morbidity. The systematic review reported that PD, as well as laparoscopic myotomy, afforded a 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 an improvement in the net health outcome.

For individuals with chronic anal fissure who fail medical treatment who receive botulinum toxin injections, the evidence includes 2 meta-analyses. Relevant outcomes are symptoms, health status measures, and treatment-related morbidity. The results of 2 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, the injections 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 an 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 5 case series. Relevant outcomes are symptoms, health status measures, and treatment-related morbidity. The 5 case series included a total of 135 patients with a median follow-up of more than 7 years. In 2 out of the 5 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 an 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, facial wound healing) who receive botulinum toxin injections, the evidence includes case series and RCTs. 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 (e.g., benign prostatic hyperplasia, low back pain, depression, tinnitus, etc.), where multiple effective treatments supported by an adequate quality evidence base are available, studies using a placebo comparator that lack scientific rigor do not permit conclusions about the net health benefit of botulinum toxin. Future studies in these clinical indications should use appropriate comparators in adequately powered prospective studies using a standardized treatment dose and adequate follow-up. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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 4 reviewers who commented on use in sialorrhea, 2 reviewers felt this was medically necessary, and 2 disagreed.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Urological Association

In 2019, the American Urological Association guideline on non-neurogenic overactive bladder states, "clinicians may offer intradetrusor onabotulinumtoxinA (100U) as a 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)."^{58,}

In 2022, the American Urological Association 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)".^{59,}

American Academy of Neurology

In 2016, the American Academy of Neurology updated its practice guidelines on use of botulinum toxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and chronic headache.^{60,} Recommendations are summarized in Table 10.

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

Recommendation	LOR
<i>Blepharospasm</i>	
<ul style="list-style-type: none"> OnabotulinumtoxinA and incobotulinumtoxinA injections should be considered AbobotulinumtoxinA may be considered 	B C
<i>Cervical dystonia</i>	
<ul style="list-style-type: none"> AbobotulinumtoxinA and rimabotulinumtoxinB should be offered OnabotulinumtoxinA and incobotulinumtoxinA should be considered 	A B
<i>Focal manifestations of adult spasticity involving the upper limb</i>	
<ul style="list-style-type: none"> AbobotulinumtoxinA, incobotulinumtoxin A, and onabotulinumtoxinA 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
<i>For focal manifestations of adult spasticity involving the lower limb</i>	
<ul style="list-style-type: none"> OnabotulinumtoxinA and abobotulinumtoxinA should be offered as treatment options There is insufficient evidence to support or refute a benefit of incobotulinumtoxinA or rimabotulinumtoxinB for treatment of adult lower-limb spasticity 	A
<i>Headache</i>	
<ul style="list-style-type: none"> To increase the number of headache-free days, onabotulinumtoxinA should be offered as a treatment option to patients with chronic headaches OnabotulinumtoxinA 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.⁶¹

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.”⁶²

American Pediatric Surgical Association

In 2017, the American Pediatric Surgical Association 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 to 6 months as many times as necessary depending on symptoms. In most cases, the symptoms will gradually improve with age.⁶³

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 for Off Label Use of Botulinum Toxins

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT04766723 ^a	A Study to Investigate the Efficacy and Safety of NT 201 (Botulinum Toxin) Compared With Placebo for the Treatment of Adult Participants With Essential Tremor in the Arm	75	Nov 2023
NCT03223298	Botulinum Toxin Versus Placebo Injections to Temporalis and Masseter Muscles	110	Dec 2022
NCT03779841 ^a	Botulinum Toxin Type A (AGN-151607) for the Prevention of Post-operative Atrial Fibrillation in Patients Undergoing Open-chest Cardiac Surgery (NOVA)	330	Feb 2023
NCT03935295	Dysport as an Adjunctive Treatment to Bracing in the Management of Adolescent Idiopathic Scoliosis	90	Apr 2023
NCT04965311	Endoscopic Botulinum Toxin Injection in the Prevention of Postoperative Pancreatic Fistula Following Distal Pancreatectomy	63	May 2025
NCT04409600	Comparison of Non-Surgical Treatment Options for Chronic Exertional Compartment Syndrome (CECS)	620	Nov 2024
NCT05125029	Double Blind RCT to Evaluate the Effect of Botulinum Toxin in Raynaud Phenomenon	36	Nov 2023
NCT05327972	DEgenerative ROtator Cuff Disease and Botulinum TOXin : a Randomized Trial	60	Dec 2024
NCT05367271	The Efficacy of Botulinum Toxin to the Flexor Digitorum Brevis Versus Corticosteroid to the Plantar Fascia for the Treatment of Refractory Plantar Fasciitis: A Randomized-Controlled Trial	50	May 2022
NCT04965311	A Phase II Trial of Pre-Operative	63	May 2025

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Endoscopic Botulinum Toxin Injection in the Prevention of Postoperative Pancreatic Fistula Following Distal Pancreatectomy		
<i>Unpublished</i>			
NCT04250844	Use of Intrapyloric Botulinum Injections in Children	100	May 2021
NCT02965976	Botulinum Toxin Type A in Preventing Complications After Surgery in Patients With Esophageal Cancer	50	Dec 2022

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. This may not be a comprehensive list of procedure codes applicable to this policy.

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.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

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	Chemodenerivation of internal anal sphincter
52287	Cystourethroscopy, with injection (s) for chemodenerivation of the bladder
64611	Chemodenerivation of parotid and submandibular salivary glands, bilateral
64612	Chemodenerivation of muscle(s); muscle(s) innervated by facial nerve, unilateral (e.g., for blepharospasm, hemifacial spasm)
64615	Chemodenerivation of muscles(s); muscles(s) innervated by facial, trigeminal, cervical spinal and accessory nerves, bilateral (e.g., for chronic migraine)
64616	Chemodenerivation of muscle(s); neck muscle(s), excluding muscles of the larynx, unilateral (e.g., for cervical dystonia, spasmodic torticollis)
64617	Chemodenerivation of muscle(s); larynx, unilateral, percutaneous (e.g., for spasmodic dysphonia), includes guidance by needle electromyography, when performed
64642	Chemodenerivation of one extremity; 1-4 muscle(s)
64643	Chemodenerivation of one extremity; each additional extremity, 1-4 muscle(s) (List separately in addition to code for primary procedure)
64644	Chemodenerivation of one extremity; 5 or more muscle(s)
64645	Chemodenerivation of one extremity; each additional extremity, 5 or more muscle(s) (List separately in addition to code for primary procedure)
64646	Chemodenerivation of trunk muscle(s); 1-5 muscle(s)
64647	Chemodenerivation of trunk muscle(s); 6 or more muscle(s)
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
G24.01-G24.9	Dystonia code range (includes 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-G51.9	Facial nerve disorders (includes disorders of the 7th cranial nerve)
G80.0-G80.9	Cerebral palsy code range
G81.10-G81.14	Spastic hemiplegia code range
H49.00-H50.9	Strabismus code range
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

ICD-10 DIAGNOSES	
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 over reactivity (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.
01-01-2010	In Coding section: <ul style="list-style-type: none"> ▪ Added HCPCS Code: J0586 ▪ Updated wording for HCPCS Code: J0585
	Added Diagnosis coding range for urinary incontinence: 788.30-788.39.
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, chronic daily headache, and tension type headache" and added "other than chronic refractory headache" to read "headaches, other than chronic refractory headaches."
	In the Documentation section: <ul style="list-style-type: none"> ▪ Removed "There must be a stated goal of treatment."

REVISIONS	
	Rationale section updated.
	In Coding section: <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.
	Reference section updated.
05-13-2011	In Coding section, added HCPCS code Q2040.
12-09-2011	Updated Description section.
	In the Policy section: <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"
	Removed the Documentation section.
	Removed the Utilization section.
	Added Policy Guidelines section.
	In Coding section: <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
	Updated the Rationale section.
	Updated the Reference section.
01-01-2012	In the Policy section: <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"
	In the Coding section: <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	In the Coding section: <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	Updated Description section.
	In Policy section: <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 over reactivity associated with neurogenic causes..." ▪ In Item A, added #12, "overactive bladder in adults that is inadequately controlled with anticholinergics." ▪ In Item B, added #23, "Facial wound healing." ▪ In Item B, added #24, "Internal anal sphincter (IAS) achalasia". ▪ Moved the "Policy Guidelines" to the "Coding" section.
	Updated Rationale section.
	In Coding section: <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>)

REVISIONS	
	<ul style="list-style-type: none"> ▪ 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 over reactivity 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.
	<p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Removed CPT codes: 64650 and 64653.
	Updated References section.
07-01-2016	Updated Description section.

REVISIONS	
	<p>In Policy section:</p> <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. <p>Updated Rationale section.</p>
10-01-2016	<p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Added ICD-10 codes effective 10-01-2016: N39.491, N39.492
03-29-2017	<p>In Policy section:</p> <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.
	<p>In Policy section:</p> <ul style="list-style-type: none"> ▪ In Policy Guidelines, added "Indications and Dosage" table.
	Updated Rationale section.
	<p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Updated Coding bullets. ▪ ICD-9 codes removed.
	Updated References section.
10-01-2018	<p>In Coding section:</p> <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.
	<p>In Policy section:</p> <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 (e.g., 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.
	<p>In Coding section:</p> <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.
	<p>In Title heading:</p> <ul style="list-style-type: none"> ▪ Removed "Treatment of Tinnitus" from the <i>See Also</i> policies.
	<p>In Policy section:</p> <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."
	<p>In Coding section:</p> <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)
10-18-2020	Policy published 07-xx-2020. Policy effective 08-xx-2020.
	Description section updated

REVISIONS	
	<p>In Policy section:</p> <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 (e.g., organic writer's cramp) b. Oromandibular dystonia (orofacial dyskinesia, Meige syndrome) c. Laryngeal dystonia (adductor spasmodic dysphonia) d. Idiopathic (primary or genetic) torsion dystonia e. Symptomatic (acquired) torsion dystonia 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:

REVISIONS	
	<p>4. Ano-rectal conditions such as:</p> <p>5. Other miscellaneous conditions such as:"</p> <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
12-13-2022	Updated Description Section
	<p>Updated Policy Guideline Section</p> <ul style="list-style-type: none"> ▪ Removed Guideline D: "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."
	Updated Rationale Section
	<p>Updated Coding Section</p> <ul style="list-style-type: none"> ▪ Removed CPT code 67345 ▪ Converted the following ICD-10 codes to ranges G51.0-G51.9, G80.0-G80.9, G81.10-G81.14, H49.00-H50.9, and G24.01-G24.9; to include all codes within the range
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