Medical Policy

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Title: Botulinum Toxin (BT)

Related Policies:	▪ *Treatment of Hyperhidrosis*

Professional / Institutional
Original Effective Date: February 1996 / June 3, 2004
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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:	Interventions of interest are:	Comparators of interest are:	Relevant outcomes include: • Symptoms

Populations	Interventions	Comparators	Outcomes
• With Hirschsprung disease who develop obstructive symptoms after a pull-through operation	• Botulinum toxin injections	• Standard of care	• 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 5 botulinum toxin agents currently available and approved by the FDA for medical use. These include onabotulinumtoxinA (Botox), abobotulinumtoxinA (Dysport), incobotulinumtoxinA (Xeomin), rimabotulinumtoxinB (Myobloc), and daxibotulinumtoxinA (Daxxify).

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.

On August 15, 2023, daxibotulinumtoxinA (Daxxify) was approved by the FDA for treatment of cervical dystonias.

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

Table 1. FDA Indications of Botulinum Toxin Products[a]

	FDA Approved Indication[a]	Botox	Dysport	Myobloc	Xeomin	Daxxify
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	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			Approved for	Approved	

	FDA Approved Indication[a]	Botox	Dysport	Myobloc	Xeomin	Daxxify
	sialorrhea			adults	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 individuals who have not responded to dilation therapy or who are considered poor surgical candidates.

12. Chronic anal fissure in individuals 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 individuals 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. Lateral epicondylitis
      d. Mechanical neck disorders

e. Myofascial pain syndrome
f. Neuropathic pain
g. Pain after hemorrhoidectomy or lumpectomy
h. Prevention of pain associated with breast reconstruction after mastectomy
i. Temporomandibular joint disorders
j. Trigeminal neuralgia

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 phonophobia

(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 was created using searches of the PubMed database. The most recent literature update was performed through August 25, 2025. 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. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Esophageal Achalasia

Esophageal achalasia results from progressive degeneration of ganglion cells in the myenteric plexus in the esophageal wall, leading to failure of relaxation of the lower esophageal sphincter

(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 (eg, injection of botulinum toxin or use of oral nitrates).

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

The 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 (ie, 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 two 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

Systematic Reviews
Shiu et al (2022) conducted a meta-analysis of 24 RCTs (N=1987 patients) published between January 2000 and June 2021 that compared the efficacy of different treatments for primary achalasia.[1,] The review compared two or more interventions including botulinum toxin, PD, botulinum toxin and PD, laparoscopic myotomy with/without fundoplication, and POEM. The primary focus was on clinical success rates, incidence of postsurgical acid reflux, and moderate-

to-severe adverse events. This analysis confirmed that the efficacy of PD is greater than botulinum toxin for achalasia after 6 months, similar to the findings from Cochrane review below. Shiu et al (2022) incorporated two additional RCTs that were absent from the Cochrane review extending these results up to a 24-month follow-up period.[2,3,]

A Cochrane review by Leyden et al (2014) identified 7 RCTs (N=178 participants) that compared onabotulinumtoxinA with endoscopic PD.[4,] 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.[5,] 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 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 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. PD and botulinum toxin have similar procedure times and can be performed under endoscopic visualization and conscious sedation.[1,] Initial success rates with botulinum toxin are comparable to PD and surgical myotomy.[5,] However, patients treated with botulinum toxin have more frequent relapses and a shorter time to relapse.[5,] More 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.[6,]

Table 2. Systematic Review/Meta-Analysis Characteristics

Study (Year)	Dates	Trials	Participants	N (Range)	Design	Duration
Leyden et al (2014)[4,]	1955-2008	7	Individuals with primary achalasia with the aim to compare endoscopic PD vs. botulinum toxin A	178 (NR)	RCT	7 trials followed up patients ranging from 1 to 12 months
Wang et al (2009)[5,]	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)[4,]: 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%
Wang et al (2009) [5,]	**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 (1.51 to 3.20); p<.0001	16.7% vs. 50%; RR, 0.36 (0.22 to 0.58)	-
Laparoscopic myotomy vs. botulinum toxin A			

Study (Year)	Symptom Remission at 1 Month	Symptom Remission at 6 Months	Symptom Remission at 12 Months
Total N	117 (2 RCTs)	NR	-
Pooled effect (95% CI); p-value	83.3% vs. 64.9%, RR, 1.28 (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, 3 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 a topical vasodilator 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 who may have a weak anal sphincter complex are advised to undergo surgical procedures that do not require division of the anal sphincter muscle (eg, botulinum toxin injection, fissurectomy, or anal advancement flap). Patients who are not at risk for developing fecal incontinence may undergo lateral internal sphincterotomy, which is considered the most effective treatment for anal fissure.

Clinical Context and Therapy Purpose
The purpose of botulinum toxin in patients with chronic anal fissure is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The 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
Boland et al (2020) conducted a systematic review of 9 RCTs (N=775 patients) published between January 2000 and February 2020 that compared treatment options for anal fissure.[7,] The primary outcome assessed was healing at 8 weeks post-treatment. Secondary outcomes included recurrence, intolerance of treatment. and complications. At 8 weeks, healing rates were 95% in the sphincterotomy group compared to 67% in the botulinum toxin group. Recurrence was lowest for sphincterotomy (7%) and highest amongst those treated with botulinum toxin injection (42%). Topical nitrites had similar outcomes to botulinum toxin injection but were poorly tolerated in comparison to other treatments. Sphincterotomy increased the risk of permanent incontinence as a complication. Potential sources of bias included heterogeneity across trials in patient compliance rates and treatment duration.

Chen et al (2014) compared outcomes of onabotulinumtoxinA injection with lateral internal sphincterotomy based on 7 RCTs.[8,] The study characteristics and results are summarized in Tables 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.[9,] Reported results for the comparison of botulinum toxin injection with sphincterotomy are consistent with those reported by Boland et al (2020) and Chen et al (2014). Botulinum toxin A injection is therefore preferably used for patients who are at a high-risk of developing fecal incontinence (eg, multiparous women or older patients).

Table 4. Systematic Review/Meta-Analysis Characteristics

Study (Year)	Dates	Trials	Participants	N (Range)	Design	Duration
Chen et al (2014)[8,]	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)[8,]: 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)[9,]: 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

A systematic review and 2 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 reviews 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 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 intrasphincterically.

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

Systematic Reviews

Roorda et al (2019) conducted a meta-analysis of 14 studies (N=278 patients) published through December 2018 on the efficacy of botulinum toxin injections in patients with Hirschsprung disease.[10,]The primary outcome assessed was proportion of patients with improvement of obstructive symptoms. Secondary outcomes included type of botulinum toxin, average dose, average age at first injections and proportion of patients with associated syndromes. Botulinum toxin injections were effective in treating obstructive symptoms in 66% of patients [event rate (ER)=0.66, p=0.004, I^2=49.5]. Secondary outcomes were not predictive for this effect. There was a significantly higher response rate within one month after botulinum toxin injections compared to greater than one month (p<.001). Botulinum toxin injections were not effective in treating enterocolitis (p=0.65). Adverse effects were observed on average in 17% of patients (p<0.001), varying from temporary incontinence to mild anal pain.

Cohort Studies

A retrospective cohort study by Svetanoff et al (2021) included 40 patients admitted for Hirschsprung-associated enterocolitis (HAEC) from January 2010 to December 2019.[11,] 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 by Roorda et al (2021) of 41 patients consecutively treated for Hirschsprung disease from 2003 and 2017in 2 academic hospitals in Amsterdam with a follow-up duration of ≥1 year after corrective surgery were analyzed.[12,] 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. These cohort studies are summarized in Tables 6 and 7.

Table 6. Summary of Cohort Study Characteristics

Author (Year)	Study Type	Country/Institution	Dates	Participants	Treatment	Follow-Up
Roorda et al (2021)[12,]	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)[11,]	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 Cohort Study Results

Study (Year)	Outcomes (Efficacy)
Roorda et al (2021)[12,]	
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**

Study (Year)	Outcomes (Efficacy)
	botulinum toxin injections: 71% (29/41)
Svetanoff et al (2021)[11,]	
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 to 326) vs. 68 days (IQR, 16 to 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 a meta-analysis and 2 later published retrospective cohort studies.. There was evidence for improvement of obstructive symptoms after botulinum toxin injections in patients that underwent surgery for Hirschsprung disease, although this effect was often transient and most patients needed multiple injections. Long-term follow-up is indicative of durability of response.

MISCELLANEOUS CONDITIONS

Clinical Context and Therapy Purpose

The purpose of botulinum toxin in patients with the miscellaneous conditions listed in Table 8 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.

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.[13,] 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.[14,] 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.[15,] Botulinum toxin A has been evaluated as a potential treatment given its efficacy in migraine.
	Essential tremor	Essential tremor is the most common cause of action tremor in adults. It classically involves the hands and is brought out by arm movement and sustained antigravity postures, affecting common daily activities such as writing, drinking from a glass, and handling eating utensils. Essential tremor is slowly progressive and can involve the head, voice, and rarely the legs, in addition to the upper limbs. Disability from the tremor can be significant, and a variety of symptomatic therapies are available.
	Tinnitus	Tinnitus is a perception of sound in proximity to the head in the absence of an external source. In patients with myoclonus of the palatal muscles or middle ear structures, botulinum toxin injections into the palate or sectioning of the tendons with the middle ear has been evaluated for symptomatic relief.
	Tourette syndrome	Tourette Syndrome is a neurological disorder characterized by repetitive, involuntary movements and vocalizations called tics. These tics can vary in severity and may include simple motions such as blinking or complex actions like jumping. Vocal tics can range from grunting to uttering inappropriate words or phrases. The exact cause of Tourette Syndrome is not known, but it is believed to involve a combination of genetic and environmental factors.
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

Indication Category	Clinical Indication	Description
		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.[16,]
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.
Gastrointestinal Disorders	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.
	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.
Others		
	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 (eg, smiling can lead to 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.

Indication Category	Clinical Indication	Description
	Facial Wound Healing	Facial wounds refer to injuries that impact the skin, muscles, blood vessels, or bones of the facial region. These wounds can range from minor cuts and abrasions to severe lacerations and fractures, often resulting from accidents, assaults, or surgical procedures. Proper and prompt treatment is crucial to minimize scarring, infection, and functional impairments, ensuring both aesthetic and medical recovery.
	Raynaud's phenomenon	Raynaud's phenomenon is characterized by episodic vasospasm typically triggered by cold exposure or emotional stress. It results in triphasic color changes of the fingers and toes, often accompanied by numbness, tingling, or pain. Primary Raynaud's occurs without associated conditions, while secondary Raynaud's is linked to underlying disorders such as systemic sclerosis, lupus, or rheumatoid arthritis and carries a higher risk of complications. Botulinum toxin A has been investigated as a potential treatment, with studies suggesting improvement in pain and digital perfusion.

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 therapies listed in Table 9 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.
	Essential	The initial approach to treatment is conservative measures such

Indication Category	Clinical Indication	Current Treatment Options
	tremor	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.
	Tourette syndrome	Medications are used to help manage the symptoms of the condition, which primarily include motor and vocal tics. Common medications include antipsychotics like haloperidol and pimozide, alpha-adrenergic agonists, and other medications like topiramate and botulinum toxin injections. The choice of medication depends on the severity of symptoms, side effects, and individual response to treatment. Non-pharmacological therapies, such as behavioral therapy, are often used in conjunction with medication to provide a comprehensive approach to managing the disorder.
Urological indications	Benign prostatic hyperplasia	Medications commonly used to treat lower urinary tract symptoms associated with benign prostatic hyperplasia include alpha-1-adrenergic antagonists, 5-alpha-reductase inhibitors, anticholinergic agents, and phosphodiesterase-5 inhibitors.
	Interstitial cystitis	There are numerous treatments and management approaches are organized in the order of increasing risk. For most patients, it is reasonable to move from 1 level (eg, first-line to second-line) when less risky approaches have failed. Less invasive treatments include self-care practices and behavior modifications, physical therapy, 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.
Gastrointestinal Disorders	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

Indication Category	Clinical Indication	Current Treatment Options
		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.
	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.
Others		
	Depression	The goal of initial treatment for depression is symptom remission and restoring baseline functioning.
	Facial Wound Healing	Early injections of botulinum toxin type A, which induces temporary muscular paralysis of facial lacerations, is proposed as a treatment option to enhance wound healing which results in less noticeable scars.
	Raynaud's phenomenon	Pharmacologic treatment is generally reserved for more severe cases and includes calcium channel blockers as the most commonly used agents. Additional options for refractory disease include phosphodiesterase-5 inhibitors, angiotensin II receptor blockers, topical nitrate, and selective serotonin reuptake inhibitors. Surgical sympathectomy or botulinum toxin injections have also been investigated as potential therapies for refractory Raynaud's.

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

Dhanasekara et al (2023) conducted a meta-analysis of 11 RCTs (n=390 botulinum toxin A, n=297 controls) published through May 2020 on the effectiveness of botulinum toxin for chronic tension-type headache prophylaxis.[17,]Headache intensity (mean, -0.50; standard deviations: -0.94, −0.06), frequency (-2.83 days/month; -4.08, -1.58), daily headache duration (-0.96; -1.86, -0.07), and the frequency of acute pain medication use (-2.2 days/month; -3.48, -0.91]) were improved with botulinum toxin A. These improvements exceeded minimal clinically important differences for headache intensity, frequency, and acute pain medication use. A 79% (28%, 150%) greater response rate was observed for botulinum toxin vs controls in improving chronic tension-type headache. This review however had some notable limitations, including the low-quality evidence and a small number of patients across studies. There is a need to establish the effects of botulinum toxin A for this indication in adequately-powered high-quality RCTs. An earlier meta-analysis by Jackson et al (2012) of 8 placebo-controlled RCTs evaluating botulinum toxin A for chronic tension-type headaches 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).[18,]

Essential Tremor

Marques et al (2024) conducted a multicenter, double-blind, RCT in adult patients with essential or isolated head tremor receiving botulinum toxin type A or placebo.[19,]The primary outcome was improvement by at least 2 points on the Clinical Global Impression of Change scale at week 6 after the second injection (week 18 after randomization). Secondary outcomes included changes in tremor characteristics from baseline to weeks 6, 12, and 24. One-hundred and seventeen (of 120) patients were randomly assigned to receive botulinum toxin (n=62) or placebo (n=55) and included in the intention-to-treat analysis. Twelve patients in the botulinum toxin group and two patients in the placebo group did not receive injections during week 12. The primary outcome was met by 31% of the patients in the botulinum toxin group as compared with 9% of those in the placebo group (relative risk, 3.37; 95% CI, 1.35 to 8.42; p=.009). Analyses of secondary outcomes at 6 and 12 weeks but not at 24 weeks were generally supportive of the primary-outcome analysis. Adverse events occurred in approximately half the patients in the botulinum toxin group and included head and neck pain, posterior cervical weakness, and dysphagia. The study had some limitations, such as loss to-follow-up of patients, potential unmasking of the trial-group assignments, and lack of control for external factors affecting tremor.

An earlier systematic review by Liao et al (2022) of 5 RCTs published before December 2021 concluded that botulinum toxin significantly reduced essential tremor severity, including hands tremor and head tremor within 6 weeks of treatment (standardized mean difference (SMD), -0.58, 95% CI, -0.28 to -0.88, p=.002, I^2=0%).[20,] The main side effect was weakness, but it did not affect the grip strength of the patients. This review had limitations, such as small sample sizes, and use of diverse assessment methods across trials.

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.[21,] 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.[22,] Multiple other outcome studies showed no difference. Well-conducted RCTs with sufficiently large sample sizes are needed.

Tourette syndrome
A Cochrane review was conducted by Pandey et al (2018) to assess the efficacy and safety of botulinum toxin for treating motor and phonic tics in people with Tourette's syndrome, and to examine its impact on premonitory urge and sensory tics.[23,] Only one RCT (N=20 patients) met the study selection criteria. The results of botulinum toxin injections on tic frequency, measured by video or self-report, and on premonitory urge, are unclear based on low-quality of evidence. The evidence for side effects of botulinum toxin was also very low. Nine individuals had muscle weakness following the injection, which could have led to unblinding of treatment group assignment. No data were available to evaluate whether botulinum injections led to immuno-resistance to botulinum toxin.

UROLOGICAL INDICATIONS

Benign Prostatic Hyperplasia
Gavi et al (2024) conducted a systematic review and meta-analysis of 7 studies (N=232) evaluating transurethral botulinum toxin A for bladder outlet obstruction, with 3 cohorts specific to benign prostatic hyperplasia (BPH) contributing to pooled estimates.[24,] Follow-up was primarily 3 to 6 months and study quality was generally low (mostly nonrandomized, low number samples). In BPH, pooled pre-post changes favored botulinum toxin A: International Prostate Symptom Score improved by -12.52 points at 3 months (95% CI, -14.48 to -10.56; I^2=0%;p<.0001); maximum flow (Qmax) increased by 4.56 mL/s at 3 months (95% CI, 1.50 to 7.62; I^2=85%; p=.003) and 2.90 mL/s at 6 months (95% CI, 1.51 to 4.29; I^2=0%; p<.0001); post-void residual decreased by -82.61 mL at 3 months (95% CI, -131.91 to -29.31; I^2=83%; p=.002) and -108.74 mL at 6 months (95% CI, -163.57 to -53.91; I^2=76%; p=.0001). Adverse events were mostly mild (hematuria, transient urinary retention, UTIs), with no serious events reported.

Shim et al (2016) reported the results of a systematic review of 3 studies (N=522) on use of botulinum toxin A to treat BPH.[25,]Study duration ranged from 8 to 24 weeks. The pooled overall SMD in the mean change in International Prostate Symptom Score for the botulinum toxin group versus the placebo group was -1.02 (95% CI, -1.97, -0.07). The other outcomes (peak flow rate (Qmax), prostate volume, and post-voided residual volume) were not statistically different between the two groups. This review showed no overall differences in efficacy and procedure-related adverse events of botulinum toxin compared with placebo for this indication.

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,[26,27,28,] mostly conducted outside of the U.S., there is a risk of urinary retention,[27,] 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.

The American Urological Association published guidelines for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome in 2011 based on a systematic review that included published evidence from January 1, 1983 to July 22, 2009.[29,] The guideline is updated periodically by conducting incremental systematic reviews to maintain guideline currency with newly published relevant literature. Most recently, an updated literature review in 2022 (search dates, June 2013 to January 2021) was published.[30,] In addition, multiple systematic reviews have been published.[31,32,33,34,] There is large variability in the botulinum toxin type, dosage, frequency and site of injection and comparators among the RCTs included in the systematic reviews. Further, several studies appear to include overlapping patient groups. These limitations make it challenging to interpret the results of these meta-analysis.

Detrusor Sphincteric Dyssynergia

Goel et al (2020) conducted a systematic review of 11 studies (N=353 patients) that evaluated the use of botulinum toxin A as the first-line treatment for detrusor external sphincter dyssynergia.[35,] Botulinum toxin improved urinary retention, bladder and urethral pressure, and leakage rate in 60%-78% of patients after one month. Most patients needed another injection after 4-9 months. A previous Cochrane review by Utomo et al (2014), because of the limited availability of eligible trials (4 RCTs), was unable to provide robust evidence in favor of botulinum toxin injections for detrusor external sphincter dyssynergia.[36,] Results were from small studies with a high risk of bias.

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.[37,38,39,]

In the systematic review and meta-analysis published by Lin et al (2018), the authors included 6 RCTs (N=321) that compared onabotulinumtoxinA or abobotulinumtoxinA with placebo or corticosteroid injections in patients with lateral epicondylitis.[37,] 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 (95% CI, -1.29 to -0.17), -0.45 (95% CI, -0.74 to -0.15), and -0.54 (95% CI, -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 (95% CI, 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. Similar results were reported by Tavassoli (2022) in a systematic review and meta-analysis of 31 RCTs (N=1948 patients) comparing local injection therapies for lateral epicondylitis: the efficacy of corticosteroids was greater than botulinum toxin within 4 weeks of treatment, with no significant therapeutic effects observed between groups in any study outcomes after 12 weeks of follow-up.[40,]

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.[41,] 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. Leonardi et al (2024) conducted a systematic review of 10 RCTs (N=651 patients) to assess the efficacy and safety of botulinum toxin injections for upper back myofascial pain syndrome.[42,] Botulinum toxin was compared with placebo, anesthetic plus dry needling, or anaesthetic injections. The methodological quality of the trials was moderate and no serious adverse events or major complications were reported. However, the results did not show that botulinum toxin had a clear advantage over the other treatment modalities. Most included studies had small sample sizes, low power, varied outcome measures, and inconsistent follow-up periods. A previous 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.[43,] 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

Wagrees et al (2025) conducted a systematic review and meta-analysis of 9 studies (7 RCTs and 2 prospective cohorts) to evaluate botulinum toxin A for chronic low back pain.[44,] Outcomes included clinically significant pain response (≥50% VAS reduction), functional improvement, and mean VAS. Pooled results showed that botulinum toxin A increased the proportion achieving clinically meaningful pain relief (RR, 4.82; 95% CI, 3.00 to 7.76) and functional improvement (RR, 3.81; 95% CI, 2.40 to 6.04) and reduced VAS scores (MD, -1.62; 95% CI, -3.13 to -0.11). Subgroup analyses indicated a benefit over normal saline (moderate-certainty evidence), but effects were comparable to those of steroids and local anesthetics (very low-certainty evidence).

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.[45,]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. Findings from a more recent small RCT by Cogne et al (2017) (N=19 patients) did not find botulinum toxin injections to be effective in relieving low back pain.[46,] Results from these two trials 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

Saini et al (2024) conducted a systematic review and meta-analysis of 14 RCTs (N=395 patients) to assess the effectiveness of botulinum toxin in the treatment of temporomandibular joint disorders.[47,] The overall risk of bias showed a low to moderate quality of evidence. Results from 6 studies were reported only narratively; four studies were used for meta-analysis on pain reduction, and five were used for meta-analysis on adverse events. The control used in the meta-analysis was placebo injections. Results of the meta-analysis (n=84, 4 RCTs) for pain reduction were statistically insignificant for the botulinum toxin group with mean differences (MD) at -1.71 (95% CI, −2.87 to −0.5) at one month, -1.53 (95% CI, −2.80 to −0.27) at three months, and -1.33 (95% CI, −2.74 to 0.77) at six months. Regarding safety, the placebo group showed a relative risk of 1.34 (95% CI, 0.48 to 6.78) and 1.17 (95% CI, 0.54 to 3.88) at 1 and 3 months respectively. Botulinum toxin was also not associated with better outcomes in terms of adverse events, maximum mouth opening, bruxism events, and maximum occlusal force. More high-quality RCTs are needed to assess the efficacy and safety of botulinum toxin for this indication.

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.[48,] Sample size in all trials was 30 or less except for 1 study. 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 compared 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 to 2 months) benefit of onabotulinumtoxinA compared with control on pain reduction.

Post Hemorrhoidectomy Pain

Lie et al (2023) conducted a systematic review and meta-analysis of 5 clinical trials (N=260 patients) published through March 2022 assessing the utility of botulinum toxin injection for post-operative pain management after conventional hemorrhoidectomy.[49,] The pooled analysis revealed that botulinum toxin injection after hemorrhoidectomy was associated with lower visual analog scale (VAS) at 24 hours post-operative [MD, -1.35 (95% CI -1.90 to -0.80), $p<0.00001$, $I^2=0\%$] and shorter time to return work [MD, -8.94 days (95% CI, -12.57 to -5.30), $p<0.00001$, $I^2=0\%$]. However, botulinum toxin injection did not differ significantly from placebo in terms of time to first defecation (p=0.22), fecal incontinence (p=0.91) and urinary retention incidence (p=0.18). Further RCTs with larger sample sizes are needed to confirm the results of this meta-analysis.

Pelvic and Genital Pain in Women

Parenti et al (2023) conducted a systematic review of 22 studies to assess the efficacy and safety of botulinum toxin use in the treatment of vaginal, vulvar and pelvic pain disorders.[50,] Botulinum toxin injection was found to be effective in improving vulvar and vaginal dyspareunia, vaginismus, and chronic pelvic pain. No irreversible side effects were detected. Major side effects reported were transient urinary or fecal incontinence, constipation and rectal pain. A meta-analysis was not performed given the use of different definitions, methods, and timing of botulinum toxin injection across studies.

Neuropathic Pain
The Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain published a systematic review and meta-analysis in 2015 which included 6 RCTs that assessed the efficacy of a single administration of botulinum toxin A (50 to 200 units subcutaneously in the region of pain) in patients with peripheral neuropathic pain.[51,] The number needed to treat for 50% pain relief was a primary measure. Within the pool of included studies, those with smaller sample sizes had a positive primary outcome (number needed to treat, 1.9; 95% CI, 1.5 to 2.4 for 4 studies) with a low placebo effect, but one large, unpublished study was negative. Overall, the published meta-analysis assigned weak GRADE recommendations for use in neuropathic pain mainly because of the weak quality of evidence.

Datta Gupta et al (2022) published the results of a meta-analysis of RCTs evaluating the use of botulinum toxin A in neuropathic pain.[52,] Of the 17 RCTs that were included (N=703), 6 reported the proportion of patients with at least a 50% reduction in VAS between baseline and final time periods in the botulinum toxin A and placebo groups. The mean RR was 4.90 (95% CI, 2.00 to 6.13; I^2=44.9%).

Trigeminal Neuralgia
Evidence for the efficacy and safety of botulinum toxin A for trigeminal neuralgia is limited to 4 RCTs (N=178 patients) summarized in at least two meta-analyses by Morra et al, 2016 and Hu et al, 2024).[53,54,]While these results reported a significant reductions in mean pain scores and attack frequency in the botulinum toxin compared with the placebo group, there are concerns about small patient numbers, limited durability, and quality of evidence. More high-quality studies are needed to further confirm its efficacy for patients with refractory trigeminal neuralgia or those not responding to medical or surgical management,.

Prevention of Pain Associated with Breast Reconstruction after Mastectomy
Li et al (2018) conducted a systematic review and meta-analysis of 10 studies (N=682 patients) published through March 2018 on the use of botulinum toxin A in breast surgery using implants deep within the pectoralis major muscle.[55,] The studies considered for inclusion consisted of six prospective controlled trials (2 RCTs and 4 other trials), three retrospective cohort studies, and one case series. The study time ranged from 4 months to 13 years, and 15 patients (3%) received botulinum toxin injection more than two times. No complications associated with botulinum toxin were mentioned, almost all the studies reported efficacy for pain control. The included studies were primarily retrospective, nonrandomized trials.

GASTROINTESTINAL DISORDERS

Internal Anal Sphincter Achalasia
Friedmacher and Puri (2012) reported the 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).[56,] 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 to 0.99; p=.04) and subsequent surgical treatment (OR, 0.18;95% CI, 0.07

to 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.[57,] 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.[58,59,] 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 this decreased to 25% at 1year. 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.

Gastroparesis

Gonzalez et al (2024) conducted a French multi-center RCT (N=40 patients) comparing the clinical efficacy of gastric POEM versus pyloric botulinum toxin injection for refractory gastroparesis.[60,] Patients were medically managed for >6 months and confirmed by gastric emptying scintigraphy (GES), with follow-up of 1 year. The primary end point was the 3-month clinical efficacy, defined as a >1-point decrease in the mean Gastroparesis Cardinal Symptom Index (GCSI) score. Secondary end points were: 1-year efficacy, GES evolution, adverse events, and quality of life. POEM showed a trend towards higher 3-month clinical success than botulinum toxin (65% vs. 40%, respectively; p=0.10), along with non-significantly higher 1-year clinical success (60% vs. 40%, respectively) on intention-to-treat analysis. The GCSI decreased in both groups at 3 months and 1 year. Only three minor adverse events occurred in the POEM group. The GES improvement rate was 72% in the POEM group versus 50% in the botulinum toxin group (non-significant).

A systematic review by Bai et al (2010) identified 15 studies on onabotulinumtoxinA to treat gastroparesis.[61,] 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[62,63,] 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.

OTHER POPULATIONS

Raynaud's Phenomenon

Pang et al (2025) reported a systematic review of 19 studies (N=398) on botulinum toxin for

Raynaud's phenomenon secondary to scleroderma.[64,] Pooled analyses showed statistically significant improvement in Quick-DASH in 5 studies (standardized mean difference [SMD], -83; 95% CI, -1.59 to -.07; I^2=0%; p=.03) and VAS-pain in 10 studies (SMD, -1.52; 95% CI, -2.14 to -.90; I^2=83%; p<.0001), while the Raynaud's Condition Score was not significantly changed (SMD, -.43; 95% CI, -1.36 to.50; I^2=80%; p=.37) in 2 studies. Given the heterogeneity in dosing and injection techniques, as well as the predominance of underpowered, mixed-design studies, additional, better-designed trials are required to determine the net health benefit.

Geary et al (2024) conducted a meta-analysis of 18 studies (N=218), including 4 RCTs, evaluating subcutaneous onabotulinumtoxinA for primary Raynaud's phenomenon of the hands.[65,] The meta-analysis estimated the probability of VAS pain improvement in 12 pooled studies at 82% (95% CI, 74.12 to 87.81; I^2=26%; p=.19); although 2 placebo-controlled RCTs showed no pain benefit. Digital ulcer healing was reported by 10 studies and had a pooled rate of 79.4% (95% CI, 62.45 to 89.90; I^2=56%; p=.02). Other outcomes (eg, vasospastic-episode frequency, temperature/perfusion metrics) were inconsistently reported and not pooled. Overall, a definitive, adequately powered RCT with standardized patient-reported and objective measures is still required.

Depression

Brin et al (2020) performed a double-blind placebo-controlled multicenter RCT (N=255 patients) evaluating the efficacy and safety of onabotulinumtoxinA compared to placebo for major depressive disorder.[66,] This was a 24-week, two-dose cohort parallel-group study of 30 units (U) and 50 U botulinum toxin in outpatient female patients. The primary endpoint was the change in Montgomery-Åsberg Depression Rating Scale (MADRS); secondary endpoints were Clinical Global Impressions-Severity and 17-item Hamilton Depression Rating Scale (HDRS) at week 6. Following a single-treatment session, neither 30 U nor 50 U botulinum toxin injections demonstrated statistically significant superiority over placebo at the primary endpoint, but 30 U injection showed consistent numerical improvement in depressive symptoms compared to placebo up to week 15 with statistical separation from placebo for MADRS changes at weeks 3 and 9. Botulinum toxin was generally well-tolerated: the only treatment-emergent adverse events reported in ≥5% in either botulinum toxin group, and more than matching placebo were headache, upper respiratory infection, and eyelid ptosis. Limitations of this study included a relatively small sample size in each treatment group, lack of generalizability to male patients, and the study design, which effectively created two parallel studies with different treatment sites and different investigators.

Magid et al (2015) published a pooled analysis[67,] of individual patient data from 3 previous RCTs (2012, 2014a, 2014b) [68,69,70,] evaluating injections of onabotulinumtoxinA in the glabellar region (forehead) for treating unipolar major depressive disorder as an adjunctive treatment. The response rate (defined as ≥50% improvement from baseline 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 HDRS, ≤10 for the MADRS) 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,[69,] short duration

of follow-up in 2 out of 3 RCTs,[69,68,] lack of clarity on allocation concealment,[68,69,70,] 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.

Facial Wound Healing

Jiang et al (2025) conducted a meta-analysis of 12 randomized trials (N=351) evaluating perioperative botulinum toxin type A to prevent or improve scars after facial surgery or trauma.[71,] Across trials, pooled effects favored botulinum toxin A on several outcomes: VAS appearance improved (SMD, 1.00; 95% CI, 0.47 to 1.53; I^2=84.5%; p=.005), Vancouver Scar Scale decreased (SMD, -0.41; 95% CI, -0.73 to -0.10; I^2=43.6%; p=.039), Observer Scar Assessment Scale decreased (SMD, -0.61; 95% CI, -1.00 to -0.13; I^2=0%; p=.039), and scar width was smaller (SMD, -1.00; 95% CI, -1.20 to -0.80; I^2=0%; p<.05); Patient Scar Assessment Scale showed no difference (SMD, -0.08; 95% CI, -0.56 to 0.39). Adverse events appeared similar to those in the control group (RR, 1.74; 95% CI, 0.41 to 7.43). High study heterogeneity and variable methods, coupled with predominantly underpowered studies, underscore the need for more rigorously designed RCTs.

Fu et al (2022) conducted a meta-analysis of 16 RCTs (N=510 patients) to evaluate the efficacy and safety of botulinum toxin A for preventing scarring.[72,] The outcomes were primarily quantified by measures including the Vancouver Scar Scale (VSS), VAS, Stony Brook Scar Evaluation Scales (SBSES), modified SBSES (mSBSES), and scar width. Patients' satisfaction and adverse events were also reported. Results showed significant superiority of botulinum toxin compared to placebo in VSS (MD, -1.32; 95% CI, -2.00 to -0.65, p=.0001), VAS (1.29; 95% CI, 1.05 to 1.52, p<.00001), SBSES or mSBSES (-0.18; 95% CI, -0.27 to -0.10, p<.0001), scar width (-0.18; 95% CI, -0.27 to -0.10, p<.0001), and patients' satisfaction (risk ratio [RR], 1.25; 95% CI, 1.06 to 1.49, p=.01). No significant difference of adverse events incidence was observed (p=.36). Despite these results, the review has several study limitations including small sample size hindering detailed subgroup analyses, publication bias, and lack of a standardized treatment algorithm. Further large-scale and well-designed RCTs are needed to assess the long-term efficacy and safety of botulinum toxin for facial post-operative scar prevention and wound healing improvements.

Section Summary: Miscellaneous conditions

Botulinum toxin has been evaluated as a treatment option for multiple neurological, urological, pain, gastrointestinal disorders , 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 (eg, benign prostatic hyperplasia, low back pain, depression, tinnitus), 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.

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 Society for Gastrointestinal Endoscopy

In 2020, the American Society for Gastrointestinal Endoscopy (ASGE) guideline on the management of achalasia recommended against the use of botulinum toxin injection as definitive therapy for achalasia patients. Botulinum toxin injection may be reserved for patients who are not candidates for other definitive therapies (Grade of Recommendation: moderate quality evidence).[73,]

American Urological Association

In 2019, the American Urological Association guideline on non-neurogenic overactive bladder stated, "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)."[74,]

In 2022, the American Urological Association guideline on diagnosis and treatment of interstitial cystitis/bladder pain syndrome stated, "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)".[30,] Options are non-directive statements that leave the decision to take an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears relatively equal or appears unclear; options may be supported by Grade A (high certainty), B (moderate certainty), or C (low certainty) evidence.

In 2024, the American Urological Association and Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction published a guideline on the diagnosis and treatment of idiopathic overactive bladder stated, "In patients with OAB who have an inadequate response to, or have experienced intolerable side effects from, pharmacotherapy or behavioral therapy, clinicians should offer sacral neuromodulation, percutaneous tibial nerve stimulation, and/or intradetrusor botulinum toxin injection. (Moderate Recommendation; Evidence Level: Grade A)." It further emphasized, "Clinicians should measure post-void residual in patients with OAB prior to intradetrusor botulinum toxin therapy. (Clinical Principle)" and "Clinicians should obtain a post-void residual in patients with OAB whose symptoms have not adequately improved or worsened after intradetrusor botulinum toxin injection. (Clinical Principle)." [75,]

American Academy of Neurology

The American Academy of Neurology updated their practice guideline on use of botulinum toxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and chronic headache in 2016 (reaffirmed April 30, 2022).[76,] Recommendations are summarized in Table 10.

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

Recommendation	LOR
Blepharospasm	
• OnabotulinumtoxinA and incobotulinumtoxinA injections should be considered • AbobotulinumtoxinA may be considered	B C
Cervical dystonia	
• AbobotulinumtoxinA and rimabotulinumtoxinB should be offered • OnabotulinumtoxinA and incobotulinumtoxinA should be considered	A B
Focal manifestations of adult spasticity involving the upper limb	
• 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

Recommendation	LOR
For focal manifestations of adult spasticity involving the lower limb	
• 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
Headache	
• 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 April 30, 2022), 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.[77,]

American Society of Colon and Rectal Surgeons

The revision of a practice parameter on the treatment of anal fissures by the American Society of Colon and Rectal Surgeons (ASCRS, 2023) 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 moderate-quality evidence, 1B." [78,]According to the 2023 survey conducted by the ASCRS, dose above 50 U of botulinum toxin appeared to correlate with higher success rate and healing rate.[79,]A 2024 guideline on the management and evaluation of chronic constipation states that, "Injecting botulinum toxin into the puborectalis and external sphincter muscle may be considered in patients with outlet dysfunction constipation related to nonrelaxing puborectalis muscle. Strength of recommendation: conditional, based on low-quality evidence." [80,]

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.[81,]

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
Ongoing			
NCT07040813	The Nordic Chronic Migraine Trial of CGRP Monoclonal Antibody and Onabotulinumtoxin A Dual Therapy Compared to CGRP mAbs Monotherapy	450	Apr 2029
NCT06684249	Efficacy of Nerve Block Versus Botox in Chronic Migraine Management	64	Jul 2025
NCT06537700	OnaBotulinumtoxin-A in Chronic Migraine Patients with Short or Long Disease History (the BACH Study)	115	Dec 2025
NCT06315790	Safety and Efficacy of Botulinum Toxin A in Patients With Trigeminal Neuralgia	80	Oct 2025
NCT06886750	The Effects of Waning of Botulinum Toxin in the Treatment of Cervical Dystonia	45	Dec 2027
NCT06047444	A Study to Evaluate the Effectiveness and Safety of Dysport® for the Prevention of Chronic Migraine in Adults	720	Dec 2026
NCT06047457	A Study to Evaluate the Effectiveness and Safety of Dysport® for the Prevention of Episodic Migraine in Adults	714	Dec 2026
NCT03654066	Prospective Single-Blinded Randomized Controlled Trial Comparing Botox or Botox With Esophageal Dilation in Patients With Achalasia	50	Jun 2026
NCT05598164	Botulinum Toxin Type A in the Treatment of Chronic Anal Fissure Without Excision	140	May 2025 (Unknown status)
NCT05590520	A Comparison of Injections of Botulinum Toxin and Topical Nitroglycerin Ointment for the Treatment of Chronic Anal Fissure: A Randomized Controlled Trial	90	Dec 2024 (Unknown status)
NCT03935295	Dysport as an Adjunctive Treatment to Bracing in the Management of Adolescent Idiopathic Scoliosis	90	Mar 2026
NCT05125029	Double Blind RCT to Evaluate the Effect of Botulinum Toxin in Raynaud Phenomenon	36	Dec 2025
NCT05327972	DEgenerative ROtator Cuff Disease and Botulinum TOXin: a Randomized Trial	60	Feb 2027

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

REVISIONS	
10-19-2007	In Policy section: ▪ B.1 replaced "Cerebral Palsy" with "spasticity".
07-18-2008	In Policy section: ▪ Added "F. The off-labeled use of botulinum toxin is considered medically necessary in the treatment of incontinence related to detrusor overactivity due to neurogenic causes (i.e. spinal cord injury), when anticholinergic therapy has failed." as an indication." ▪ Specified H.13. Overactive bladder by adding "except as specified above."
10-19-2009	In Header: ▪ Added reference to related policies of: Treatment of Hyperhidrosis and Treatment of Tinnitus
	Updated Description section.
	In Policy section: ▪ 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.
	In Coding section: ▪ Added CPT codes: 31513, 31570, 31571, 43201, 43236. ▪ Added Diagnosis coding range for urinary incontinence: 788.30-788.39.
01-01-2010	In Coding Section: ▪ Added HCPCS Code: J0586 ▪ Updated wording for HCPCS Code: J0585
02-25-2011	Medical Policy Title updated. ▪ Removed "(i.e. Botox®, Myobloc ®)" to read "Botulinum Toxin (BT)."
	In Policy Language section: ▪ Updated formatting and wording. ▪ Added medically necessary indication #11: "Chronic refractory migraine." ▪ In the investigational indications section, Item #1, removed "including migraine, chronic daily headache, and tension type headache" and added "other than chronic refractory headache" to read "headaches, other than chronic refractory headaches."
	In the Documentation section: ▪ Removed "There must be a stated goal of treatment."
	Rationale section updated.
	In Coding section: ▪ Added CPT code: 64611 (2011 Coding updates) ▪ Added Diagnosis codes: 346.01, 376.03, 346.11, 346.13, .346.21, 346.23, 346.51, 346.53, 346.71, 346.73, 346.91, 346.93.
	Reference section updated.
05-13-2011	In Coding section, added HCPCS code Q2040.
12-09-2011	Updated Description section.
	In the Policy section: • In Item A, #11, inserted "headaches" to read "Chronic refractory migraine headaches" • In Item B, #9, inserted "(see separate policy on Treatment of Tinnitus)"

REVISIONS	
	• In Item B, added the following indications: o "#21. Prevention of pain associated with breast reconstruction after mastectomy o #22. Hirschsprung's disease"
	Removed the Documentation section.
	Removed the Utilization section.
	Added Policy Guidelines section.
	In Coding section: ▪ Added the following CPT/HCPCS codes: 46505, C9278 ▪ Added the following Diagnosis codes: 333.71, 333.79, 333.81, 333.82, 333.83, 333.84, 340, 351.0, 351.1, 351.9, 435.9, 705.21, 754.51, 784.49
	Updated the Rationale section.
	Updated the Reference section.
01-01-2012	In the Policy section: ▪ In Item A, #6, removed "in patients who have not responded to dilation therapy or who are considered poor surgical candidates" to read " Esophageal achalasia"
	In the Coding section: ▪ Removed HCPCS codes: C9278, Q2040 ▪ Added HCPCS code: J0588 ▪ Added Diagnosis codes: 333.71, 333.79, 333.81, 333.82, 333.83, 333.84 (Diagnosis code, 333.7 was replaced with the appropriate codes for the policy.)
01-15-2013	In the Coding section: ▪ Added CPT code: 52287 and 64615 (Effective 01-01-2013) ▪ Updated CPT code 64612 nomenclature (Effective 01-01-2013)
01-30-2014	Updated Description section.
	In Policy section: ▪ In Item A, #9, replaced "(urge incontinence), either idiopathic or due to" with "associated with" to read "Incontinence due to detrusor 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: ▪ Removed CPT codes: 64613 and 64614 *(Deleted codes, effective December 31, 2013)* ▪ Added CPT codes: 64616, 64617, 64642, 64643, 64644, 64645, 64646, 64647*(New codes, effective January 1, 2014)* ▪ Added ICD-10 Diagnosis codes *(Effective October 1,2014)*
	Updated Reference section.
04-15-2014	In Policy section: ▪ In Item B 1 removed the parenthesis around "(migraine)" to read, "headaches other than chronic refractory migraine headaches" In Policy Guidelines: ▪ Added information pertaining to cervical dystonia and chronic migraine.
	In Coding section: ▪ Updated coding instructions.
01-01-2015	In Coding section: ▪ Revised CPT Codes: 43201, 43236 (Effective January 1, 2015)

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02-19-2016	Updated Description section.
	In Policy section: ▪ 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.
	In Coding section: ▪ Removed CPT codes: 64650 and 64653.
	Updated References section.
07-01-2016	Updated Description section.
	In Policy section: ▪ In Item A 10 a, removed "(key criteria include migraine headaches lasting at least 4 hours on at least 15 days per month; migraine headaches for at least 3 months; absence of medication overuse)" and added "(see Policy Guidelines)" to read "Meet International Classification of Headache Disorders (ICHD) diagnostic criteria for chronic migraine headache; and" ▪ In Policy Guidelines, added Item 2.
	Updated Rationale section.
10-01-2016	In Coding section: ▪ Added ICD-10 codes effective 10-01-2016: N39.491, N39.492
03-29-2017	In Policy section:

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	▪ In Item C, removed "may be considered not medically necessary" and added "is noncovered" to read, "The use of botulinum toxin as a treatment of wrinkles or other cosmetic indications is noncovered."
02-15-2018	Updated Description section.
	In Policy section: ▪ In Policy Guidelines, added "Indications and Dosage" table.
	Updated Rationale section.
	In Coding section: ▪ Updated Coding bullets. ▪ ICD-9 codes removed.
	Updated References section.
10-01-2018	In Coding section: ▪ Added ICD-10 codes: G51.31, G51.32, G51.33. ▪ Removed ICD-10 code: G51.3.
	Updated References section.
11-20-2018	Updated Description section.
	In Policy section: ▪ 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.
	In Coding section: ▪ Removed coding bullets.
	Updated References section.
10-11-2019	Policy published 09-11-2019. Policy effective 10-11-2019.
	In Title heading: ▪ Removed "Treatment of Tinnitus" from the *See Also* policies.
	In Policy section: ▪ In Policy Guidelines, added new Item 4, "The safety and efficacy of combination therapy with botulinum toxin and calcitonin gene related peptide (CGRP) has not been studied in the treatment of migraine headache."
	In Coding section: ▪ 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
	In Policy section: ▪ 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: 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

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	e. Symptomatic (acquired) torsion dystonia 3. Upper and lower limb spasticity as well spastic conditions related to: a. Cerebral palsy b. Stroke c. Acquired spinal cord or brain injury d. Hereditary spastic paraparesis e. Spastic hemiplegia f. Neuromyelitis optica g. Multiple sclerosis or Schilder's disease" ▪ 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: 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: "1. Neurological indications such as: 2. Urological indications such as: 3. Pain due to multiple etiologies such as: 4. Ano-rectal conditions such as: 5. Other miscellaneous conditions such as:" ▪ In Item B 1 b removed "such as benign essential tremor (upper extremity)" to read Essential tremor" ▪ In Item B 3 e removed "fibromyalgia / fibromyositis" to read "Myofascial pain syndrome" ▪ In Item B removed "Sialorrhea (drooling) except that associated with Parkinson's disease". ▪ Policy Guidelines updated
	Rationale section updated
	References updated

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12-13-2022	Updated Description Section
	Updated Policy Guideline Section ▪ 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
	Updated Coding Section ▪ 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
	Updated References Section
11-17-2023	Updated Description Section
	Updated Policy Section ▪ Section B3d removed "after neck dissection." Now reads "neuropathic pain"
	Updated Rationale Section
	Updated Coding Section ▪ Removed ICD-10 codes
	Updated References Section
12-03-2024	Updated Description Section
	Updated Rationale Section
	Updated References Section
11-26-2025	Updated Description Section
	Updated Rationale Section
	Updated Reference Section

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