

Medical Policy



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Title: Botulinum Toxin (BT)

*See also: Treatment of Hyperhidrosis
Treatment of Tinnitus*

Professional

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Populations	Interventions	Comparators	Outcomes
Individuals: • With dystonia or spasticity resulting in functional impairment and/or 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
Individuals: • With strabismus	Interventions of interest are: • Botulinum toxin injections	Comparators of interest are: • Conservative measures • Surgery	Relevant outcomes include: • Symptoms • Functional outcomes • Treatment-related morbidity
Individuals: • With blepharospasm or facial nerve (VII) disorders	Interventions of interest are: • Botulinum toxin injections	Comparators of interest are: • Medication • Surgery	Relevant outcomes include: • Symptoms • Functional outcomes • Treatment-related morbidity
Individuals: • With chronic migraine headache	Interventions of interest are: • Botulinum toxin injections	Comparators of interest are: • Complementary treatment (eg, acupuncture) • Medication	Relevant outcomes include: • Symptoms • Medication use • Treatment-related morbidity
Individuals: • With esophageal achalasia	Interventions of interest are: • Botulinum toxin injections	Comparators of interest are: • Pneumatic dilation • Laparoscopic myotomy • Medication	Relevant outcomes include: • Symptoms • Functional outcomes • Treatment-related morbidity
Individuals: • With sialorrhea associated with Parkinson disease	Interventions of interest are: • Botulinum toxin injections	Comparators of interest are: • Medication	Relevant outcomes include: • Symptoms • Functional outcomes • Treatment-related morbidity
Individuals: • With sialorrhea not associated with Parkinson disease	Interventions of interest are: • Botulinum toxin injections	Comparators of interest are: • Medication	Relevant outcomes include: • Symptoms • Functional outcomes • Treatment-related morbidity
Individuals: • With internal anal sphincter achalasia	Interventions of interest are: • Botulinum toxin injections	Comparators of interest are: • Surgery	Relevant outcomes include: • Symptoms • Health status measures • Treatment-related morbidity
Individuals: • With chronic anal fissure	Interventions of interest are: • Botulinum toxin injections	Comparators of interest are: • Surgery	Relevant outcomes include: • Symptoms • Health status measures • Treatment-related morbidity
Individuals: • With urinary incontinence due to detrusor overactivity associated with neurogenic causes or overactive bladder	Interventions of interest are: • Botulinum toxin injections	Comparators of interest are: • Conservative measures • Medication	Relevant outcomes include: • Symptoms • Medication use • Treatment-related morbidity
Individuals: • With urologic issues other than detrusor overactivity or overactive bladder	Interventions of interest are: • Botulinum toxin injections	Comparators of interest are: • Conservative measures • Medication	Relevant outcomes include: • Symptoms • Medication use • Treatment-related morbidity
Individuals: • With other indications (eg, musculoskeletal pain, postsurgical pain, neuropathic pain, tremors)	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*. Four formulations of botulinum toxin have been approved by the U.S. Food

and Drug Administration (FDA). Labeled indications of these agents differ; however, all are FDA-approved for treating cervical dystonia in adults. Botulinum toxin products are also used for a range of off-label indications.

OBJECTIVE

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

BACKGROUND

Botulinum Toxins

There are 7 distinct botulinum serotypes designated as type A, B, C-1, D, E, F, and G. In the United States, 4 preparations of botulinum are commercially available, three using type A serotype and one using type B. The brand names of the botulinum toxin products were changed in 2009; trade names and product formulations did not. The 3 formulations of botulinum toxin type A are currently called onabotulinumtoxinA (Botox), abobotulinumtoxinA (Dysport), and incobotulinumtoxinA (Xeomin). Botox has been available on the U.S. market the longest and has been the most widely used formulation. Xeomin, the newest product marketed in the United States, consists of the pure neurotoxin without complexing proteins and is the only product stable at room temperature for up to 4 years. RimabotulinumtoxinB contains botulinum toxin type B, currently marketed as Myobloc.

Among the botulinum toxin products, onabotulinumtoxinA (Botox) is approved by the Food and Drug Administration (FDA) for the most indications. FDA-approved indications for the various botulinum toxin products are summarized in Table 1.

Table 1. FDA-Indications of Botulinum Toxin Products^a

Drug	FDA-Approved Indications
Botox	<ul style="list-style-type: none"> • Treatment of 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 • Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition in adults who have an inadequate response to or are intolerant of an anticholinergic medication • Prophylaxis of headaches in adults with chronic migraine (≥ 15 d/mo with headache lasting 4 hours a day or longer) • Treatment of spasticity in adults • Treatment of cervical dystonia in adults to reduce the severity of abnormal head position and neck pain • Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adults • Treatment of blepharospasm associated with dystonia in patients ≥ 12 years of age • Treatment of strabismus in patients ≥ 12 years of age <p>Safety and effectiveness has not been established for:</p> <ul style="list-style-type: none"> • Prophylaxis of episodic migraine (14 headache days or fewer per month) • Treatment of upper- or lower-limb spasticity in pediatric patients • Treatment of hyperhidrosis in body areas other than axillary
Dysport	<ul style="list-style-type: none"> • Treatment of cervical dystonia in adults • Treatment of spasticity in adults • Treatment of lower-limb spasticity in pediatric patients ≥ 2 years of age
Xeomin	<ul style="list-style-type: none"> • Treatment of cervical dystonia in adults • Treatment of upper-limb spasticity in adult patients • Treatment of blepharospasm with onabotulinumtoxinA prior treatment in adults • Treatment of chronic sialorrhea in adults

Drug	FDA-Approved Indications
Myobloc	• Treatment of cervical dystonia in adults to reduce the severity of abnormal head position and neck pain

FDA: 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 may be greatest in children treated for spasticity but symptoms can also occur in adults.

Three products, Botox (marketed as Botox Cosmetic), Dysport, and Xeomin are approved for temporarily improving the appearance of glabellar (frown) lines in adults.

The botulinum toxin products have also been used for a wide variety of off-label indications.

In rare cases, patients do not respond to botulinum toxin (primary resistance), and a small percentage of adults develop secondary resistance after long-term treatment. Reasons for resistance include injection of incorrect muscles, unrealistic expectations of a complete cure, and interference from associated disorders that mask perception of response.¹ In 3% to 10% of adults, true secondary resistance arises due to the development of antibodies that specifically neutralize the activity of botulinum toxin (eg,^{2,3}). That neutralizing antibodies directly cause resistance has been shown in a case study in which a patient with severe dystonia, secondary resistance, and detectable neutralizing antibodies was treated with repeated plasma exchange and depletion of serum antibodies; subsequent treatment with the same botulinum toxin type was successful.⁴ Non-neutralizing antibodies may also develop in patients but have no effect on outcomes. The predisposing factors are not completely understood but include the use of higher doses, shorter intervals between repeat treatments, and younger age.⁵ In 2 studies of pediatric patients treated for spasticity, neutralizing antibodies were detected in 28% to 32% of patients.^{6,7} Recommendations for avoiding eventual resistance are using the lowest dose possible to obtain a clinical response and scheduling intervals of 10 to 12 weeks between injections, if possible.

Patients who develop secondary resistance to botulinum toxin type A may stop treatment for several months and then undergo retreatment with likely success; however, the duration of response is often short, because neutralizing antibodies may redevelop quickly.⁸ Alternatively, the patient may be administered botulinum toxin type B, with which neutralizing antibodies to toxin type A will not interfere. However, the duration of effect is shorter, and adverse effects have occurred at higher frequencies than for botulinum toxin type A.^{5,9}

Confirmation of neutralizing antibodies to botulinum toxin type A in research studies (mice) has most often been accomplished using 2 techniques: (1) an injection of patient serum¹⁰ or (2) an in vitro toxin-neutralizing assay based on a mouse diaphragm nerve-muscle preparation.¹¹ While sensitive, neither assay is appropriate for a clinical laboratory setting. Other assay formats have been explored, such as immunoprecipitation, Western blot, and enzyme-linked immunosorbent assay. However, unless only the protein sequences that specifically react with neutralizing antibodies are employed, these formats detect both neutralizing and non-neutralizing antibodies,^{6,12,13} and would therefore result in significant

numbers of false-positive results. An option for some patients might be to inject toxin into the frontal muscle above 1 eyebrow; a toxin-responsive patient would have asymmetry of the forehead on attempted frowning, whereas a nonresponsive patient would not.¹³

REGULATORY STATUS

In 1991, Botox® (Allergan) was approved by the U.S. Food and Drug Administration (FDA). In 2000, Myobloc® (Solstice Neurosciences) was approved by FDA. In 2009, Dysport® (Medicis Pharmaceutical, now Ipsen Biopharm) was approved by FDA. In 2010, Xeomin® (Merz Pharmaceuticals) was approved by FDA.¹⁴

POLICY

- A. The use of botulinum toxin may be considered **medically necessary** for the following:
1. Cervical dystonia (spasmodic torticollis; applicable whether congenital, due to child birth injury, or traumatic injury). For this use, cervical dystonia must be associated with sustained head tilt or abnormal posturing with limited range of motion in the neck AND a history of recurrent involuntary contraction of one or more of the muscles of the neck, eg, sternocleidomastoid, splenius, trapezius, or posterior cervical muscles. (See additional details in Policy Guidelines.)
 2. Strabismus.
 3. Blepharospasm or facial nerve (VII) disorders (including hemifacial spasm).
 4. Upper limb spasticity.
 5. Dystonia/spasticity resulting in functional impairment (interference with joint function, mobility, communication, nutritional intake) and/or pain in patients with any of the following:
 - a. Focal dystonias:
 - Focal upper limb dystonia (eg, organic writer's cramp), or
 - Oromandibular dystonia (orofacial dyskinesia, Meige syndrome), or
 - Laryngeal dystonia (adductor spasmodic dysphonia), or
 - Idiopathic (primary or genetic) torsion dystonia, or
 - Symptomatic (acquired) torsion dystonia.
 - b. Spastic conditions:
 - Cerebral palsy, or
 - Spasticity related to stroke, or
 - Acquired spinal cord or brain injury, or
 - Hereditary spastic paraparesis, or
 - Spastic hemiplegia, or
 - Neuromyelitis optica, or
 - Multiple sclerosis or Schilder's disease.
 6. Esophageal achalasia in patients who have not responded to dilation therapy or who are considered poor surgical candidates.
 7. Sialorrhea (drooling) associated with Parkinson's disease.

8. Chronic anal fissure.
 9. Urinary incontinence due to detrusor overreactivity associated with neurogenic causes (eg, spinal cord injury, multiple sclerosis) in patients unresponsive to or intolerant of anticholinergics.
 10. Prevention (treatment) of chronic migraine headache in the following situations:
 - a. Initial 6-month trial. Adult patients who:
 - Meet International Classification of Headache Disorders (ICHD) diagnostic criteria for chronic migraine headache (see Policy Guidelines); 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 (eg, antidepressants, antihypertensives, antiepileptics). Patients who have contraindications to preventive medications are not required to undergo a trial of these agents.
 - b. Continuing treatment beyond 6 months:
 - Migraine headache frequency reduced by at least 7 days per month compared with pretreatment level, or
 - Migraine headache duration reduced at least 100 hours per month compared with pretreatment level.
 11. Overactive bladder in adults unresponsive to or intolerant of anticholinergics.
- 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. Headaches, except as noted above for prevention (treatment) of chronic migraine headache.
 2. Chronic low back pain.
 3. Joint pain.
 4. Mechanical neck disorders.
 5. Neuropathic pain after neck dissection.
 6. Myofascial pain syndrome / fibromyalgia / fibromyositis.
 7. Pain after hemorrhoidectomy or lumpectomy.
 8. Tremors such as benign essential tremor (upper extremity).
 9. Tinnitus (see separate policy, *Treatment of Tinnitus*).
 10. Sialorrhea (drooling) except that associated with Parkinson's disease.
 11. Chronic motor tic disorder, and tics associated with Tourette's syndrome (motor tics).
 12. Lateral epicondylitis.
 13. Benign prostatic hyperplasia.
 14. Interstitial cystitis.
 15. Detrusor sphincteric dyssynergia (after spinal cord injury).
 16. Anismus.
 17. Gastroparesis.

18. Prevention of pain associated with breast reconstruction after mastectomy.
 19. Hirschsprung's disease.
 20. Facial wound healing.
 21. Internal anal sphincter (IAS) achalasia.
 22. Temporomandibular joint disorders.
 23. Trigeminal neuralgia.
 24. Depression.
- C. The use of botulinum toxin as a treatment of wrinkles or other cosmetic indications is **noncovered**.
- D. The use of assays to detect antibodies to botulinum toxin is considered **experimental / investigational**.

Policy Guidelines

1. Cervical dystonia is a movement disorder (nervous system disease) characterized by sustained muscle contractions. This results in involuntary, abnormal, squeezing and twisting muscle contractions in the head and neck region. These muscle contractions result in sustained abnormal positions or posturing. Sideways or lateral rotation of the head and twisting of the neck is the most common finding in cervical dystonia. Muscle hypertrophy occurs in most patients. When using botulinum toxin to treat cervical dystonia, the postural disturbance and pain must be of a severity to interfere with activities of daily living; and the symptoms must have been unresponsive to a trial of standard conservative therapy. In addition, before using botulinum toxin, alternative causes of symptoms such as cervicogenic headaches must have been considered and excluded.
2. International Classification of Headache Disorders (ICHD-3) diagnostic criteria for chronic migraine headache include the following:
 - a. Headaches at least 15 days per month for more than 3 months; have features of migraine headache on at least 8 days.
 - b. Features of migraine headache:
 - Lasts 4 to 72 hours;
 - Has at least 2 of the following 4 characteristics:
 - Unilateral
 - Pulsating
 - Moderate or severe pain intensity
 - Aggravates or causes avoidance of routine physical activity
 - Associated with:
 - Nausea and/or vomiting
 - Photophobia and photophobia

(In ICHD-2, absence of medication overuse was one of the diagnostic criteria for chronic migraine. In the ICHD-3, this criterion was removed from the chronic migraine diagnosis and "medication overuse headache" is now a separate diagnostic category.)

3. Continuing treatment with botulinum toxin beyond 6 months for chronic migraine: The policy includes the requirement that migraine headache frequency be reduced by at least 7 days per month compared to pretreatment level, or that migraine headache duration be reduced by at least 100 hours per month compared to 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 (15) that would allow them to meet the ICHD-2 diagnostic criteria for chronic migraine. A 50% reduction in frequency is a common outcome measure for assessing the efficacy of headache treatments and is one of the endpoints of the PREEMPT study.

FDA Labeled Indications and Dosage¹⁻⁴

Agent	FDA Labeled Contraindications	Dosing and Administration
Botox® (onabotulinum toxin A)	<ul style="list-style-type: none"> • Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication • Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication • Prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer) • Treatment of spasticity in adult patients • Treatment of cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain • Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients • Treatment of blepharospasm associated with dystonia in patients ≥12 years of age • Treatment of strabismus in patients ≥12 years of age <p>Important Limitations: Safety and effectiveness of BOTOX have not been established for:</p> <ul style="list-style-type: none"> • Prophylaxis of episodic migraine (14 headache days or fewer per month) • Treatment of upper or lower limb spasticity in pediatric patients • Treatment of hyperhidrosis in body areas other than axillary 	<ul style="list-style-type: none"> • Overactive Bladder: Recommended total dose 100 Units, as 0.5 mL (5 Units) injections across 20 sites into the detrusor • Detrusor Overactivity associated with a Neurologic Condition: Recommended total dose 200 Units, as 1 mL (~6.7 Units) injections across 30 sites into the detrusor • Chronic Migraine: Recommended total dose 155 Units, as 0.1 mL (5 Units) injections per each site divided across 7 head/neck muscles • Upper Limb Spasticity: Select dose based on muscles affected, severity of muscle activity, prior response to treatment, and adverse event history; Electromyographic guidance recommended • Lower Limb Spasticity: Recommended total dose 300 Units to 400 Units divided across ankle and toe muscles • Cervical Dystonia: Base dosing on the patient's head and neck position, localization of pain, muscle hypertrophy, patient response, and adverse event history; use lower initial dose in botulinum toxin naïve patients • Axillary Hyperhidrosis: 50 Units per axilla • Blepharospasm: 1.25 Units-2.5 Units into each of 3 sites per affected eye • Strabismus: The dose is based on prism diopter correction or previous response to treatment with BOTOX

Agent	FDA Labeled Contraindications	Dosing and Administration
Dysport® (abobotulinum toxin A)	<ul style="list-style-type: none"> • Treatment of adults with cervical dystonia • Temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients < 65 years of age • Treatment of spasticity in adults • Treatment of lower limb spasticity in pediatric patients 2 years of age and older 	<ul style="list-style-type: none"> • Cervical dystonia: initial dose 500 units IM divided among affected muscles; re-treat every 12 – 16 weeks or long • Glabellar lines: total dose of 50 units IM no more than every 3 months • Spasticity: upper limb 500 Units to 1000 Units; lower limb up to 1500 Units; should not occur in intervals of less than 12 weeks • Lower limb spasticity in pediatric patients: 10 – 15 Units/kg per limb
Myobloc® (rimabotulinum toxin B)	<ul style="list-style-type: none"> • Treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia 	Patients previously tolerating botulinum toxin injections: 2,500 to 5,000 units divided among affected muscles
Xeomin® (incobotulinum toxin A)	Treatment or improvement of adult patients with: <ul style="list-style-type: none"> • upper limb spasticity • cervical dystonia • blepharospasm with onabotulinumtoxinA (Botox®) prior treatment • temporary improvement in the appearance of moderate to severe glabellar lines with corrugator and/or procerus muscle activity 	<ul style="list-style-type: none"> • Upper Limb Spasticity in Adults: recommended total dose is up to 400 Units no sooner than every 12 weeks • Cervical Dystonia: recommended initial total dose is 120 Units per treatment session • Blepharospasm: base initial dosing on previous dosing for onabotulinumtoxinA (Botox); if not known, the recommended starting dose is 1.25 Units-2.5 Units per injection site • Glabellar Lines: recommended dose is 20 Units per treatment session divided into five equal intramuscular injections of 4 Units each (two injections in each corrugator muscle and one injection in the procerus muscle; wait a minimum of three months before retreatment)

RATIONALE

This policy was originally created in 1997 and was updated regularly with searches of the MEDLINE database. Most recently, the literature was reviewed through August 6, 2018. For studies published before 2000, it is assumed that Botox, the only FDA-approved agent at that time, was used.

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

Study Selection Criteria

Methodologically credible studies were selected for all indications 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 longer 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.

Dystonia or Spasticity

Clinical Context and Therapy Purpose

The purpose of botulinum toxin in patients who have dystonia or spasticity resulting in functional impairment and/or pain is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does use of botulinum toxin improve the net health outcome in patients with dystonia or spasticity resulting in functional impairment and/or pain?

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

Patients

The relevant population of interest is individuals with dystonia or spasticity resulting in functional impairment and/or pain.

Interventions

The therapy being considered is botulinum toxin.

Comparators

The following therapies are currently being used to treat dystonia or spasticity: conservative measures and medications (eg, levodopa, anticholinergic drugs, tetrabenazine, clonazepam, baclofen, zolpidem, dopamine receptor blockers).

Outcomes

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

Timing

Follow-up ranges from 8 to 12 weeks to assess outcomes.

Setting

Patients with dystonia or spasticity may be managed by neurologists; botulinum toxin is administered via intramuscular injection in an outpatient setting.

Systematic Reviews

A Cochrane review by Castelão et al (2017), which was an update of a Cochrane Review first published in 2005, identified 8 double-blind RCTs (total N=1010 patients) with moderate overall risk of bias that compared the efficacy and safety of botulinum toxin type A with placebo in cervical dystonia.¹⁵ The primary efficacy outcome was reductions in cervical dystonia-specific impairment. The primary safety outcome was the proportion of participants with any adverse event. All RCTs evaluated the effect of a single botulinum toxin type A treatment session, using doses from 150 to 236 U of onabotulinumtoxinA (Botox), 120 to 240 U of incobotulinumtoxinA (Xeomin), or 250 to 1000 U of abobotulinumtoxinA (Dysport). Treatment resulted in reduction of 8.06 points (95% confidence interval [CI], 6.08 to 10.05; $I^2=0\%$) on the Toronto Western Spasmodic Torticollis Rating Scale at week 4 after injection compared with placebo. While there were no differences in withdrawals due to adverse events between the active and placebo treatment groups, botulinum toxin type A was associated with an increased risk of an adverse event (relative risk [RR], 1.19; 95% CI, 1.03 to 1.36; $I^2=16\%$) with dysphagia (9%) and diffuse weakness/tiredness (10%) the most common treatment-related adverse events.

A systematic review and meta-analysis by Dong et al (2017) identified 22 RCTs (total N=1804 participants) that evaluated the efficacy of botulinum toxin type A for upper-limb spasticity after stroke or traumatic brain injury.¹⁶ Compared with placebo, botulinum toxin type A treatment resulted in decrease of muscle tone after week 4 (standardized mean difference [SMD], -0.98; 95% CI, -1.28 to -0.68; $I^2=66\%$, $p=0.004$), week 6 (SMD = -0.85; 95% CI, -1.11 to -0.59; $I^2=1.2\%$; $p=0.409$), week 8 (SMD = -0.87; 95% CI, -1.15 to -0.6; $I^2=0\%$, $p=0.713$), week 12 (SMD = -0.67; 95% CI, -0.88 to -0.46; $I^2=0\%$; $p=0.896$), and week 12 (SMD = -0.73; 95% CI, -1.21 to -0.24; $I^2=63.5\%$; $p=0.065$). A systematic review and meta-analysis by Baker and Pereira (2016) identified 25 RCTs that evaluated the efficacy of botulinum toxin type A for limb spasticity on reducing activity restriction and improving quality of life (QOL) outcomes.¹⁷ Reviewers reported pooled analysis for 6 RCTs that included upper- and lower-limb trials but were unable to pool studies for QOL measures. Evidence quality for the upper-limb was low/very low. Pooled results showed a significant increase in active function with botulinum toxin type A at 4 to 12 weeks for the upper-limb (SMD=0.32; 95% CI, 0.01 to 0.62; $p=0.04$) and these effects were maintained for up to 6 months (mean difference [MD], 1.87; 95% CI, 0.53 to 3.21; $p=0.006$). Reviewers reported no conclusion for efficacy in lower-limb or for QOL measures in either limb.

A Cochrane review of 4 RCTs (total N=441 participants) by Marques et al (2016) compared botulinum toxin type B with placebo in cervical dystonia.¹⁸ The primary efficacy outcome was overall improvement on any validated symptomatic rating scale. All trials evaluated the effect of a single treatment session using doses between 2500 U and 10,000 U. Compared with placebo,

botulinum toxin type B was associated with an improvement of 14.7% (95% CI, 9.8% to 19.5%) in patients' baseline clinical status with a placebo-corrected reduction of 2.2 points (95% CI, 1.25 to 3.15 points) in the Toronto Western Spasmodic Torticollis Rating Scale at week 4 after injection.

Another Cochrane review of 3 RCTs by Duarte et al (2016) compared botulinum toxin type A with botulinum toxin type B in cervical dystonia.¹⁹ The primary efficacy outcome was improvement on any validated symptomatic rating scale, and the primary safety outcome was the proportion of participants with adverse events. All trials evaluated the effect of a single treatment session using multiple dosing regimens. Reviewers reported no difference between the 2 types of botulinum toxin in terms of overall efficacy or safety.

A systematic review by Dashtipour et al (2015) identified 16 RCTs and noncomparative controlled studies evaluating abobotulinumtoxinA in adults with upper-limb spasticity due to stroke.²⁰ Total botulinum toxin dose ranged from 500 to 1500 U. Reviewers did not pool study findings, but did report that most studies found a statistically significant benefit of botulinum toxin for functioning (as measured by the Modified Ashworth Scale).

A systematic review and meta-analysis by Marsh et al (2014) identified 18 studies evaluating botulinum toxin type A for treatment of cervical dystonia; five were RCTs, and the remainder were observational studies.²¹ A pooled analysis found the mean duration of effect of botulinum toxin to be 93.2 days (95% CI, 91.8 to 94.6 days) using the fixed-effects model, and 95.2 days (95% CI, 88.9 to 101.4 days) using the random-effects model. Most studies included did not have control groups.

In a systematic review, Foley et al (2013) identified 16 RCTs comparing injection of botulinum toxin with placebo injections or a nonpharmacologic treatment of moderate-to-severe upper-extremity spasticity following stroke.²² Studies evaluated the impact of treatment on activity limitations. Ten trials (total N=1000 patients) had data suitable for pooling. In a pooled analysis of effect size, botulinum toxin was associated with a moderate treatment effect compared with other interventions (SMD=0.54; 95% CI, 0.35 to 0.71; $p<0.001$). In another systematic review, Baker et al (2013) pooled RCT data and found a statistically significant benefit of botulinum toxin type A for treating limb spasticity.²³ Evidence was limited on botulinum toxin for spasticity-related pain.

This evidence review section is based on a TEC Assessment (1996, updated 2004) that focused on the use of botulinum toxin for the treatment of focal dystonia or spasticity, the American Academy of Neurology (AAN) 2008 assessment of movement disorders and spasticity,²⁴⁻²⁷ and additional controlled trials and systematic reviews identified by MEDLINE literature searches.

The AAN assessment concluded that the evidence was AAN level A (established as effective, should be done) for equinus varus deformity in children with cerebral palsy and AAN level B (probably effective, should be considered) for upper extremity, for adductor spasticity, and for pain control in conjunction with adductor-lengthening surgery in children with cerebral palsy. The evidence was rated level B for treatment of adult spasticity in the upper- and lower-limb for reducing muscle tone and improving passive function, but insufficient evidence to recommend an optimum technique for muscle localization at the time of injection. The evidence was rated level B for upper-limb focal dystonia but insufficient for lower-limb focal dystonia, and was rated level B for adductor laryngeal dystonia but insufficient for abductor laryngeal dystonia.²⁷

Randomized Controlled Trials

Poststroke-Related Spasticity

Wein et al (2018) reported on the results of a double-blind RCT that evaluated the efficacy and safety of onabotulinumtoxinA in adults (n=468) with poststroke lower-limb spasticity.²⁸ The primary end point was change in Modified Ashworth Scale score from baseline between onabotulinumtoxinA and placebo arm at approximately 12-week intervals. Injections were into the ankle plantarflexors (onabotulinumtoxinA 300 U into ankle plantarflexors; ≤ 100 U, optional lower-limb muscles). Of 468 enrolled, 413 (88%) completed the trial. At the end of blinded phase at 4 to 6 weeks, there were small but statistically significant improvements with onabotulinumtoxinA during for the primary end point (onabotulinumtoxinA, -0.8; placebo, -0.6, $p=0.01$).

Wissel et al (2016) assigned 273 poststroke adults to a 22- to 34-week treatment with onabotulinumtoxinA or placebo and subsequently open-label onabotulinumtoxinA up to 52 weeks.²⁹ End points included change in pain and responder analysis (defined as proportion of patients with baseline pain ≥ 4 achieving a $\geq 30\%$ improvement in pain and a $\geq 50\%$ improvement in pain interference with work at week 12). Mean pain reduction from baseline at week 12 was -0.77 (95% CI, -1.14 to -0.40) with onabotulinumtoxinA compared with -0.13 (95% CI, -0.51 to 0.24; $p<0.05$) with placebo. Respective proportion of responders was 53.7% and 37.0%.

A double-blind RCT published by Gracies et al (2015) assigned 243 adults with a stroke or brain trauma in the last 5 months to a single injection of abobotulinumtoxinA 500 U (n=81) or 1000 U (n=81) or placebo (n=81).³⁰ The primary end point was the change in muscle tone in the primary target muscle group from baseline to 4 weeks as measured by Modified Ashworth Scale (MAS). At both doses, abobotulinumtoxinA resulted in greater tone reduction as evidenced by statistically significant reduction in placebo-corrected MAS scores from baseline to week 4 (abobotulinumtoxinA 500 U group, -0.9; 95% CI -1.2 to -0.6; $p<0.001$; abobotulinumtoxinA 1000 U group, -1.1; 95% CI, -1.4 to -0.8; $p<0.001$ vs placebo).

Shaw et al (2011) randomized 333 patients with poststroke upper-limb spasticity to physical therapy plus Dysport (n=170) or to physical therapy alone (n=163).³¹ The primary outcome, improved function at 1 month according to the Action Research Arm Test, did not differ significantly among groups. Improved function using Action Research Arm Test scores also did not differ significantly between groups at 3 or 12 months. Change in muscle tone, based on mean change in the Motor Assessment Scale score significantly favored the Dysport group (-0.6) over the placebo group (-0.1) at 1 month ($p<0.001$), but not at 3 and 12 months.

Other RCTs have shown that botulinum toxin injection improves outcomes in patients with poststroke upper-limb spasticity.³²

Cerebral Palsy

Most trials that established the efficacy of abobotulinumtoxinA in treating focal spasticity in patients with cerebral palsy have been small. Delgado et al (2016) reported on a relatively larger RCT in which 249 cerebral palsy children with dynamic equinus foot deformity were randomized to abobotulinumtoxinA 10 or 15 U/kg per leg, or placebo.³⁴ The primary outcome measure was change in MAS score from baseline to week 4. Of the 246 patients randomized, 226 completed the trial and analysis included 235 (98%) patients. Results showed that both doses of abobotulinumtoxinA resulted in greater improvement in placebo-corrected MAS scores (-0.49; 95% CI, -0.75 to -0.23; $p<0.001$; -0.38; (95% CI, -0.64 to -0.13; $p=0.003$ respectively).

Section Summary: Dystonia and Spasticity

Multiple RCTs and systematic reviews with meta-analyses have supported the efficacy of botulinum toxin for treating dystonia and spasticity.

Strabismus

Strabismus is a condition in which the eyes are not in proper alignment.

Clinical Context and Therapy Purpose

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

The question addressed in this evidence review is: Does use of botulinum toxin improve the net health outcome in patients with strabismus?

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

Patients

The relevant population of interest is individuals with strabismus.

Interventions

The therapy being considered is botulinum toxin.

Comparators

The following therapies are currently being used to treat strabismus: initial conservative management of strabismus addresses vision impairment caused by amblyopia and therapy may include the refractive error correction with prescription of glasses or contact lenses and/or occlusion therapy or pharmacologic or optical penalization of the preferred eye. In addition, surgical procedures may be necessary to correct conditions that obstruct the visual axis (eg, cataract, ptosis, hemangioma).

Outcomes

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

Timing

Follow-up ranges from 6 months to 1 year to monitor outcomes.

Setting

Patients with strabismus may be managed by neurologists; botulinum toxin is injected into selected extraocular muscles to reduce the misalignment of the eyes in an outpatient setting.

Systematic Reviews

A Cochrane review by Rowe and Noonan (2012) evaluated the literature on botulinum toxin for strabismus.³⁵ Reviewers identified 4 RCTs, all of which were published in the 1990s. Three trials compared botulinum toxin injection with surgery, and one compared botulinum toxin injection with a noninvasive treatment control group. Among the trials that used surgery as a comparator, two found no statistically significant differences in outcomes between groups, and one found a higher

rate of a satisfactory outcome in the surgery group (defined as <8 prism diopters). The trial comparing botulinum toxin with no intervention did not find a significant difference in outcomes in the 2 groups. Complications after botulinum toxin included transient ptosis and vertical deviation; combined complication rates ranged from 24% to 56% in the studies.

Randomized Controlled Trials

For patients who failed prior surgery, Tejedor and Rodriguez (1999) conducted a trial that included 55 children with strabismus who remained symptomatic after surgical alignment.³⁶ Patients were randomized to a second surgery (28 patients) or botulinum toxin injection (n=27). Motor and sensory outcomes did not differ significantly in the 2 groups. For instance, at 3 years, 67.8% of children in the reoperation group and 59.2% of children in the botulinum toxin group were within 8 prism diopters of orthotropias (p=0.72). Lee et al (1994) randomized 47 patients with acute unilateral sixth nerve palsy to botulinum toxin treatment or a no treatment control group.³⁷ The final recovery rate was 20 (80%) of 25 in the botulinum toxin group and 19 (86%) of 22 in the control group.

Section Summary: Strabismus

Several RCTs from the 1990s have reported mixed results on the efficacy of botulinum toxin for strabismus. This evidence has not established that botulinum toxin improves outcomes for patients with strabismus. However, treatment for strabismus is a noninvasive alternative to surgery.

Blepharospasm

Blepharospasm is a progressive neurologic disorder characterized by involuntary contractions of the eyelid muscles; it is classified as a focal dystonia.

Clinical Context and Therapy Purpose

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

The question addressed in this evidence review is: Does use of botulinum toxin improve the net health outcome in patients with blepharospasm?

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

Patients

The relevant population of interest is individuals with blepharospasm.

Interventions

The therapy being considered is botulinum toxin.

Comparators

The following therapies are currently being used to treat blepharospasm: medication (ie, zolpidem) or surgery.

Outcomes

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

Timing

Follow-up ranges from 4 to 8 weeks to monitor outcomes.

Setting

Patients with blepharospasm may be managed by neurologists; botulinum toxin is injected into select eyelid muscles in an outpatient setting.

Systematic Reviews

Dashtipour et al (2015) reported on the results of a systematic review that evaluated 5 RCTs (374 patients with blepharospasm, 172 patients with hemifacial spasm) of abobotulinumtoxinA.³⁸ All trials showed statistically significant benefits for the treatment of blepharospasm and hemifacial spasm.

Randomized Controlled Trials

RCTs have evaluated Botox, Dysport, and Xeomin for the treatment of blepharospasm and found these agents to be effective at improving symptoms.³⁹⁻⁴¹ No RCTs evaluating Myobloc for treating blepharospasm were identified in literature searches.

Section Summary: Blepharospasm

Multiple RCTs and a systematic review have found that botulinum toxin injection is an effective treatment of blepharospasm.

Headache

Botulinum toxin for treatment of pain from migraine and from chronic tension-type headaches was addressed in a TEC Assessment (2004).²⁵ The Assessment concluded that the evidence was insufficient for either indication. Because the placebo response rate is typically high in patients with headache, assessment of evidence focuses on randomized, placebo-controlled trials. More recent literature is discussed below, organized by type of headache. Recent studies have focused on frequency of headache as an outcome measure in addition to pain and headache severity.

Clinical Context and Therapy Purpose

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

The question addressed in this evidence review is: Does use of botulinum toxin improve the net health outcome in patients with chronic migraine headache?

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

Patients

The relevant population of interest is individuals with chronic migraine headache.

Interventions

The therapy being considered is botulinum toxin.

Comparators

The following therapies are currently being used to treat chronic migraine headache: Pain-relieving medications taken during migraine attacks and are designed to stop symptoms and include aspirin,

ibuprofen, acetaminophen, sumatriptan, rizatriptan, almotriptan, naratriptan, zolmitriptan, frovatriptan, eletriptan, ergotamine, caffeine combination drugs and anti-nausea medications. Preventive medications are drugs taken regularly to reduce the severity or the frequency of migraines and include β -blockers, antidepressants, pain killers, and erenumab-aooe. Complementary treatment (eg, acupuncture) may also be considered.

Outcomes

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

Timing

Follow-up ranges from 4 to 8 weeks to monitor outcomes.

Setting

Patients with chronic migraine headache may be managed by general physicians or pain specialists; botulinum toxin is injected into the skin of selected areas in head and neck in an outpatient setting.

Migraine Headache

Migraines can be categorized by headache frequency. According to the Third Edition of the International Headache Classification (ICHD-3), migraine without aura (previously known as common migraine) is defined as at least 5 attacks per month meeting other diagnostic criteria.⁴² Chronic migraine is defined as attacks on at least 15 days per month for more than 3 months, with features of migraine on at least 8 days per month.

Systematic Reviews

The Agency for Healthcare Research and Quality published a comparative effectiveness review, conducted by Shamliyan et al (2013), on preventive pharmacologic treatments for migraine in adults.⁴³ The investigators identified 15 double-blind RCTs evaluating botulinum toxin for migraine prevention: 13 used onabotulinumtoxinA and two used abobotulinumtoxinA. In a meta-analysis of 3 RCTs, onabotulinumtoxinA was more effective than placebo in reducing the number of chronic migraine episodes per month by at least 50% (RR=1.5; 95% CI, 1.2 to 1.8). In another pooled analysis, onabotulinumtoxinA was associated with a significantly higher rate of treatment discontinuation due to adverse events than placebo (RR=3.2; 95% CI, 1.4 to 7.10). Five RCTs compared the efficacy of onabotulinumtoxinA with another medication (topiramate or divalproex sodium). Findings were not pooled, but, for the most part, there were no statistically significant differences in outcomes between the 2 drugs.

Jackson et al (2012) conducted a meta-analysis of RCTs on botulinum toxin type A for the prophylactic treatment of headache in adults; the analysis addressed migraines and other types of headache.⁴⁴ Reviewers included RCTs that were at least 4 weeks in duration, had reduction in headache frequency or severity as an outcome, and used patient-reported outcomes. Reviewers categorized eligibility criteria as addressing episodic (<15 headaches per month) or chronic headache (≥ 15 days per month). Ten trials on episodic migraine and 7 trials on chronic migraine were identified. All trials on episodic migraine and 5 of 7 trials on chronic migraine were placebo-controlled; the other 2 trials compared botulinum toxin injections with oral medication. A pooled analysis for chronic migraine (5 trials) found a statistically significantly greater reduction in the frequency of headaches per month with botulinum toxin than with a control intervention (absolute difference, -2.30; 95% CI, -3.66 to -0.94). In contrast, in a pooled analysis of episodic migraine (9

trials), there was no statistically significant difference between groups in the change in monthly headache frequency (absolute difference, -0.05; 95% CI, -0.25 to 0.36).

Previously, Shuhendler et al (2009) conducted a meta-analysis of trials on botulinum toxin for treating episodic migraines.⁴⁵ Reviewers identified 8 randomized, double-blind, placebo-controlled trials evaluating the efficacy of botulinum toxin type A injections. A pooled analysis of the main study findings found no significant differences between the botulinum toxin type A and placebo groups in change in the number of migraines per month. After 30 days of follow-up, the SMD was -0.06 (95% CI, -0.14 to 0.03; $p=0.18$). After 90 days, the SMD was -0.05 (95% CI, -0.13 to 0.04; $p=0.28$). A subgroup analysis examining trials using low-dose botulinum toxin type A (<100 U) compared with trials using high-dose botulinum toxin type A (≥ 100 U) did not find a statistically significant effect of botulinum toxin type A compared with placebo in either stratum.

Randomized Controlled Trials

A pair of multicenter RCTs that evaluated onabotulinumtoxinA (Botox) for chronic migraine was published in 2010. The trials reported findings from the double-blind portions of the industry-sponsored PREEMPT (Phase 2 Research Evaluating Migraine Prophylaxis Therapy) trials 1 and 2.^{46,47} Trial designs were similar. Both included a 24-week double-blind, placebo-controlled phase prior to an open-label phase. The trials recruited patients meeting criteria for migraine and excluded those with complicated migraine. To be eligible, patients had to report at least 15 headache days during the 28-day baseline period, each headache lasting at least 4 hours. At least 50% of the headaches had to be definite or probable migraine. The investigators did not require that the frequent attacks occur for more than 3 months or exclude patients who overused pain medication, two of the ICHD-2 criteria for chronic migraine. Eligible patients were randomized to 2 cycles of Botox injections 155 U or placebo, with 12 weeks between cycles. Randomization was stratified by frequency of acute headache pain medication used during baseline and whether patients overused acute headache pain medication. (Medication overuse was defined as baseline intake of simple analgesics on at least 15 days, or other medications for at least 10 days, and medication use at least 2 days per week.)

The primary end point in PREEMPT 1 was mean change from baseline in frequency of headache episodes for 28 days ending with week 24. A headache episode was defined as a headache lasting at least 4 hours. Prespecified secondary outcomes included, among others, change in frequency of headache days (calendar days in which pain lasted at least 4 hours), migraine days (calendar days in which a migraine lasted at least 4 hours), and migraine episodes (migraine lasting at least 4 hours). Based on availability of data from PREEMPT 1 and other factors, the protocol of the PREEMPT 2 trial was amended (after study initiation but before unmasking) to make frequency of headache days the primary end point. The trialists noted that, to control for potential type I error related to changes to the outcome measures, a more conservative p value (0.01) was used. Several QOL measures were also used in the trials, including the 6-item Headache Impact Test-6 (HIT-6) and the Migraine Specific Quality of Life Questionnaire (MSQ v.2). Key findings of both trials are described below.

PREEMPT 1 randomized 679 patients.⁴⁶ Mean number of migraine days during baseline was 19.1 in each group. The mean number of headache episodes during the 28-day baseline period was 12.3 in the Botox group and 13.4 in the placebo group. Approximately 60% of patients had previously used at least 1 prophylactic medication and approximately 68% overused headache pain medication during baseline. A total of 296 (87%) of 341 patients in the Botox group and 295 (87%) of 338

patients in the placebo group completed the 24-week double-blind phase. The primary outcome (change from baseline in frequency of headache episodes over a 28-day period) did not differ significantly between groups. The number of headache episodes decreased by a mean of 5.2 in the Botox group and 5.3 in the placebo group ($p=0.344$). Similarly, the number of migraine episodes did not differ significantly. There was a decrease of 4.8 migraine episodes in the Botox group and of 4.9 in the placebo group ($p=0.206$). In contrast, there was a significantly greater decrease in the number of headache days and the number of migraine days in the Botox group than in the placebo group. The decrease in frequency of headache days was 7.8 in the Botox group and 6.4 in the placebo group, a difference of 1.4 headache days per 28 days ($p=0.006$). Corresponding numbers for migraine days were 7.6 and 6.1, respectively ($p=0.002$). There was significantly greater improvement in QOL in the Botox group vs the placebo group. The proportion of patients with severe impact of headaches (ie, HIT-6 score, ≥ 60) in the Botox group decreased from 94% at baseline to 69% at 24 weeks; in the placebo group, it decreased from 95% at baseline to 80%, a between-group difference of 11% ($p=0.001$). The authors did not report MSQ scores, but stated that there was statistically significant greater improvement in the 3 MSQ role function domains at week 24 (restrictive, $p<0.01$; preventive, $p=0.05$; emotional, $p<0.002$). Adverse events were experienced by 203 (60%) patients in the Botox group and 156 (47%) patients in the placebo group. Eighteen (5%) patients in the Botox group and 8 (2%) in the placebo group experienced serious adverse events. Treatment-related adverse events were consistent with the known safety profile of Botox.

PREEMPT 2 randomized 705 patients.⁴⁷ Mean number of migraine days during baseline period was 19.2 in the Botox group and 18.7 in the placebo group. Mean number of headache episodes during the 28-day baseline period was 12.0 in the Botox group and 12.7 in the placebo group. Approximately 65% of patients had previously used at least 1 prophylactic medication and approximately 63% overused headache pain medication during baseline. A total of 311 (90%) of 347 patients in the Botox group and 334 (93%) of 358 patients in the placebo group completed the 24-week, double-blind phase. The primary outcome, change from baseline frequency of headache days over a 28-day period (a different primary outcome from PREEMPT 1), differed significantly between groups and favored Botox treatment. The number of headache days decreased by a mean of 9.0 in the Botox group and 6.7 in the placebo group, an absolute difference of 2.3 days per 28 days ($p<0.001$). Mean number of migraine days also decreased significantly, more in the Botox group (8.7) than in the placebo group (6.3; $p<0.001$). Unlike PREEMPT 1, there was a significantly greater decrease in headache episodes in PREEMPT 2 in the Botox group (5.3) than in the placebo group (4.6; $p=0.003$). Change in frequency of migraine episodes was not reported.

Similar to PREEMPT 1, QOL measures significantly improved in the Botox group. The proportion of patients reporting that their headaches had a severe impact (score of at least 60 on the HIT-6) decreased in the Botox group from 93% at baseline to 66% at 24 weeks; in the placebo group, it decreased from 91% at baseline to 77%. There was a between-group difference of 10% ($p=0.003$). The trialists reported statistically significantly greater improvement in the 3 MSQ role function domains at week 24 (restrictive, preventive, emotional, $p<0.001$ for each domain). Adverse events were experienced by 226 (65%) patients in the Botox group and 202 (56%) patients in the placebo group. Fifteen (4%) patients in the Botox group and 8 (2%) in the placebo group experienced serious adverse events. As in PREEMPT 1, treatment-related adverse events in PREEMPT 2 were consistent with the known safety profile of Botox.

Also published was a pooled analysis of findings from the PREEMPT 1 and 2 trials; this analysis by Dodick et al (2010) was also industry-sponsored.⁴⁸ There were 688 patients in the Botox group and 696 in the placebo group in the pooled analysis of outcomes at week 24. In the combined analyses, there was a significantly greater reduction in change from baseline in frequency of headache days, migraine days, headache episodes, and migraine episodes in the Botox group than in the placebo group. For example, the pooled change in mean frequency of headache days was 8.4 in the Botox group and 6.6 in the placebo group ($p < 0.001$). Mean difference in number of headache days over a 28-day data collection period was 1.8 (95% CI, 1.13 to 2.52). The pooled change in frequency of headache episodes was 5.2 in the Botox group and 4.9 in the placebo group, a relative difference of 0.3 episodes (95% CI, 0.17 to 1.17; $p = 0.009$). Between-group differences, though statistically significant, were relatively small and might not be clinically meaningful. In the pooled analysis, the trialists also reported the proportion of patients with at least a 50% decrease from baseline in the frequency of headache days at each time point (every 4 weeks from week 4 to week 24). For example, at week 24, the proportion of participants with at least a 50% reduction in headache days was 47.1% in the Botox group and 35.1% in the placebo group. In contrast, the difference in the proportion of patients experiencing at least a 50% reduction in headache episodes did not differ significantly between groups at 24 weeks or at most other time points, with the exception of week 8. The published report did not report the proportion of participants who experienced at least a 50% reduction in migraine days or migraine episodes. The pooled analysis showed statistically significant differences for the change in proportion of patients with severe headache impact as assessed using the HIT-6 and change in MSQ domains. Pooled results of PREEMPT studies at 56 week also reported that repeated treatment (≤ 5 cycles) of onabotulinumtoxinA was effective, safe, and well-tolerated in adults with chronic migraine.^{49,50}

Several issues are worth noting about the methods and findings of the PREEMPT studies. There was a statistically significant difference in headache episodes in PREEMPT 2 but not PREEMPT 1 (for which it was the primary outcome); the primary outcome was changed after initiation of PREEMPT 1. Moreover, one of the main secondary outcomes in PREEMPT 1 (change in the number of migraine episodes) was not reported in the second trial; the trialists did not discuss this omission. In addition, the individual studies did not include threshold response to treatment (eg, at least a 50% reduction in headache or migraine frequency) as a key outcome. The pooled analysis did report response rates, but as secondary efficacy outcomes.

Most patients in both trials fulfilled criteria for medication overuse headache, and therefore many might have been experiencing secondary headaches rather than chronic migraines. If patients had secondary headaches, detoxification alone might have been sufficient to change their headache pattern to an episodic one. The clinical relevance of less than a 2-day difference in reduction in number of headache days is uncertain, though consistent with reductions previously reported in several medication trials.

Another RCT that assessed use of botulinum toxin for treating chronic migraine was published by Cady et al (2011).⁵¹ The trial included patients who met ICHD-2 criteria for chronic migraine. Patients were randomized to treatment with Botox ($n = 29$) or topiramate ($n = 30$). At the 12-week follow-up, the end of the double-blind phase of the trial, treatment effectiveness did not differ significantly between groups. For the primary end point (Physician Global Assessment at week 12), physicians noted improvement in 19 (79%) of 24 patients in the Botox group and 17 (71%) of 24 patients in the topiramate group; 9 patients (15%) were not available for this analysis.

Section Summary: Migraine Headache

For chronic migraine, a meta-analysis of RCTs found that onabotulinumtoxinA was more effective than placebo in reducing the number of chronic migraine episodes per month, although it was also associated with a significantly higher rate of treatment discontinuation due to adverse events than placebo.

Non-Migraine Headache

Medication Overuse Headache

According to the ICHD-2 (and ICHD-3), the diagnostic classification of medication overuse headache differs from chronic migraine.⁵² Silberstein et al (2013) published a subanalysis of pooled PREEMPT data limited to patients with headache medication overuse at baseline.⁵³ A total of 904 patients who indicated they had medication overuse headache were included; 445 were randomized to the botulinum toxin group and 459 to the placebo group. At the end of week 24, there was a significantly greater reduction in outcomes, including headache days, headache episodes, and moderate-to-severe headache days, in the botulinum toxin group than in the placebo group. For example, the number of headache days per month decreased by a mean of 8.2 in the botulinum toxin group and 6.2 in the placebo group ($p < 0.001$). This is a single analysis of RCT data and provides insufficient evidence that botulinum toxin is effective for patients with the diagnosis of medication overuse headache.

Tension Headache

The meta-analysis by Jackson et al (2012), discussed above, identified 7 RCTs evaluating botulinum toxin for treating chronic tension-type headaches; all were placebo-controlled.⁴⁴ A pooled analysis of these 7 studies did not find a statistically significant difference in change in the monthly number of headache days in the botulinum toxin group vs the placebo group (difference, -1.43; 95% CI, -3.13 to 0.27). The largest trial (Silberstein et al [2006]⁵⁴) included 300 patients randomized to 1 of 4 doses of botulinum toxin or placebo. Overall, there was no statistically significant difference between the botulinum toxin groups and the placebo group in mean change from baseline to 90 days in number of headache days per month.

Chronic Daily Headache

Although chronic daily headache is not recognized in the ICHD, it is commonly defined to include different kinds of chronic headache (eg, chronic or transformed migraine, daily persistent headache). It may also include chronic tension-type headache (addressed above). The meta-analysis by Jackson (2012) identified 3 RCTs comparing botulinum toxin type A with placebo in patients having at least 15 headaches per month.⁴⁴ A pooled analysis of data from these 3 trials found a significantly greater reduction in the number of headaches per month with botulinum toxin than with placebo (absolute difference, -2.06; 95% CI, -3.56 to -0.56). Individually, only one (Ondo et al [2004]⁵⁵) of the 3 trials found a statistically significant benefit with botulinum toxin treatment. Ondo included 60 patients, some with chronic migraines and chronic tension-type headache. The Ondo trial found significantly greater reduction in the number of headache-free days over weeks 8 to 12 with botulinum toxin than with placebo ($p < 0.05$), but there was no statistically significant between-group difference in reduction in headache-free days over the entire 12-week study period ($p = 0.07$). The other 2 trials evaluated more patients: 355 in Mathew et al (2005)⁵⁶ and 702 in Silberstein et al (2005).⁵⁷ Neither found a statistically significant difference in the reduction in the number of headache days per month with botulinum toxin. The available evidence from RCTs is conflicting and insufficient for conclusions.

Cluster Headache

No controlled trials were identified for cluster headache.

Cervicogenic Headache

Systematic Reviews: A Cochrane review of treatment of mechanical neck disorders, conducted by Peloso et al (2007), included 6 RCTs (total N=273 patients) assessing botulinum toxin and placebo for chronic neck disorders with or without radicular findings or headache.⁵⁸ A meta-analysis of 4 studies (n=139 patients) for pain outcomes found no statistically significant results. Reviewers concluded that a range of doses did not show significant differences compared with placebo or other comparators.

Randomized Controlled Trials: Linde et al (2011) published a double-blind, placebo-controlled crossover study that included 28 patients with treatment-resistant cervicogenic headache.⁵⁹ Patients were randomized to botulinum toxin type A or placebo; there was at least an 8-week period between treatments. The trial did not find significant differences between active and placebo treatment in the primary outcome, reduction in the number of days with moderate-to-severe headache. Three other RCTs, published between 2000 and 2008, randomized patients with chronic, whiplash-related headache to botulinum toxin type A treatment or placebo.⁶⁰⁻⁶² One trial reported trends toward improvement with treatment for various outcomes; most were not statistically significant.⁶⁰ Another reported no significant differences for several pain-related outcomes.⁶² The other reported a significant improvement in pain with treatment, but trial design was flawed because the placebo group reported less pain at baseline.⁶¹

Section Summary: Non-Migraine Headache

For patients with an episodic pattern of migraine (ie, <15 episodes per month), the published evidence does not suggest that botulinum toxin improves net health outcome for patients. For tension headache, RCTs and systematic reviews do not indicate that botulinum toxin improves outcomes. For other headache types, the evidence is inconclusive to confirm efficacy.

Esophageal Achalasia

Esophageal achalasia is a primary motor disorder characterized by abnormal lower esophageal sphincter relaxation.

Clinical Context and Therapy Purpose

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

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

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

Patients

The relevant population of interest is individuals with esophageal achalasia.

Interventions

The therapy being considered is botulinum toxin.

Comparators

The following therapies are currently being used to treat esophageal achalasia: medication (ie, zolpidem), pneumatic dilation, or laparoscopic myotomy.

Outcomes

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

Timing

Follow-up ranges from 4 to 8 weeks to monitor outcomes.

Setting

Patients with esophageal achalasia may be managed by neurologists; botulinum toxin is injected into selected eyelid muscles in an outpatient setting.

Systematic Reviews

A Cochrane review by Leyden et al (2014) identified 7 RCTs (total N=178 participants) on the treatment of primary esophageal achalasia with botulinum toxin or endoscopic pneumatic dilation.⁶³ A pooled analysis of data from 5 trials did not find a statistically significant difference in the rate of initial remission with pneumatic dilation vs botulinum toxin injection (RR=1.11; 95% CI, 0.97 to 1.27). Remission at 6 and 12 months favored the pneumatic dilation group. No serious adverse events were reported after botulinum toxin injection; however, there were 3 cases of perforation after pneumatic dilation.

Section Summary: Esophageal Achalasia

A systematic review of RCTs reported similar initial remission rates of esophageal achalasia after botulinum toxin injection and pneumatic dilation. Pneumatic dilation was associated with higher longer term remission rates but is more invasive, and perforation has been reported.

Sialorrhea (Drooling)Clinical Context and Therapy Purpose

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

The question addressed in this evidence review is: Does use of botulinum toxin improve the net health outcome in patients with sialorrhea?

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

Patients

The relevant population of interest is individuals with sialorrhea.

Interventions

The therapy being considered is botulinum toxin.

Comparators

The following therapies are currently being used to treat sialorrhea: nonmedication treatments such as chewing gum or hard candy, which encourage swallowing, may reduce drooling in social

situations. For patients with more severe symptoms, glycopyrrolate, other anticholinergic medications (eg, oral hyoscyamine and amitriptyline; sublingual ipratropium bromide and sublingual atropine) may also be used.

Outcomes

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

Timing

The timing of interest ranges from 4 to 8 weeks to evaluate changes in symptoms, functional outcomes, use and treatment-related morbidity.

Setting

Patients with sialorrhea may be managed by neurologists; botulinum toxin is injected into the salivary glands in an outpatient setting.

Sialorrhea Associated with Parkinson Disease

Several RCTs have evaluated botulinum toxin injections in patients with Parkinson disease. For example, Lagalla et al (2006) randomized 32 patients with Parkinson disease to placebo or botulinum toxin type A; evaluation at 1 month postinjection resulted in significant improvements compared with placebo in drooling frequency, saliva output, and familial and social embarrassment.⁶⁴ Dysphagia scores were not significantly improved. Moreover, Ondo et al (2004) randomized 16 patients with Parkinson disease to botulinum toxin type B or placebo.⁶⁵ The botulinum toxin group had significantly better outcomes than the placebo group at 1 month on 4 drooling outcomes. Groups did not differ on salivary gland imaging or on a dysphagia scale. Mancini et al (2003) assigned 20 patients with Parkinson disease to injections of either a saline placebo or botulinum toxin type A.⁶⁶ The treatment group had significantly better outcomes than the placebo group on a drooling scale at 1 week; the effect disappeared by 3 months.

Section Summary: Sialorrhea Associated with Parkinson Disease

RCTs have consistently found benefit of botulinum toxin injection on sialorrhea in patients with Parkinson disease.

Sialorrhea Not Associated with Parkinson Disease

Systematic Reviews

Several systematic reviews have evaluated botulinum toxin for treating sialorrhea in people with conditions other than Parkinson disease. Squires et al (2014) reviewed the research on botulinum toxin injections for drooling in patients with amyotrophic lateral sclerosis/motor neuron disease.⁶⁷ Reviewers included RCTs and controlled and uncontrolled observational studies. They identified 12 studies, of which 8 had no control groups. There were 2 small RCTs, each with fewer than 20 patients. Sample sizes in the non-RCTs ranged from 5 to 26 patients. Due to heterogeneity, study findings were not pooled. Only one of the 2 RCTs reported drooling outcomes; it found a significantly greater reduction in saliva volume with botulinum toxin than with placebo at 2 weeks.

Rodwell et al (2012) published a systematic review evaluating botulinum toxin injections in the salivary gland to treat sialorrhea in children with cerebral palsy and neurodevelopment disability.⁶⁸ Reviewers identified 5 RCTs; trial sample sizes ranged from 6 to 48 participants. One of the RCTs (N=6) was terminated due to adverse events. In a pooled analysis of data 4 weeks postintervention

in 3 RCTs, the mean score on the Drooling Frequency and Severity Scale was significantly lower in children who received botulinum toxin injections than a control intervention (MD = -2.71 points; 95% CI, -4.82 to -0.60; $p < 0.001$). The clinical significance of this difference in Drooling Frequency and Severity Scale scores is unclear. Data were not pooled for other outcomes. The systematic review also identified 11 prospective case series. The rate of adverse events associated with botulinum toxin injection in the RCTs and case series ranged from 2% to 41%. Dysphagia occurred in 2 (33%) of the 6 participants in an RCT terminated early and in 2 (2%) of 126 patients in a case series. There was 1 reported chest infection, 1 case of aspiration pneumonia, and, in 1 case series, 6 (5%) of 126 patients experienced an increased frequency of pulmonary infections. In 7 studies, there were reports of patients with difficulty swallowing and/or chewing following botulinum toxin treatment.

Randomized Controlled Trials

Gonzalez et al (2017) reported the results of an RCT in which 40 adults with cerebral palsy were randomized to onabotulinumtoxinA or observation.⁶⁹ The trial had greater than 80% power to detect a 39% difference in the proportion of patients who achieved at least a 50% reduction in drooling quotient. The primary efficacy outcome was drooling quotient. This quotient, measured as a proportion, is a semi-quantitative method that assesses the presence of newly formed saliva on the lips every 15 seconds with 40 observations in 10 minutes, expressed as a percentage based on the ratio between the number of observed drooling episodes and the total number of observations. The proportion of patients who achieved at least a 50% reduction in drooling quotient in the treated group vs control after 8 weeks and 80 weeks was 45% vs 0.0% ($p = 0.001$) and 20% vs 0% ($p = 0.106$). While the treatment effect was large, the trial did not use a placebo group and was unblinded.

A large RCT on botulinum toxin for treating sialorrhea in children with cerebral palsy was published by Reid et al (2008).⁷⁰ Forty-eight children with cerebral palsy ($n = 31$) and other neurologic disorders ($n = 17$) were randomized to a single injection of botulinum toxin type A 25 U compared with no treatment. Drooling was assessed by using the Drooling Impact Scale. Scores differed significantly between groups at 1 month, and a beneficial effect of botulinum toxin injection remained at 6 months.

Retrospective Studies

A retrospective review by Chan et al (2013) focused on the long-term safety of botulinum toxin type A injection for treating sialorrhea in children.⁷¹ Reviewers included 69 children; 47 (68%) had cerebral palsy. Children received their first injection of botulinum toxin type A at a mean age of 9.9 years; mean follow-up was 3.1 years. During the study period, the children received a total of 120 botulinum toxin injections. Complications occurred in 19 (28%) of 69 children and in 23 (19%) of 120 injections. Fifteen of 23 complications were minor, including 6 cases of dysphagia. There were 8 major complications: 3 cases of aspiration pneumonia, 2 cases of severe dysphagia, and 3 cases of loss of motor control of the head. Complications were associated with 5 hospitalizations and 2 cases of nasogastric tube placement.

Section Summary: Sialorrhea Not Associated with Parkinson Disease

Although there is evidence of improvement as measured on drooling scales following botulinum toxin injections in children with cerebral palsy, the clinical significance is uncertain, and there are concerns about the safety of injecting botulinum toxin into the salivary gland in this population. The evidence on botulinum toxin for treating sialorrhea in patients with amyotrophic lateral

sclerosis/motor neuron disease is inconclusive due to the paucity of controlled studies, small sample sizes of available studies, and limited reporting of drooling outcomes.

Anal Applications

Internal anal sphincter (IAS) achalasia is a defecation disorder in which the internal anal sphincter is unable to relax. Symptoms include severe constipation and soiling.

Chronic anal fissure is a tear in the lower half of the anal canal that is maintained by contraction of the IAS and is treated surgically with an internal sphincterotomy. Because the anal sphincter contraction could be characterized as a dystonia, botulinum toxin is a logical medical approach.

Clinical Context and Therapy Purpose

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

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

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

Patients

The relevant populations of interest are individuals with IAS achalasia or with chronic anal fissure.

Interventions

The therapy being considered is botulinum toxin.

Comparators

The following therapies are currently being used to treat IAS achalasia: surgical management (posterior IAS myectomy).

The following therapies are currently being used for individuals with chronic anal fissure: medication (ie, nitroglycerin, topical anesthetic creams, eg, lidocaine hydrochloride, oral nifedipine, or diltiazem).

Outcomes

The general outcomes of interest are symptoms, health status measures, and treatment-related morbidity.

Timing

Follow-up ranges from 6 months to a year to monitor outcomes.

Setting

Patients with IAS achalasia and chronic anal fissure may be managed by general physicians, surgeons, and gastroenterologist; botulinum toxin is injected intrasphincteric in an outpatient setting.

Internal Anal Sphincter Achalasia

A meta-analysis of studies on treatment of IAS achalasia was published by Friedmacher and Puri (2012).⁷² Reviewers only identified 2 prospective case series and 14 retrospective case series (total N=395 patients) of IAS achalasia. Most patients (229/395 [58%]) in the series were treated with posterior IAS myectomy and 166 (42%) were treated with intrasphincteric botulinum toxin injection. A meta-analysis of data from the observational studies found that regular bowel movements were more frequent after myectomy (odds ratio [OR], 0.53; 95% CI, 0.29 to 0.99; p=0.04). Moreover, the rate of transient fecal incontinence was significantly higher after botulinum toxin injection (OR=0.07; 95% CI, 0.01 to 0.54; p<0.01) and the rate of subsequent surgical intervention was higher after botulinum toxin injection (OR=0.18; 95% CI, 0.07 to 0.44; p<0.001). Other outcomes, including continued use of laxatives or rectal enemas and overall complication rates, did not differ between treatments.

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.⁷³ Of the 7 studies, 2 were RCTs and the others comparative and observational studies. Both RCTs were single site from the same author group and conducted in Egypt, enrolling 15 and 24 patients, respectively.^{74,75} Improvement was defined as patients returning to their normal habits. The first RCT used biofeedback and the other used surgery as the comparator. In the first RCT, 50% of individuals in the biofeedback group reported improvement initially at 1 month but it dropped down to 25% by the end of year. The respective proportions of patients in the botulinum toxin arm were 70.8% and 33.3%. In the second RCT, surgery improved outcomes in all patients at 1 month but that percentage dropped to 66.6% at 1 year. The respective proportions of patients in the botulinum toxin arm were 87% and 40%, respectively. While these results would suggest temporary improvement, methodologic limitations, including small sample size and lack of blinded assessment, limit the interpretation of these RCTs.

Section Summary: Internal Anal Sphincter Achalasia

There is a lack of high-quality RCTs evaluating botulinum toxin injection as a treatment of IAS achalasia. A meta-analysis of observational data and a systematic review suggested that posterior IAS myectomy results in greater improvements in health outcomes than botulinum toxin injections.

Anal Fissure

Systematic Reviews

A systematic review by Yiannakopoulou (2012) identified 2 RCTs comparing botulinum toxin with placebo, 1 RCT comparing botulinum toxin with lidocaine pomme, 5 RCTs comparing botulinum toxin with nitrates, and 8 RCTs comparing botulinum toxin with surgery.⁷⁶ A meta-analysis was not performed due to heterogeneity among studies. The author noted that the studies tended to be small and of short duration, and that the superiority of botulinum toxin over surgery had not been demonstrated. However, because this minimally invasive option can be repeated, it is a reasonable option prior to surgery.

Randomized Controlled Trials

Brisinda et al (2007) conducted a trial and reported 92% healing rates for botulinum toxin type A and 70% for nitroglycerin ointment (p<0.001).⁷⁷ Another trial by Brisinda et al (2004) found that the efficacy and tolerability of onabotulinumtoxinA and abobotulinumtoxinA to treat anal fissures were similar.⁷⁸ Brisinda et al (1999) compared the results of nitroglycerin ointment with botulinum

toxin type A in a randomized trial of 50 patients.⁷⁹ After 2 months, 96% of the fissures were healed in the botulinum group compared with 60% in the nitroglycerin group.

Maria et al (1998) randomized 30 patients with chronic anal fissure to 2 injections of botulinum toxin type A, on either side of the fissure, or 2 injections of saline.⁸⁰ After 2 months, 11 (73%) patients in the treated group and 2 (13%) patients in the control group had healed fissures ($p=0.003$); 13 (87%) patients in the treated group and 4 (26%) in the control group had symptomatic relief ($p=0.003$). Four patients in the treated group were later retreated. No relapses occurred during an average of 16 months of follow-up.

Others have reported both supportive⁸¹ and contradictory⁸² data from randomized trials comparing the same treatments. RCTs of botulinum toxin vs sphincterotomy, and a meta-analysis of these studies, have reported significantly higher healing rates with sphincterotomy, but authors concluded that botulinum toxin was a viable first option for patients who are not good surgical candidates or who want to minimize the likelihood of incontinence.⁸³⁻⁸⁵

Section Summary: Anal Fissure

There is evidence on botulinum toxin for treatment of anal fissure from numerous small RCTs. Botulinum toxin has not been found to have better outcomes than surgery, but studies have found that healing rates after botulinum toxin are reasonably high and that it is a less invasive than surgery.

Urologic Applications

Clinical Context and Therapy Purpose

The purpose of botulinum toxin in patients with urologic conditions including urinary incontinence due to detrusor overactivity associated with overactive bladder (OAB) or neurogenic causes or urologic issues other than detrusor overactivity or OAB is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does use of botulinum toxin improve the net health outcome in patients with urologic conditions?

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

Patients

The relevant populations of interest are individuals with urinary incontinence due to detrusor overactivity associated with OAB or neurogenic causes or urologic issues other than detrusor overactivity or OAB.

Interventions

The therapy being considered is botulinum toxin.

Comparators

The following therapies are currently being used to treat urinary incontinence: conservative measures and pharmacotherapy (antimuscarinic agents, β -adrenergic therapy).

Outcomes

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

Timing

Follow-up ranges from 6 months to a year to monitor outcomes.

Setting

Patients with urinary incontinence may be managed by general physicians, urologists, and/or gynecologists; botulinum toxin is injected intradetrusor in an outpatient setting.

OAB and Neurogenic Detrusor Overactivity

Systematic Reviews

Drake et al (2017) reported on the results of a network meta-analysis of 56 RCTs that compared the efficacy of onabotulinumtoxinA, mirabegron, and anticholinergics in adults with idiopathic OAB.⁸⁶ While all treatments were more efficacious than placebo after 12 weeks, patients who received onabotulinumtoxinA (100 U) reported the greatest reductions in urinary incontinence episodes, urgency episodes, and micturition frequency, and the highest odds of achieving decreases of 100% and 50% or greater from baseline in urinary incontinence episodes per day. The exclusion of studies with a high risk of bias had little impact on the conclusions. Freemantle et al (2016) also reported on the results of a network meta-analysis of 19 RCTs comparing onabotulinumtoxinA, mirabegron, anticholinergic drugs, or placebo.⁸⁷ Both onabotulinumtoxinA and mirabegron were more efficacious than placebo at reducing the frequency of urinary incontinence, urgency, urination, and nocturia. OnabotulinumtoxinA was more efficacious than mirabegron (50 mg and 25 mg) in completely resolving daily episodes of urinary incontinence and urgency and in reducing the frequency of urinary incontinence, urgency, and urination.

A network meta-analysis by Cheng et al (2016) assessed 1915 patients with neurogenic detrusor overactivity from 6 RCTs.⁸⁸ Using the mean number of urinary incontinence episodes per week as the primary outcome measure, reviewers reported that treatment with onabotulinumtoxinA 200 U and 300 U compared with placebo reduced the mean number of urinary incontinence episodes at week 6 by 10.72 (95% CI, -13.4 to -8.04; $p < 0.001$) and -11.42 (95% CI, -13.91 to -8.93; $p < 0.001$), respectively. Treatment with onabotulinumtoxinA was associated greater frequency of urinary tract infections (RR=1.47; 95% CI, 1.29 to 1.67; $p < 0.001$), urinary retention (RR=5.58, 95% CI, 3.53 to 8.83; $p < 0.001$), hematuria (RR=1.70; 95% CI, 1.01 to 2.85; $p = 0.05$), and muscle weakness (RR=2.59; 95% CI, 1.36 to 4.91; $p = 0.004$).

Cui et al (2015) identified 6 double-blind RCTs comparing botulinum toxin type A with placebo for treating patients with idiopathic OAB.⁸⁹ In a pooled analysis of 3 studies, patients treated with botulinum toxin were significantly more likely to be incontinence-free at the end of the study (OR=4.89; 95% CI, 3.11 to 7.70). Moreover, a pooled analysis of 5 studies found significantly greater reduction in the number of incontinence episodes per day in the group treated with botulinum toxin (SMD = -1.68; 95% CI, -2.06 to -1.31). Cui et al (2013) also published another systematic review evaluating botulinum toxin type for OAB.⁹⁰ Previously, Duthie et al (2011) published a Cochrane review of RCTs evaluating botulinum toxin injections for patients with idiopathic or neurogenic OAB.⁹¹ Reviewers identified 19 trials that compared treatment using botulinum toxin with placebo or another intervention. Two studies included botulinum toxin type B; the remainder included botulinum toxin type A. Outcomes varied, which made it difficult to pool findings. A pooled analysis of 3 trials found change in urinary frequency episodes at 4 to 6 weeks a

significantly better outcome with botulinum toxin injection than with placebo (MD = -6.50; 95% CI, -8.92 to -4.07). A pooled analysis of 3 trials on change in incontinence episodes at 4 to 6 weeks also found a significantly greater improvement with botulinum toxin (MD = -1.58; 95% CI, -2.16 to -1.01).

Other systematic reviews have included both controlled and uncontrolled studies. A systematic review by Soljanik (2013) identified 28 studies evaluating onabotulinumtoxinA for the treatment of neurogenic detrusor overactivity or neurogenic OAB; 6 studies were RCTs.⁹² The reviewer reported that studies with comparative data found superior outcomes with onabotulinumtoxinA compared with placebo. Data from the RCTs were not pooled. Serious adverse events were not reported. However, adverse events after intradetrusor botulinum toxin injection included postvoid residual urine (50%), urinary retention (23.7%), and urinary tract infection (UTI; 16.7%). Also, Mehta et al (2013) identified 14 studies evaluating botulinum toxin type A for treating neurogenic detrusor overactivity after spinal cord injury; only one was an RCT.⁹³ Studies tended to have large effect sizes (>0.8) for outcomes including bladder capacity and reflex detrusor volume. Rates of incontinence episodes decreased after treatment with botulinum toxin type A from 23% to 1.3% per day. Previously, Karsenty et al (2008) identified 18 studies evaluating botulinum toxin type A to treat patients who were refractory to anticholinergics.⁹⁴ Most studies reported statistically significant improvements in clinical and urodynamic outcomes, without major adverse events.

Randomized Controlled Trials

Representative large, double-blind RCTs are described below. Herschorn et al (2017) reported on the results of a double-blind RCT that compared the efficacy and safety of onabotulinumtoxinA or solifenacin vs placebo in patients with OAB, urinary incontinence, and an inadequate response to or were intolerant of an anticholinergic.⁹⁵ The primary end point included change from baseline in the number of urinary incontinence episodes per day and the proportion of patients with a 100% reduction (dry) in the number of incontinence episodes per day. While both onabotulinumtoxinA and solifenacin fared better than placebo in terms of change from baseline in incontinence episodes per day (-3.19 or -2.56 vs -1.33; both $p < 0.001$), the incontinence reduction was significantly greater for onabotulinumtoxinA vs solifenacin ($p = 0.022$). At week 12, 33.8% (vs placebo $p < 0.001$), 24.5% (vs placebo $p = 0.028$), and 11.7% of patients receiving onabotulinumtoxinA, solifenacin, and placebo, respectively, were dry.

Nitti et al (2017) reported on the results of open-label RCT in which 557 patients with OAB, 3 or more urgency urinary incontinence episodes in 3 days, and 8 or more micturitions per day inadequately managed with anticholinergics were randomized to onabotulinumtoxinA 100 U or placebo.⁹⁶ Coprimary end points were the change from baseline in the number of urinary incontinence episodes per day and the proportion of patients with a positive response on the Treatment Benefit Scale at posttreatment week 12. OnabotulinumtoxinA significantly decreased the daily frequency of urinary incontinence episodes vs placebo (-2.65 vs -0.87, $p < 0.001$) and 22.9% vs 6.5% of patients became completely continent. A larger proportion of onabotulinumtoxinA than placebo-treated patients reported a positive response on the Treatment Benefit Scale (60.8% vs 29.2%, $p < 0.001$). Uncomplicated UTI was the most common adverse event.

Amundsen et al (2016) reported on the findings of a multicenter open-label RCT that assigned 381 women with refractory urgency urinary incontinence to cystoscopic intradetrusor injection of onabotulinumtoxinA ($n = 192$) or sacral neuromodulation ($n = 189$).⁹⁷ The primary outcome measure was change in the mean number of daily urgency urinary incontinence episodes from baseline to 6 months as measured with monthly 3-day diaries. Per protocol, analysis of data from 364 women

showed that onabotulinumtoxinA group had statistically significant greater reduction in the primary outcome compared with sacral neuromodulation group (-3.9 vs -3.3 episodes per day, $p=0.01$). However, the mean difference of 0.63 (95% CI, 0.13 to 1.14) was of uncertain clinical importance. Additionally, UTIs (35% vs 11%, respectively; risk difference, -23%; 95% CI, -33% to -13%; $p<0.001$) and need for transient self-catheterization (8% and 2% at 1 and 6 months in the onabotulinumtoxinA group) were higher in the onabotulinumtoxinA group than in the sacral neuromodulation group. Outcomes at 2 years of the open-label extension follow-up reported that no difference between the 2 therapies in reducing urgency urinary incontinence symptoms.⁹⁸

Nitti et al (2013) published data from an industry-supported study that included 557 patients with OAB and urinary incontinence inadequately controlled by anticholinergics.⁹⁹ Patients were randomized to an intradetrusor injection of onabotulinumtoxinA 100 U or placebo. At the 12-week follow-up, there was a statistically significantly greater reduction in the daily frequency of urinary incontinence episodes in the group that received botulinum toxin (-2.65) than in the placebo group (0.87; $p<0.001$). The other primary end point was the proportion of patients with a positive response at week 12 using the Treatment Benefit Scale. A significantly larger proportion of patients in the botulinum toxin group than in the placebo group reported a treatment benefit (60.8% vs 29.2%, $p<0.001$). A total of 22.9% of patients in the botulinum toxin group and 6.5% of patients in the placebo group became completely continent. In the first 12 weeks after injection, UTIs occurred in 43 (15.5%) of 278 patients in the botulinum toxin group and 16 (5.9%) of 272 patients in the placebo group. Urinary retention was reported by 15 (5.4%) patients in the botulinum toxin group and 1 (0.4%) patient in the placebo group. Between-group p values were not reported for adverse events.

In a prespecified subgroup analysis of data from this RCT and another placebo-controlled trial (Chapple et al [2013]¹⁰⁰), Sievert et al (2014) evaluated the efficacy of onabotulinumtoxinA by number of anticholinergic therapies used.¹⁰¹ Patients had used a mean of 2.4 anticholinergic therapies before enrolling in the study. At week 12, reduction in the daily number of urinary incontinence episodes was significantly greater in the onabotulinumtoxinA group than in the control group, whether or not 1, 2, 3, or more prior anticholinergics had been used. Mean reduction in daily incontinence episodes for patients with 1 prior anticholinergic was 2.82 in the onabotulinumtoxinA group and 1.52 in the placebo group ($p<0.001$); with 3 or more prior anticholinergics, it was 2.92 and 0.73, respectively ($p<0.001$). Results with a follow-up of 3.5 years (extension phase) reported durable and consistent mean reductions in urinary incontinence episodes ranging from -3.1 to -3.8.¹⁰²

An industry-supported RCT by Ginsberg et al (2012) included 416 patients with neurogenic detrusor activity associated with multiple sclerosis or spinal cord injury.¹⁰³ Patients were randomized to injections with onabotulinumtoxinA 200 U, onabotulinumtoxinA 300 U, or placebo. Decrease in the mean number of weekly incontinence episodes at week 6 (the primary end point) was significantly greater in both active treatment groups (-21 in the 200-U group, -23 in the 300-U group) than in the placebo group (-9; $p<0.001$). Urinary retention was a common adverse event. Among patients who did not catheterize at baseline, 35% were in the 200-U group, 42% were in the 300-U group, and 10% were on placebo-initiated catheterization. A total of 329 (79%) of 416 patients completed the 52-week study; however, outcomes like the number of weekly incontinence episodes were not reported at 52 weeks.

Section Summary: OAB and Neurogenic Detrusor Overactivity

Numerous RCTs and observational data studies have reported improvements in outcomes following botulinum toxin treatment in patients with neurogenic detrusor overactivity or OAB unresponsive to anticholinergic medication. Despite the risk of adverse events, including urinary retention and UTI, evidence would suggest that botulinum toxin improves the net health outcome.

Other Urologic Issues*Detrusor Sphincter Dyssynergia*

Systematic Reviews: Systematic reviews have addressed treating detrusor sphincter dyssynergia with botulinum toxin injection. Mehta et al (2012) conducted a meta-analysis on botulinum toxin injection as a treatment of detrusor external sphincter dysfunction and incomplete voiding after spinal cord injury.¹⁰⁴ Reviewers identified 2 RCTs and multiple uncontrolled studies. The RCTs included the de Seze study (discussed below) and a second study of 5 patients.

A systematic review by Karsenty et al (2006) reviewed trials of botulinum toxin type A injected into the urethral sphincter to treat different types of lower urinary tract dysfunction, grouped into neurogenic detrusor sphincter dyssynergia and non-neurogenic obstructive sphincter dysfunction.¹⁰⁵ In the former group, reviewers cited 10 small studies (N range, 3-53 patients; 3 studies included patients in both categories). Most patients were quadriplegic men unable to self-catheterize or patients (of both sexes) with multiple sclerosis. All studies except two were case reports or case series; both exceptions were controlled studies and included in the Mehta meta-analysis. The authors of both reviews noted that, while most of the available studies have reported improvements with botulinum toxin injections, there are few published studies, and those published have small sample sizes.

Randomized Controlled Trials: De Seze et al (2002) studied 13 patients with chronic urinary retention due to detrusor sphincter dyssynergia from spinal cord disease (traumatic injury, multiple sclerosis, congenital malformations) who were randomized to perineal botulinum toxin type A or lidocaine injections into the external urethral sphincter.¹⁰⁶ In the botulinum group, there was a significant decrease in the primary outcome of postvoid residual volume compared with no change in the control group (lidocaine injection). Improvements were also seen in satisfaction scores and other urodynamic outcomes.

Section Summary: Detrusor Sphincter Dyssynergia

There is a lack of adequately powered, scientifically rigorous RCTs to establish the efficacy of botulinum toxin in patients with detrusor sphincter dyssynergia.

Benign Prostatic Hyperplasia

The use of botulinum toxin to treat symptoms of benign prostatic hyperplasia (BPH) is premised in part on a static component related to prostate size and a dynamic component related to the contraction of smooth muscle within the gland. Botulinum therapy treats this latter component. Marchal et al (2012) published a systematic review on use of botulinum toxin to treat BPH.¹⁰⁷ Reviewers identified 25 studies, including controlled and uncontrolled studies and abstracts in journal supplements. There were 6 RCTs, three published as full articles and three published as abstracts (2 RCTs were included in a meta-analysis). Reviewers reported that the mean postvoiding residue, both in pre- and posttreatment, did not differ significantly; pooled results were not reported for between-group outcomes. One of the RCTs, by Maria et al (2003), reported on 30 patients with BPH randomized to intraprostatic botulinum toxin type A or saline injection.¹⁰⁸ Inclusion criteria were

moderate-to-severe symptoms of BPH based on the American Urological Association score and a mean peak urinary flow rate of no more than 15 mL per second with a void volume of 150 mL or less. After 2 months, the American Urological Association symptom score decreased by 65% among those receiving botulinum toxin compared with no significant change in the control group. Mean peak urinary flow rate was significantly increased in the treatment group.

Section Summary: Benign Prostatic Hyperplasia

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

Interstitial Cystitis

Interstitial cystitis (IC) is a chronic condition characterized by pain, urgency, and frequent urination of small volumes.

Systematic Reviews: Wang et al (2016) reported the findings of meta-analysis that included 7 RCTs and a retrospective study.¹⁰⁹ Reviewers rated only one of the 7 RCTs as high quality (ie, low risk of bias) while five were rated as moderate, and the other was rated as a high risk of bias. Moreover, reviewers reported a statistically significant effect on multiple outcome measures. However, the trials that generated these data suffered from multiple sources of bias, leading reviewers to conclude that "further well-designed, large-scale RCTs are required to confirm the findings of this analysis."

The systematic review by Tirumuru et al (2010) identified 3 RCTs and 7 prospective cohort studies evaluating intravesical botulinum toxin type A injections for IC/painful bladder syndrome.¹¹⁰ Sample sizes of all studies were relatively small (range, 10-67 patients; total N=260 patients). Treatment protocols varied (eg, dose of botulinum toxin, number of injection sites, location of injection sites). Meta-analyses were not performed due to heterogeneity among studies. All 3 RCTs were conducted outside of the United States. Two studies reported response rates as an outcome measure (both used a 7-point Global Response Assessment scale). One study found a significantly higher response rate with botulinum toxin plus hydrodistension than with hydrodistension-only, and the other found a significantly higher response rate with bacillus Calmette-Guérin therapy than with botulinum toxin. Some adverse events, in particular dysuria and voiding difficulty, were reported and 19 (7%) of 260 patients self-catheterized at some time after treatment.

Randomized Controlled Trials: Three RCTs evaluating botulinum toxin for treatment of IC and/or bladder pain syndrome have been published. One, by Akiyama et al (2015), lacked blinding and reported only 1 month of comparative data.¹¹¹ The 2 recent double-blind, placebo-controlled trials are described next.

The RCT by Kuo et al (2016) included 60 Taiwanese patients (52 women, 8 men) with IC/painful bladder syndrome who had failed at least 6 months of conventional therapy.¹¹² To be eligible, patients had to fail at least 2 types of treatment modalities (ie, oral medications, intravesical treatment with heparin or hyaluronic acid). Individuals with a variety of comorbid conditions were excluded, including those with urinary retention. Participants received intravesical injection of botulinum toxin type A (Botox 100 U) or normal saline (placebo), followed by hydrodistention under general anesthesia. The primary end point was the reduction in pain on a 10-point visual analog scale (VAS) score 8 weeks after treatment. There was a significantly greater reduction in the mean

VAS score in the botulinum toxin group (-2.6) than in the placebo group (-0.9; $p=0.021$). Secondary outcomes, including overall subjective success (assessed by a Global Response Assessment), Interstitial Cystitis Symptom Index, urinary frequency, and nocturia did not differ significantly between groups. The incidence of adverse events was significantly higher in the botulinum toxin group than in the placebo group at 8 weeks ($p=0.033$). For example, 16 (40%) patients in the botulinum group and 1 (5%) in the placebo group reported dysuria at 8 weeks.

The RCT by Manning et al (2014) included 54 women with IC or BPS refractory to at least 2 recognized treatments.¹¹³ Patients with voiding difficulty, bladder malignancy, and recurrent UTI were excluded. The primary outcome was the O'Leary-Sant (OLS) Questionnaire score, which assesses on daytime frequency, nocturia, urgency, and bladder pain. Patients received hydrodistention under general anesthesia, with either an injection of botulinum toxin type A (Dysport 500 U) or normal saline (placebo). The OLS score at 3 months did not differ significantly between groups. Scores were 20.4 (95% CI, 17.1 to 23.7) in the botulinum toxin group, and 25.3 (95% CI, 21.9 to 28.8) in the placebo group (MD=3.7; 95% CI, -0.34 to 7.6; $p=0.12$). However, in the subgroups of 42 patients without UTIs, the OLS score was significantly improved with botulinum toxin than with placebo (MD=6.1; 95% CI, 2.5 to 9.6; $p=0.02$). Adverse events were not reported.

Section Summary: Interstitial Cystitis

There is insufficient evidence that botulinum toxin improves the net health outcome in patients with IC. RCTs have had mixed findings on efficacy outcomes, and botulinum toxin has been associated with adverse events (eg, dysuria). Moreover, there is insufficient evidence comparing botulinum toxin injection with alternative treatments.

Other Indications

Clinical Context and Therapy Purpose

The purpose of botulinum toxin in patients with other conditions including tremors, musculoskeletal pain, neuropathic pain, and postsurgical pain is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does use of botulinum toxin improve the net health outcome in patients with conditions such as tremors, musculoskeletal pain, neuropathic pain, and postsurgical pain?

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

Patients

The relevant population of interest is individuals with conditions such as tremors such as benign essential tremor [upper extremity], chronic low back pain, lateral epicondylitis, joint pain, myofascial pain syndrome, temporomandibular joint disorders, trigeminal neuralgia, pain after hemorrhoidectomy, facial wound healing, pelvic and genital pain in women, neuropathic pain after neck dissection, tinnitus, pain associated with breast reconstruction after mastectomy, Hirschsprung disease, gastroparesis, and depression.

Interventions

The therapy being considered is botulinum toxin.

Comparators

The following therapies are currently being used to treat tremors: conservative measures and pharmacotherapy (including β -blockers, anticonvulsants).

The following therapies are currently being used to treat musculoskeletal pain, neuropathic pain, and postsurgical pain: conservative measures and pharmacotherapy including non-steroidal anti-inflammatory drugs, anticonvulsants, antidepressants, and opioids.

Outcomes

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

Timing

Follow-up ranges from 4 to 12 weeks to monitor outcomes.

Setting

Patients with tremors, musculoskeletal pain, neuropathic pain, and postsurgical pain may be managed by general physicians, pain specialists, neurologists, and/or endocrinologists; botulinum toxin is injected in an appropriate muscle in an outpatient setting.

Tremor

A tremor can be defined as alternate or synchronous contractions of antagonistic muscles. Some patients may be disabled by severe or task-specific tremors. Tremors are also a frequent component of dystonias, and successful treatment of dystonias can reduce tremors.

Three randomized, placebo-controlled studies have addressed essential hand tremors; the trial by Brin et al (2001) enrolled 133 patients, and the trial by Jankovic et al (1996) enrolled 25 patients.^{114,115} These RCTs reported inconsistent findings using tremor symptom scales and neither reported functional outcomes. The third trial, by Mittal et al (2017), randomized 30 patients with essential tremor and Parkinson disease tremor to incobotulinumtoxinA in a crossover design.¹¹⁶ Treatment efficacy was evaluated by the tremor subsets of the Unified Parkinson's Disease Rating Scale, the Patient Global Impression of Change 4, and an evaluation set for 8 weeks after each of the 2 sets of treatments. There were statistically significant improvements in clinical rating scores of rest tremor and tremor severity at 4 and 8 weeks after the incobotulinumtoxinA injection and of action/postural tremor at 8 weeks; however, there was no statistically significant difference in grip strength at 4 weeks between the 2 groups. Other studies have shown that 30% to 70% patients who receive onabotulinumtoxinA for tremor develop moderate-to-severe hand weakness. Botulinum toxin has been investigated in patients with tremors unrelated to dystonias in case reports and case series.

Section Summary: Tremor

The clinical significance of contradictory findings from 2 RCTs in patients with tremor are unclear. While a third small crossover trial has reported a statistically significant reduction in tremors in patients with Parkinson disease, a larger trial with longer term follow-up is required to replicate these findings and provide long-term follow-up to mitigate the risk of developing hand weakness over the course of time.

Musculoskeletal, Neuropathic, and Postsurgical Pain

Chronic Low Back Pain

Only 1 RCT of botulinum toxin type A treatment in patients with low back pain has been published.¹¹⁷ The trial, by Foster et al (2001), enrolled 31 consecutive patients with chronic low back pain of at least 6 months in duration and more predominant pain on 1 side. Patients were injected with Botox 40 U at 5 lumbosacral locations for a total of 200 U (treated group) or saline placebo (placebo group). Injections were made on one side of the back only, depending on predominance of pain. At 8 weeks, 60% of treated patients and 12.5% of placebo patients showed reductions in VAS pain scores ($p=0.009$). Perceived functional status (Oswestry Disability Index) at 8 weeks showed that 66.7% of treated patients and 18.8% of placebo patients were responders ($p=0.011$).

Section Summary: Chronic Low Back Pain

The population with chronic low back pain is heterogeneous. Results of a small RCT in a group of selected subjects cannot be used to generalize results for the whole population with chronic low back pain. Furthermore, studies should examine the long-term effectiveness of repeated courses of botulinum toxin to determine the durability of repeated treatments.

Lateral Epicondylitis

Lin et al (2017) published a systematic review and meta-analysis that included 6 RCTs (total $N=321$ participants) comparing botulinum toxin with placebo or corticosteroid injections.¹¹⁸ Reviewers assessed SMDs in pain relief and grip strength at 3 time points: 2 to 4, 8 to 12, and 16 weeks or more after injection. Compared with placebo, botulinum toxin injection significantly reduced pain at all 3 time points (SMD = -0.73; 95% CI, -1.29 to -0.17; SMD = -0.45; 95% CI, -0.74 to -0.15; SMD = -0.54; 95% CI, -0.99 to -0.11, respectively). Botulinum toxin was less effective than corticosteroid at 2 to 4 weeks (SMD=1.15; 95% CI, 0.59 to 1.78), and both treatments appeared similar in efficacy after 8 weeks.

Krogh et al (2013) published a systematic review and meta-analysis on the comparative effectiveness of injection therapies for lateral epicondylitis.¹¹⁹ Seventeen trials, four of which evaluated botulinum toxin, were identified. In a meta-analysis, botulinum toxin showed marginal benefit (SMD = -0.50; 95% CI, -0.81 to -0.08). All trials were at high risk of bias, and the treatment was associated with temporary paresis of finger extension.

Another relevant systematic review was conducted by Sims et al (2014).¹²⁰ The systematic review addressed nonsurgical treatment of lateral epicondylitis. Reviewers identified 58 RCTs. Four addressed treatment with botulinum toxin, and the remainder addressed other treatments (eg, corticosteroid injection, iontophoresis, prolotherapy). All trials were placebo-controlled. Three of the trials did not report significant differences in pain scores or grip strength over 18 weeks. The other 3 RCTs found significant improvements in pain scores, but not in grip strength. All studies had patients in treatment groups who reported transient weakness in finger extension.

Section Summary: Lateral Epicondylitis

Several systematic reviews have identified a small number of RCTs evaluating botulinum toxin for treating epicondylitis. The RCTs were generally considered to be at high risk of bias, had mixed findings, and all reported transient adverse events for patients treated with botulinum toxin. The RCTs evaluating botulinum toxin were all placebo-controlled, and potential alternative treatments are available for this condition that could have been compared with botulinum toxin. A systematic

review that included trials comparing botulinum toxin with corticosteroid injections reported that botulinum toxin was less effective than corticosteroid at 2 to 4 weeks and both treatments appeared similar in efficacy after 8 weeks.

Other Joint Pain

Two case series of patients with chronic joint pain refractory to conservative management studied the effect of botulinum toxin type A injections into several joints of patients with arthritis and into the knee joint of patients with chronic knee pain (1 case series specified that Dysport was to be used).^{121,122} Both patient groups reported significant reductions in joint pain and improvements in function compared with baseline, lasting for 3 to 12 months. Although the results of several trials of botulinum toxin injections into joints for chronic pain favored treatment, some did not.

Section Summary: Other Joint Pain

Due to the lack of consistent findings from well-designed studies, the evidence is insufficient that botulinum toxin for treatment of other joint pain improves the net health outcome.

Myofascial Pain Syndrome

Myofascial pain syndrome is characterized by muscle pain with increased tone and stiffness associated with myofascial trigger points. Patients are often treated with trigger point injections with saline, dilute anesthetics, or dry needling. These injections, while established therapy, have been controversial because it is unclear whether any treatment effect is due to the injection, dry needling of the trigger point, or a placebo effect. The optimal study design to evaluate the efficacy of botulinum toxin injection for treating myofascial pain syndrome would be a double-blind RCT to minimize the placebo effect and would compare botulinum toxin injections with dry needling and/or with anesthetic injection.

Systematic Reviews: Several systematic reviews of RCTs have evaluated botulinum toxin injection for myofascial pain syndrome. More recently, a Cochrane review by Soares et al (2014) identified 4 RCTs (total N=233 patients).¹²³ All RCTs were placebo-controlled and double-blind. Three were prospective, and one used a crossover design. Follow-up in the prospective studies was 12 weeks in 2 studies and 4 weeks in the third. Due to heterogeneity among studies, reviewers did not pool analyses. The primary outcomes were change in pain as assessed by validated instruments. Three of the 4 studies found that botulinum toxin did not significantly reduce pain intensity. Another 2014 systematic review had similar findings.¹²⁴

A systematic review that included a meta-analysis was published by Langevin et al (2011).¹²⁵ A pooled analysis from 4 placebo-controlled trials did not find a statistically significant benefit of botulinum toxin. The SMD was -0.21 (95% CI, -0.50 to 0.70).

Randomized Controlled Trials: An industry-sponsored RCT by Nicol et al (2014), not included in the systematic reviews, focused on patients with myofascial pain who had responded to an initial injection of botulinum toxin type A.¹²⁶ A total of 114 patients received an initial injection and 54 responders were subsequently randomized to a second injection of botulinum toxin or saline placebo 14 weeks after the initial injection. At week 26 after the initial injection, but not at week 20, there was a significantly greater improvement in the mean visual numeric scores for pain in the botulinum toxin group than in the placebo group ($p=0.019$). There was no significant difference between groups at week 26, compared with baseline, in QOL using the 36-Item Short-Form Health Survey. Thus, this trial had mixed outcomes and restricted study participation to a responder.

group. As a result, this inclusion criterion could have biased the proportion of patients who initially experienced a placebo response, thereby making blinding more difficult for those familiar with side effects of the active treatment.

Section Summary: Myofascial Pain

Several RCTs have evaluated botulinum toxin for treatment of myofascial pain syndrome. Studies were double-blind, but compared botulinum toxin with placebo, rather than common alternative treatments. Most trials, as well as a pooled analysis of study findings, did not report improved health outcomes with botulinum toxin.

Temporomandibular Joint Disorders

A systematic review by Chen et al (2015) evaluated the literature on botulinum toxin for treatment of temporomandibular joint disorders.¹²⁷ Eligibility included RCTs comparing any dose or type of botulinum toxin with any alternative intervention or placebo. Five RCTs met the inclusion criteria; two were parallel- group studies, and two were crossover studies. Study sizes tended to be small; all but one included 30 or more participants. Three of the 5 studies were judged to be at high risk of bias. All studies administered a single injection of botulinum toxin and followed patients up at least 1 month later. Four studies used a placebo (normal saline) control group and the fifth used botulinum toxin to fascial manipulation. The primary outcome was a validated pain scale. Data were not pooled due to heterogeneity among trials. In a qualitative review of the studies, only 2 of the 5 trials found a significant short-term (1-to-2 months) benefit of botulinum toxin compared with control on pain reduction.

Section Summary: Temporomandibular Joint Disorders

A systematic review of RCTs found insufficient evidence that botulinum toxin improves the net health outcome in patients with temporomandibular joint disorders. Studies have tended to be small, have a high risk of bias, and only 2 of 5 RCTs found that botulinum toxin reduced pain more than a comparator.

Trigeminal Neuralgia

Systematic Reviews: Morra et al (2016) published a systematic review that included 4 RCTs (total N=178 patients).¹²⁸ Pooled results showed that patients receiving botulinum toxin type A were 2.87 (95 % CI, 1.76 to 4.69; $p<0.001$) times more likely to be responder (defined as patients with >50% reduction in mean pain score from baseline to end point) than the controls, with no significant detected heterogeneity ($p=0.31$; $I^2=4\%$). Further, there was reduction in the paroxysms frequency per day (MD = -29.79; 95 % CI, -38.50 to -21.08; $p<0.001$).

Randomized Controlled Trials: Three RCTs using botulinum toxin to treat trigeminal neuralgia were identified; all were double-blind, placebo-controlled, conducted in China, and appear to have been done by the same research group. No industry funding was reported. Sample sizes in the trials were relatively small, with fewer than 30 in any one. More recently, an RCT by Zhang et al (2014) included 84 patients with trigeminal neuralgia for at least 4 months who had failed other treatments (most commonly carbamazepine, gabapentin, or opioids), had a mean pain intensity score of at least 4, and had a mean attack frequency of at least 4 per day.¹²⁹ Medication treatment remained unchanged during the trial. Patients were randomized to 1 of 3 groups: a single injection of normal saline (placebo) (n=28), botulinum toxin 25 U/l (n=27), or botulinum toxin 75 U/l (n=29). The primary efficacy outcome was the proportion of responders, defined as at least a 50% reduction in the mean pain score from baseline to 8 weeks. Pain severity was measured on an 11-

point VAS (0-10 points). Mean baseline VAS scores were similar across the 3 groups (range, 6.24-7.18). At week 8, the proportion of responders was 32.1% in the placebo group, 70.4% in the 25-U group, and 86.2% in the 75-U group ($p<0.002$). No severe adverse events were reported, and no patients discontinued study participation due to adverse events. No severe or long-lasting adverse events were reported.

An RCT by Shehata et al (2013) in Egypt included 20 women diagnosed with intractable idiopathic trigeminal neuralgia, defined as insufficient response to medication treatments for 3 months prior to study participation.¹³⁰ Patients were randomized to a single injection of botulinum toxin type A or placebo. The primary efficacy outcome was reduction in pain, as measured by a 10-point VAS, and change in frequency of paroxysms. Baseline VAS scores were similar (8.3 in the botulinum toxin group, 8.3 in the placebo group). At 12 weeks postinjection, the VAS score decreased by 6.5 points in the botulinum toxin group and by 0.3 points in the placebo group ($p<0.001$). Paroxysm frequency was a secondary outcome. The baseline frequency of paroxysm was 39.2 in the botulinum toxin group and 36.7 in the placebo group. After 12 weeks, the mean frequency of paroxysms per day was 4.0 per day and 36.1 per day, respectively ($p<0.001$).

The third trial, published by Wu et al (2012), included 42 patients with trigeminal neuralgia.¹³¹ To be eligible for participation, patients had to have a mean pain intensity of at least 4 and a mean attack frequency of at least 4 per day despite medication therapy. Most patients were taking medication at baseline (eg, opioids, carbamazepine, gabapentin); medications remained unchanged during the trial. Patients were randomized to botulinum toxin type A 75 U or saline (placebo). They were followed for 12 weeks. The primary end points were pain severity and pain attack frequency. Symptoms were recorded by patients each morning, for the previous 24-hour period using a VAS. Both of the primary end points were statistically significantly better in the treatment group than in the control group. The proportion of patients with at least a 50% reduction in the mean pain score from baseline to 12 weeks (a secondary end point) was 15 (68%) of 22 in the botulinum toxin group and 3 (15%) of 20 in the placebo group ($p<0.01$). No severe or long-lasting adverse events were reported.

Section Summary: Trigeminal Neuralgia

Three small RCTs from China and one from Egypt have assessed patients who had failed medication treatment; the RCTs found a statistically significant benefit for botulinum toxin type added to their medication regimen vs placebo on pain intensity and attack frequency. Limitations of the evidence base included studies from only a single research group, the small overall number of patients evaluated, relatively short follow-up (8-12 weeks), and lack of reported statistical power analysis. In the absence of power analysis, there is a higher chance of spurious statistically significant findings.

Pain Control After Hemorrhoidectomy

Several small RCTs of botulinum toxin intrasphincter injection for controlling pain after hemorrhoidectomy have been published. A trial by Patti et al (2005) randomized 30 patients to botulinum toxin 20 U or saline injection and reported a significantly shorter duration of postoperative pain at rest and during defecation in the treated group.¹³² A trial by Patti et al (2006), which also included 30 patients, found significant differences in postoperative maximum resting pressure change from baseline with botulinum toxin vs topical glyceryl trinitrate ($p<0.001$).¹³³ In addition, there was a significant reduction in postoperative pain at rest ($p=0.01$) but not during defecation. There was no difference in healing.

Section Summary: Pain Control After Hemorrhoidectomy

RCTs evaluating botulinum toxin injection after hemorrhoidectomy have suggested improvement in pain control; however, findings need confirmation in larger trials.

Facial Wound Healing

Ziade et al (2013) reported on a trial including 30 adults presenting to the emergency department with facial wounds without tissue loss.¹³⁴ Patients were assigned to have an injection of botulinum toxin (n=11) or no injection (n=13) within 72 hours of the suturing of the wounds. The primary outcomes were scores on the following scales at 1 year: Patient Scar Assessment Scale (PSAS), Observer Scar Assessment Scale (OSAS), Vancouver Scar Scale (VSS), and a 1 to 10 VAS. The PSAS is a patient-reported outcome, the OSAS and VSS were assessed clinically by a blinded independent evaluator, and the VAS was assessed using photograph analysis by a team of 6 medical specialists. Patients were not blinded to treatment group, and thus PSAS scores might have been a more subjective outcome, whereas it is likely that OSAS, VSS, and VAS scores were objectively assessed. Twenty-four (80%) of 30 patients were available for the 1-year follow-up. There were no significant differences between groups in the PSAS, OSAS, and VSS scores. For example, median OSAS score was 8 in the botulinum toxin group and 9 in the control group. However, a significant between-group difference was found for the VAS score, favoring the botulinum toxin group. Median VAS score was 8.25 for the botulinum group and 6.35 for the control group ($p<0.001$). These results demonstrated a lack of consistency in finding a benefit across outcomes—there was no significant difference in the patient-reported or clinically assessed outcomes, only in the outcome based on photographic analysis.

Previously, Gassner et al (2006) conducted a small RCT of botulinum toxin–induced immobilization of facial lacerations to improve wound healing compared with placebo (n=31).¹³⁵ The outcome was determined by blinded assessment of photographs of wound healing at intervals using a VAS. The trialists reported enhanced wound healing in the treatment arm (8.9) compared with the placebo arm (7.2; $p=0.003$).

Section Summary: Facial Wound Healing

There are few RCTs evaluating botulinum toxin for facial wound healing, and the available trials offer inconsistent evidence of benefit.

Pelvic and Genital Pain in Women

Randomized Controlled Trials: One double-blind, randomized, placebo-controlled trial by Abbott et al (2006) evaluated 60 women with chronic pelvic pain and pelvic floor spasm.¹³⁶ Patients received injections of botulinum toxin type A or placebo. Pain scores were reduced for both groups, but there were no significant differences between groups. The trial likely was underpowered to detect clinically significant differences in outcomes between groups.

Nonrandomized Studies: Other studies include a small, open-label trial by Dykstra et al (2006) that tested botulinum toxin type A injections in painful vulvar tissue to alleviate provoked vestibulodynia (n=19).¹³⁷ Patients receiving up to 2 doses had significantly reduced pain compared with baseline for 8 (lower dose) to 14 weeks (higher dose). A prospective cohort study by Jarvis et al (2004) tested different doses of botulinum toxin in 12 women with pelvic floor muscle hypertonicity and

history of chronic pelvic pain.¹³⁸ Compared with baseline, there were nonsignificant reductions in pelvic pain and nonsignificant improvements in QOL.

Section Summary: Pelvic and Genital Pain in Women

A single inadequately powered RCT that evaluated botulinum toxin to treat pelvic or genital pain in women failed to demonstrate statistically significant reduction in pain scores compared with placebo.

Neuropathic Pain After Neck Dissection

Two open-label trials of 16 and 23 patients, respectively, who had failed conservative therapy investigated various doses of botulinum toxin type A injected into the area of complaint.^{139,140} For both studies, which were conducted by the same group, results indicated significant reductions in pain compared with baseline and trends toward improved QOL.

Section Summary: Neuropathic Pain After Neck Dissection

Lack of a randomized, placebo-controlled trial, controlling for strong placebo effects in pain therapy, render the results of 2 open-label trials inconclusive for the use of botulinum toxin to treat neuropathic pain after neck dissection.

Tinnitus

Systematic Reviews: Slengerik-Hansen et al (2016) reported the findings of a systematic review of 22 studies, which mainly included case reports and case series with a total of 51 treated patients.¹⁴¹ Reviewers acknowledged that selected studies suffered from an extremely low evidence level with several sources of bias.

Randomized Controlled Trials: Stidham et al (2005) explored the use of botulinum toxin type A injections for tinnitus treatment under the theory that blocking the autonomic pathways would reduce the perception of tinnitus.¹⁴² In this trial, 30 patients were randomized in a double-blind study to 3 subcutaneous injections of botulinum toxin type A around the ear followed by placebo injections 4 months later, or placebo injections first, followed by botulinum toxin type A. The trialists reported that 7 patients had reduced tinnitus after the botulinum toxin type A injections, which was statistically significant compared with the placebo groups in which only 2 patients reported reduced tinnitus ($p < 0.005$). Tinnitus Handicap Inventory scores were also significantly lower between pretreatment and 4 months after botulinum toxin type A injections. However, no other significant differences were noted between both treatments at 1 and 4 months postinjection. Trial limitations included sample size and lack of intention-to-treat analysis.

Section Summary: Tinnitus

The evidence for botulinum toxin in patients with tinnitus consists mostly of case reports and case series. Well-conducted RCTs with sufficiently large sample sizes are needed to demonstrate that botulinum toxin improves the net health outcomes in patients with tinnitus.

Pain Associated with Breast Reconstruction After Mastectomy

There are no published RCTs evaluating botulinum toxin for pain associated with breast reconstruction after mastectomy. A systematic review by Winocour et al (2014) identified 7 studies on perioperative injection of botulinum toxin type A following breast reconstruction surgery.¹⁴³ They consisted of 2 prospective controlled cohort studies, 3 retrospective controlled cohort studies, and 2 case series. Most studies were small; only 1 (N=293) had more than 50 participants. Three studies

assessed postoperative pain and all three found that at least some outcomes were significantly better in the botulinum toxin group than in the comparison group.

Section Summary: Pain Associated with Breast Reconstruction After Mastectomy

The evidence for botulinum toxin in patients with pain associated with breast reconstruction after mastectomy mostly consists of observational studies. Well-conducted RCTs with sufficiently large sample sizes are needed to demonstrate that botulinum toxin improves the net health outcomes in these patients.

Hirschsprung Disease

The published literature on use of botulinum toxin injection to treat Hirschsprung disease consists of small case series.¹⁴⁴⁻¹⁴⁶ The largest prospective case series, published by Minkes and Langer (2000), included 18 children (median age, 4 years) with persistent obstructive symptoms after surgery for Hirschsprung disease.¹⁴⁵ Patients received injections of botulinum toxin (Botox) into 4 quadrants of the sphincter. The total dose of botulinum toxin during the initial series of injections was 15 to 60 U. Twelve (67%) of 18 patients improved for more than 1 month and the remaining 6 (33%) either showed no improvement or improved for less than 1 month. Ten children had 1 to 5 additional injections due to either treatment failure or recurrence of symptoms; retreatment was not based on a standardized protocol.

A series by Patrus et al (2011) retrospectively reviewed outcomes in 22 patients with Hirschsprung disease treated over 10 years; subject had received a median of 2 (range, 1-23) botulinum toxin injections for postsurgical obstructive symptoms.¹⁴⁶ The formulation of botulinum toxin was not specified. Median follow-up (time from first injection to time of chart review) was 5.0 years (range, 0-10 years). At chart review, 2 (9%) of 22 patients had persistent symptoms. Eighteen (80%) children had a "good response" to the initial treatment (not defined), and 15 (68%) had additional injections. The authors reported that the number of hospitalizations for obstructive symptoms decreased significantly after botulinum toxin injection (median, 0) compared with preinjection (median, 1.5; $p=0.003$). The authors did not report whether patients received other treatments during the follow-up period in either case series.

Section Summary: Hirschsprung Disease

The evidence for botulinum toxin in patients with Hirschsprung disease mostly consists of observational studies. Well-conducted RCTs with sufficiently large sample sizes are needed to demonstrate that botulinum toxin improves the net health outcome in such patients.

Gastroparesis

Systematic Reviews: A systematic review by Bai et al (2010) identified 15 studies on botulinum toxin injection to treat gastroparesis.¹⁴⁷ Two studies were RCTs; the remainder was case series or open-label observational studies. Reviewers stated that, while the nonrandomized studies generally found improvements in subjective symptoms and gastric emptying after botulinum toxin injections, the RCTs did not confirm the efficacy of botulinum toxin for treating gastroparesis. Reviewers concluded that there was insufficient evidence to recommend botulinum toxin for gastroparesis. Brief summaries of the 2 RCTs follow.

Randomized Controlled Trials: Arts et al (2007) published a randomized crossover study with 23 patients.¹⁴⁸ The trial included consecutive patients at a single institution who had symptoms suggestive of gastroparesis and established delayed gastric emptying for solids and liquids. Patients

received, in random order, injections of Botox or saline during gastrointestinal endoscopies, with a 4-week interval between injections. Symptoms were assessed using the Gastroparesis Cardinal Symptom Index (GCSI), which has a maximum score of 45. There were no statistically significant differences in improvement after botulinum toxin injection or saline injection for either solid or liquid emptying times. For example, liquid half-emptying time was 8.2 minutes after Botox injection and 22.5 minutes after saline injection ($p>0.05$). In addition, in pooled analyses, mean total GCSI score did not differ significantly after Botox (6.1) compared with saline treatment (3.8; $p>0.05$).

The other RCT, by Friedenberg et al (2008), was a single-center, double-blind trial with 32 patients.¹⁴⁹ Patients had delayed gastric emptying and GCSI scores of 27 or higher. They received an injection of Botox ($n=16$) or saline placebo ($n=16$). All patients completed the trial. Patients were evaluated with gastric emptying scintigraphy prior to treatment and at a 1-month follow-up. The proportion of patients with at least a 9-point reduction in GCSI score at 1 month (the primary end point) was 6 (37.5%) of 16 in the Botox group and 9 (56.3%) of 16 in the placebo group; the difference between groups was not statistically significant. Improvement in gastric emptying after 1 month (a secondary end point) also did not differ significantly between groups.

Section Summary: Gastroparesis

Two small inadequately powered RCTs failed to show a benefit of botulinum toxin for treatment of gastroparesis. Additional adequately powered RCTs are needed.

Depression

Magid et al (2015) published a meta-analysis of 3 placebo-controlled randomized trials evaluating botulinum toxin type A for treating unipolar major depressive disorder.¹⁵⁰ Sample sizes were small; a total of 59 patients were treated with botulinum toxin and 75 with placebo. In a pooled analysis of individual patient data, there was a significantly higher response rate in the botulinum toxin group (54.2%) than in the placebo group (10.7%; OR=7.3; 95% CI, 2.4 to 22.5). Other outcomes also favored the botulinum toxin group. No RCTs compared botulinum toxin with antidepressant treatment, which is standard of care.

Section Summary: Depression

A pooled analysis of 3 small RCTs showed a statistically significant benefit of botulinum toxin compared with placebo. Studies were small and did not compare botulinum toxin with antidepressants.

SUMMARY OF EVIDENCE

For individuals who have dystonia or spasticity resulting in functional impairment and/or pain (eg, interference with joint function, mobility, communication, nutritional intake) who receive botulinum toxin injections, the evidence includes multiple RCTs and meta-analyses. Relevant outcomes are symptoms, functional outcomes, medication use, and treatment-related morbidity. The data support the efficacy of botulinum toxin for improving dystonia or spasticity in patients with various conditions. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have strabismus who receive botulinum toxin injections, the evidence includes several RCTs. Relevant outcomes are symptoms, functional outcomes, and treatment-related morbidity. RCTs evaluating botulinum toxin have reported mixed findings; treatment with botulinum toxin is a noninvasive alternative to surgery and is associated with fewer harms. The evidence is

sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have blepharospasm or facial nerve (cranial nerve VII) disorders who receive botulinum toxin injections, the evidence includes several RCTs. Relevant outcomes are symptoms, functional outcomes, and treatment-related morbidity. RCTs and a systematic review have found symptom improvements in patients treated with botulinum toxin compared with alternative interventions. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have chronic migraine headache who receive botulinum toxin injections, the evidence includes several RCTs and meta-analyses. Relevant outcomes are symptoms, medication use, and treatment-related morbidity. RCTs have reported mixed findings; a meta-analysis found that botulinum toxin reduced the frequency of headaches per month compared with placebo or medication. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have esophageal achalasia who receive botulinum toxin injections, the evidence includes a number of RCTs and a systematic review of RCTs. Relevant outcomes are symptoms, functional outcomes, and treatment-related morbidity. The systematic review found similar efficacy and less harm with botulinum toxin than with pneumatic dilation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have sialorrhea (drooling) associated with Parkinson disease who receive botulinum toxin injections, the evidence includes several RCTs. Relevant outcomes are symptoms, functional outcomes, and treatment-related morbidity. RCTs have consistently found that botulinum toxin provides benefit. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have sialorrhea (drooling) not associated with Parkinson disease who receive botulinum toxin injections, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, and treatment-related morbidity. Available individual RCTs are small and have not consistently found a clinically meaningful improvement with botulinum toxin therapy. In several trials, rates of adverse events were notably high, making the risk-benefit ratio of botulinum toxin therapy uncertain. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have IAS achalasia who receive botulinum toxin injections, the evidence includes 2 RCTs and multiple nonrandomized studies, which have been summarized in a systematic reviews and meta-analysis. Relevant outcomes are symptoms, health status measures, and treatment-related morbidity. In a systematic review of nonrandomized studies comparing botulinum toxin injection with myectomy, outcomes were more favorable after surgery. Though the 2 RCTs reported temporary improvement in symptoms after botulinum toxin injections, methodologic limitations, including small sample sizes, lack of blinded assessments, and lack of use of validated outcome measures, limit the interpretation of these RCTs. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have chronic anal fissure who receive botulinum toxin injections, the evidence includes a number of RCTs and a systematic review. Relevant outcomes are symptoms, health status measures, and treatment-related morbidity. Studies have found similar efficacy with botulinum toxin or surgery, and less potential harm with toxin injections. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have urinary incontinence due to detrusor overactivity associated with OAB or with neurogenic causes who receive botulinum toxin injections, the evidence includes numerous RCTs. Relevant outcomes are symptoms, medication use, and treatment-related morbidity. Studies have shown that botulinum toxin is effective at reducing symptoms in patients unresponsive to anticholinergic medications. There are adverse events associated with botulinum toxin (eg, urinary retention, urinary tract infection), but patients may find that benefits outweigh harms. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with urologic issues other than detrusor overactivity or OAB (eg, detrusor sphincter dyssynergia, BPH, IC) who receive botulinum toxin injections, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, medication use, and treatment-related morbidity. Available RCTs for these conditions are small and have reported mixed findings on the benefit of botulinum toxin. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have other indications (eg, tremors such as benign essential tremor [upper extremity], chronic low back pain, lateral epicondylitis, joint pain, myofascial pain syndrome, temporomandibular joint disorders, trigeminal neuralgia, pain after hemorrhoidectomy, facial wound healing, pelvic and genital pain in women, neuropathic pain after neck dissection, tinnitus, pain associated with breast reconstruction after mastectomy, Hirschsprung disease, gastroparesis, and depression) who receive botulinum toxin injections, evidence includes case series or a few small, flawed RCTs. Relevant outcomes are symptoms, functional outcomes, medication use, and treatment-related morbidity. Evidence of benefit from large, well-conducted RCTs is lacking for these indications. The evidence is insufficient to determine the effects of the technology on health outcomes.

CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

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

2011 Input

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

considered botulinum toxin medically necessary for patients with chronic migraines generally thought its use should be limited to patients unresponsive to other treatments.

2008 Input

Input was received on a number of indications from 3 academic medical centers and 5 physician specialty societies while this policy was under review in 2008. Nearly all reviewers agreed with the investigational determination for use in headaches and on the investigational role for antibody testing. Among the 4 reviewers who commented on use in sialorrhea, 2 reviewers felt this was medically necessary, and two disagreed.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Urological Association

In 2012 (updated 2014), the American Urological Association (AUA) issued a guideline on non-neurogenic overactive bladder in adults.¹⁵¹ The guideline includes intradetrusor onabotulinumtoxinA injection as a third-line treatment option in “carefully selected and thoroughly-counseled” patients who are refractory to first- and second-line treatments and are willing to perform self-catheterization if needed for postvoid retention.

In 2014, AUA issued a guideline on diagnosis and treatment of interstitial cystitis/bladder pain syndrome.¹⁵² The guidelines include intradetrusor onabotulinumtoxinA injection as a fourth-line treatment, following conservative therapies, pain management, physical therapy, oral medications, intravesical treatments, cystoscopy, and fulguration. The guideline noted that some patients require intermittent self-catheterization after botulinum toxin injection and that the treatment is relatively contraindicated for patients with evidence of impaired bladder emptying.

American Academy of Neurology

In 2016, the American Academy of Neurology (AAN) updated its practice guidelines on use of botulinum toxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and chronic headache.¹⁵³ The update replaced 2008 guidelines for these conditions. The updates are listed in Table 2.

Table 2. Recommendations for Use of Botulinum Toxin to Treat Various Disorders

	Recommendation	LOR
Blepharospasm	<ul style="list-style-type: none"> • OnabotulinumtoxinA and incobotulinumtoxinA injections should be considered • AbobotulinumtoxinA may be considered 	B C
Cervical dystonia	<ul style="list-style-type: none"> • AbobotulinumtoxinA and rimabotulinumtoxin B should be offered • OnabotulinumtoxinA and incobotulinumtoxinA should be considered 	A B
Focal manifestations of adult spasticity involving the upper limb	<ul style="list-style-type: none"> • AbobotulinumtoxinA, incobotulinumtoxin A, and onabotulinumtoxin A should be offered • RimabotulinumtoxinB should be considered as treatment options. • OnabotulinumtoxinA should be considered as a treatment option before tizanidine for treating adult upper-extremity spasticity 	A B B
For focal manifestations of adult spasticity involving the lower limb	<ul style="list-style-type: none"> • OnabotulinumtoxinA and abobotulinumtoxin A should be offered as treatment options. • There is insufficient evidence to support or refute a benefit of incobotulinumtoxin A or rimabotulinumtoxin B for treatment of adult lower-limb spasticity 	A
Headache		

Recommendation	LOR
• To increase the number of headache-free days, onabotulinumtoxin A should be offered as a treatment option to patients with chronic headaches	A
• Onabotulinumtoxin A should be considered to reduce headache impact on health-related quality of life. Chronic migraine refers to migraine attacks occurring 15 days or more monthly for at least 3 months, with attacks lasting 4 hours or more.	B
• OnabotulinumtoxinA should not be offered as a treatment for episodic migraines. Episodic migraine refers to migraine with a lesser frequency of attack.	A

LOR: level of recommendation.

In 2011, the American Academy of Neurology (AAN), Quality Standards Subcommittee, published an update of evidence-based recommendations for treating essential tremor.¹⁵⁴ The report reaffirmed the Academy's previous position that botulinum toxin is "possibly effective" and may be considered to reduce limb tremor associated with essential tremor. These recommendations were reaffirmed by the AAN in 2014 and endorsed by the International Essential Tremor Foundation.¹⁵⁵

In 2010, AAN's Quality Standards Subcommittee and the Child Neurology Society's Practice Committee published a practice parameter on the pharmacologic treatment of spasticity in children and adolescents with cerebral palsy.¹⁵⁶ Botulinum toxin A was considered an effective and generally safe treatment for localized/segmental spasticity requiring treatment. There were insufficient data on use of botulinum toxin B. ANN's website indicates the practice parameter was reaffirmed in 2013.¹⁵⁷

In 2008, AAN's Therapeutics and Technology Assessment Subcommittee published evidence-based recommendations on botulinum toxin for treatment of autonomic disorders and pain.¹⁵⁸ The subcommittee recommended that botulinum toxin be offered as a treatment option for detrusor activity, should be considered for drooling and for detrusor sphincter dyssynergia after spinal cord injury, and may be considered for low back pain.

American Society of Colon and Rectal Surgeons

The 2017 revision of a practice parameter on the treatment of anal fissures by the American Society of Colon and Rectal Surgeons has recommended that:

"Botulinum toxin has similar results compared with topical therapies as first-line therapy for chronic anal fissures, and modest improvement in healing rates as second-line therapy following treatment with topical therapies. Grade of Recommendation: Strong recommendation based on low- and very-low-quality evidence."¹⁵²

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

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

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02270736	Clinical Study to Investigate the Efficacy and Safety of NT 201 Compared to Placebo in the Treatment of Chronic Troublesome	249	Apr 2019

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Contains Public Information

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Drooling Associated With Neurological Disorders and/or Intellectual Disability		
NCT02414425	Effect and Tolerance of Botulinum A Toxin Rectal Injections on Fecal Incontinence (FI_TOXIN)	200	Jul 2019
Unpublished			
NCT02555982	Evaluation of Botulinum Toxin Injection Efficacy in the Treatment of Head Essential Tremor	120	Dec 2017 (unknown)

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

CODING

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

CPT/HCPCS

- 31513 Laryngoscopy, indirect; with vocal cord injection
- 31570 Laryngoscopy, direct, with injection into vocal cord(s), therapeutic;
- 31571 Laryngoscopy, direct, with injection into vocal cord(s), therapeutic; with operating microscope or telescope
- 43201 Esophagoscopy, flexible, transoral; with directed submucosal injection(s), any substance
- 43236 Esophagogastroduodenoscopy, flexible, transoral; with directed submucosal injection(s), any substance
- 46505 Chemodenervation of internal anal sphincter
- 52287 Cystourethroscopy, with injection (s) for chemodenervation of the bladder
- 64611 Chemodenervation of parotid and submandibular salivary glands, bilateral
- 64612 Chemodenervation of muscle(s); muscle(s) innervated by facial nerve, unilateral (eg, for blepharospasm, hemifacial spasm)
- 64615 Chemodenervation of muscles(s); muscles(s) innervated by facial, trigeminal, cervical spinal and accessory nerves, bilateral (eg, for chronic migraine)
- 64616 Chemodenervation of muscle(s); neck muscle(s), excluding muscles of the larynx, unilateral (eg, for cervical dystonia, spasmodic torticollis)
- 64617 Chemodenervation of muscle(s); larynx, unilateral, percutaneous (eg, for spasmodic dysphonia), includes guidance by needle electromyography, when performed
- 64642 Chemodenervation of one extremity; 1-4 muscle(s)
- 64643 Chemodenervation of one extremity; each additional extremity, 1-4 muscle(s) (List separately in addition to code for primary procedure)
- 64644 Chemodenervation of one extremity; 5 or more muscle(s)
- 64645 Chemodenervation of one extremity; each additional extremity, 5 or more muscle(s) (List separately in addition to code for primary procedure)
- 64646 Chemodenervation of trunk muscle(s); 1-5 muscle(s)
- 64647 Chemodenervation of trunk muscle(s); 6 or more muscle(s)
- 67345 Chemodenervation of extraocular muscle
- J0585 Injection, onabotulinumtoxinA, 1 unit

J0586 Injection, abobotulinumtoxinA, 5 units
 J0587 Injection, rimabotulinumtoxinB, 100 units
 J0588 Injection, incobotulinum A, 1 unit

ICD-10 Diagnoses

G11.4 Hereditary spastic paraplegia
 G24.09 Other drug induced dystonia
 G24.1 Genetic torsion dystonia
 G24.2 Idiopathic nonfamilial dystonia
 G24.3 Spasmodic torticollis
 G24.4 Idiopathic orofacial dystonia
 G24.5 Blepharospasm
 G35 Multiple sclerosis
 G43.019 Migraine without aura, intractable, without status migrainosus
 G43.111 Migraine with aura, intractable, with status migrainosus
 G43.119 Migraine with aura, intractable, without status migrainosus
 G43.511 Persistent migraine aura without cerebral infarction, intractable, with status migrainosus
 G43.519 Persistent migraine aura without cerebral infarction, intractable, without status migrainosus
 G43.711 Chronic migraine without aura, intractable, with status migrainosus
 G43.719 Chronic migraine without aura, intractable, without status migrainosus
 G43.811 Other migraine, intractable, with status migrainosus
 G43.919 Migraine, unspecified, intractable, without status migrainosus
 G43.B1 Ophthalmoplegic migraine, intractable
 G43.C1 Periodic headache syndromes in child or adult, intractable
 G51.0 Bell's palsy
 G51.31 Clonic hemifacial spasm, right
 G51.32 Clonic hemifacial spasm, left
 G51.33 Clonic hemifacial spasm, bilateral
 G51.4 Facial myokymia
 G51.8 Other disorders of facial nerve
 G51.9 Disorder of facial nerve, unspecified
 G80.0 Spastic quadriplegic cerebral palsy
 G80.1 Spastic diplegic cerebral palsy
 G80.2 Spastic hemiplegic cerebral palsy
 G81.11 Spastic hemiplegia affecting right dominant side
 G81.12 Spastic hemiplegia affecting left dominant side
 G81.13 Spastic hemiplegia affecting right nondominant side
 G81.14 Spastic hemiplegia affecting left nondominant side
 H49.01 Third [oculomotor] nerve palsy, right eye
 H49.02 Third [oculomotor] nerve palsy, left eye
 H49.03 Third [oculomotor] nerve palsy, bilateral
 H49.11 Fourth [trochlear] nerve palsy, right eye
 H49.12 Fourth [trochlear] nerve palsy, left eye
 H49.13 Fourth [trochlear] nerve palsy, bilateral
 H49.21 Sixth [abducent] nerve palsy, right eye
 H49.22 Sixth [abducent] nerve palsy, left eye

H49.23	Sixth [abducent] nerve palsy, bilateral
H49.31	Total (external) ophthalmoplegia, right eye
H49.32	Total (external) ophthalmoplegia, left eye
H49.33	Total (external) ophthalmoplegia, bilateral
H49.41	Progressive external ophthalmoplegia, right eye
H49.42	Progressive external ophthalmoplegia, left eye
H49.43	Progressive external ophthalmoplegia, bilateral
H49.881	Other paralytic strabismus, right eye
H49.882	Other paralytic strabismus, left eye
H49.883	Other paralytic strabismus, bilateral
H50.011	Monocular esotropia, right eye
H50.012	Monocular esotropia, left eye
H50.021	Monocular esotropia with A pattern, right eye
H50.022	Monocular esotropia with A pattern, left eye
H50.031	Monocular esotropia with V pattern, right eye
H50.032	Monocular esotropia with V pattern, left eye
H50.041	Monocular esotropia with other noncomitancies, right eye
H50.042	Monocular esotropia with other noncomitancies, left eye
H50.05	Alternating esotropia
H50.06	Alternating esotropia with A pattern
H50.07	Alternating esotropia with V pattern
H50.08	Alternating esotropia with other noncomitancies
H50.111	Monocular exotropia, right eye
H50.112	Monocular exotropia, left eye
H50.121	Monocular exotropia with A pattern, right eye
H50.122	Monocular exotropia with A pattern, left eye
H50.131	Monocular exotropia with V pattern, right eye
H50.132	Monocular exotropia with V pattern, left eye
H50.141	Monocular exotropia with other noncomitancies, right eye
H50.142	Monocular exotropia with other noncomitancies, left eye
H50.15	Alternating exotropia
H50.16	Alternating exotropia with A pattern
H50.17	Alternating exotropia with V pattern
H50.18	Alternating exotropia with other noncomitancies
H50.21	Vertical strabismus, right eye
H50.22	Vertical strabismus, left eye
H50.311	Intermittent monocular esotropia, right eye
H50.312	Intermittent monocular esotropia, left eye
H50.32	Intermittent alternating esotropia
H50.331	Intermittent monocular exotropia, right eye
H50.332	Intermittent monocular exotropia, left eye
H50.34	Intermittent alternating exotropia
H50.40	Unspecified heterotropia
H50.411	Cyclotropia, right eye
H50.412	Cyclotropia, left eye
H50.42	Monofixation syndrome
H50.43	Accommodative component in esotropia
H50.51	Esophoria

H50.52	Exophoria
H50.53	Vertical heterophoria
H50.54	Cyclophoria
H50.55	Alternating heterophoria
H50.611	Brown's sheath syndrome, right eye
H50.612	Brown's sheath syndrome, left eye
H50.69	Other mechanical strabismus
H50.811	Duane's syndrome, right eye
H50.812	Duane's syndrome, left eye
H50.89	Other specified strabismus
H50.9	Unspecified strabismus
H51.0	Palsy (spasm) of conjugate gaze
H51.11	Convergence insufficiency
H51.12	Convergence excess
H51.21	Internuclear ophthalmoplegia, right eye
H51.22	Internuclear ophthalmoplegia, left eye
H51.23	Internuclear ophthalmoplegia, bilateral
H51.8	Other specified disorders of binocular movement
H51.9	Unspecified disorder of binocular movement
J38.5	Laryngeal spasm
J38.7	Other diseases of larynx
K22.0	Achalasia of cardia
K60.0	Acute anal fissure
K60.1	Chronic anal fissure
K60.2	Anal fissure, unspecified
L74.510	Primary focal hyperhidrosis, axilla
L74.511	Primary focal hyperhidrosis, face
L74.512	Primary focal hyperhidrosis, palms
L74.513	Primary focal hyperhidrosis, soles
M43.6	Torticollis
N39.41	Urge incontinence
N39.42	Incontinence without sensory awareness
N39.44	Nocturnal enuresis
N39.46	Mixed incontinence
N39.491	Coital incontinence
N39.492	Postural (urinary) incontinence
N39.498	Other specified urinary incontinence
Q66.0	Congenital talipes equinovarus
R32	Unspecified urinary incontinence
R49.8	Other voice and resonance disorders

REVISIONS

10-19-2007	In Policy section: <ul style="list-style-type: none"> ▪ B.1 replaced "Cerebral Palsy" with "spasticity".
07-18-2008	In Policy section: <ul style="list-style-type: none"> ▪ Added "F. The off-labeled use of botulinum toxin is considered medically necessary in the treatment of incontinence related to detrusor overactivity due to neurogenic causes

	(i.e. spinal cord injury), when anticholinergic therapy has failed." as an indication." <ul style="list-style-type: none"> Specified H.13. Overactive bladder by adding "except as specified above."
10-19-2009	In Header: <ul style="list-style-type: none"> Added reference to related policies of: Treatment of Hyperhidrosis and Treatment of Tinnitus Updated Description section. In Policy section: <ul style="list-style-type: none"> Updated formatting and wording. Added medically necessary indication C4: "Incontinence due to detrusor overreactivity (urge incontinence), either idiopathic or due to neurogenic causes (e.g., spinal cord injury, multiple sclerosis), that is inadequately controlled with anticholinergic therapy." Clarified the list of experimental / investigational indications. This list was previously reflected as "...including, but not limited to...", so the additional indications added do not constitute a policy language change. Revised denial of treatment of wrinkles or other cosmetic indications from "not medically necessary" to "non-covered". Added Rationale section. In Coding section: <ul style="list-style-type: none"> Added CPT codes: 31513, 31570, 31571, 43201, 43236. Added Diagnosis coding range for urinary incontinence: 788.30-788.39.
01-01-2010	In Coding Section: <ul style="list-style-type: none"> Added HCPCS Code: J0586 Updated wording for HCPCS Code: J0585
02-25-2011	Medical Policy Title updated. <ul style="list-style-type: none"> Removed "(i.e. Botox®, Myobloc ®)" to read "Botulinum Toxin (BT)." In Policy Language section: <ul style="list-style-type: none"> Updated formatting and wording. Added medically necessary indication #11: "Chronic refractory migraine." In the investigational indications section, Item #1, removed "including migraine, chronic daily headache, and tension type headache" and added "other than chronic refractory headache" to read "headaches, other than chronic refractory headaches." In the Documentation section: <ul style="list-style-type: none"> Removed "There must be a stated goal of treatment." Rationale section updated. In Coding section: <ul style="list-style-type: none"> Added CPT code: 64611 (2011 Coding updates) Added Diagnosis codes: 346.01, 376.03, 346.11, 346.13, .346.21, 346.23, 346.51, 346.53, 346.71, 346.73, 346.91, 346.93. Reference section updated.
05-13-2011	In Coding section, added HCPCS code Q2040.
12-09-2011	Updated Description section. In the Policy section: <ul style="list-style-type: none"> In Item A, #11, inserted "headaches" to read "Chronic refractory migraine headaches" In Item B, #9, inserted "(see separate policy on Treatment of Tinnitus)" In Item B, added the following indications: <ul style="list-style-type: none"> #21. Prevention of pain associated with breast reconstruction after mastectomy #22. Hirschsprung's disease" Removed the Documentation section. Removed the Utilization section. Added Policy Guidelines section. In Coding section:

	<ul style="list-style-type: none"> • Added the following CPT/HCPCS codes: 46505, C9278 ▪ Added the following Diagnosis codes: 333.71, 333.79, 333.81, 333.82, 333.83, 333.84, 340, 351.0, 351.1, 351.9, 435.9, 705.21, 754.51, 784.49
	Updated the Rationale section.
	Updated the Reference section.
01-01-2012	<p>In the Policy section:</p> <ul style="list-style-type: none"> ▪ In Item A, #6, removed "in patients who have not responded to dilation therapy or who are considered poor surgical candidates" to read " Esophageal achalasia"
	<p>In the Coding section:</p> <ul style="list-style-type: none"> ▪ Removed HCPCS codes: C9278, Q2040 ▪ Added HCPCS code: J0588 ▪ Added Diagnosis codes: 333.71, 333.79, 333.81, 333.82, 333.83, 333.84 (Diagnosis code, 333.7 was replaced with the appropriate codes for the policy.)
01-15-2013	<p>In the Coding section:</p> <ul style="list-style-type: none"> ▪ Added CPT code: 52287 and 64615 (Effective 01-01-2013) ▪ Updated CPT code 64612 nomenclature (Effective 01-01-2013)
01-30-2014	Updated Description section.
	<p>In Policy section:</p> <p>In Item A, #9, replaced "(urge incontinence), either idiopathic or due to" with "associated with" to read "Incontinence due to detrusor overreactivity associated with neurogenic causes..."</p> <p>In Item A, added #12, "overactive bladder in adults that is inadequately controlled with anticholinergics."</p> <p>In Item B, added #23, "Facial wound healing."</p> <p>In Item B, added #24, "Internal anal sphincter (IAS) achalasia".</p> <p>Moved the "Policy Guidelines" to the "Coding" section.</p>
	Updated Rationale section.
	<p>In Coding section:</p> <p>Removed CPT codes: 64613 and 64614 (<i>Deleted codes, effective December 31, 2013</i>)</p> <p>Added CPT codes: 64616, 64617, 64642, 64643, 64644, 64645, 64646, 64647 (<i>New codes, effective January 1, 2014</i>)</p> <p>Added ICD-10 Diagnosis codes (<i>Effective October 1,2014</i>)</p>
	Updated Reference section.
04-15-2014	<p>In Policy section:</p> <ul style="list-style-type: none"> ▪ In Item B 1 removed the parenthesis around "(migraine)" to read, "headaches other than chronic refractory migraine headaches" <p>In Policy Guidelines:</p> <ul style="list-style-type: none"> ▪ Added information pertaining to cervical dystonia and chronic migraine.
	<p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Updated coding instructions.
01-01-2015	<p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Revised CPT Codes: 43201, 43236 (Effective January 1, 2015)
02-19-2016	Updated Description section.
	<p>In Policy section:</p> <ul style="list-style-type: none"> ▪ In Item A 6, added "in patients who have not responded to dilation therapy or who are considered poor surgical candidates" to read, "Esophageal achalasia in patients who have not responded to dilation therapy or who are considered poor surgical candidates" ▪ In Item A 9, added "Urinary" to read, "Urinary incontinence due to detrusor overreactivity associated with neurogenic causes (e.g., spinal cord injury, multiple sclerosis), that is inadequately controlled with anticholinergics*." ▪ Deleted previous Item A 10.

	<ul style="list-style-type: none"> ▪ 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 International 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: <ul style="list-style-type: none"> ▪ Removed CPT codes: 64650 and 64653.
	Updated References section.
07-01-2016	Updated Description section.
	In Policy section: <ul style="list-style-type: none"> ▪ In Item A 10 a, removed "(key criteria include migraine headaches lasting at least 4 hours on at least 15 days per month; migraine headaches for at least 3 months; absence of medication overuse)" and added "(see Policy Guidelines)" to read "Meet International Classification of Headache Disorders (ICHD) diagnostic criteria for chronic migraine headache; and" ▪ In Policy Guidelines, added Item 2.
	Updated Rationale section.
10-01-2016	In Coding section: <ul style="list-style-type: none"> ▪ Added ICD-10 codes effective 10-01-2016: N39.491, N39.492
03-29-2017	In Policy section: <ul style="list-style-type: none"> ▪ In Item C, removed "may be considered not medically necessary" and added "is noncovered" to read, "The use of botulinum toxin as a treatment of wrinkles or other cosmetic indications is noncovered."
02-15-2018	Updated Description section.
	In Policy section: <ul style="list-style-type: none"> ▪ In Policy Guidelines, added "Indications and Dosage" table.
	Updated Rationale section.
	In Coding section: <ul style="list-style-type: none"> ▪ Updated Coding bullets. ▪ ICD-9 codes removed.
	Updated References section.
10-01-2018	In Coding section:

	<ul style="list-style-type: none"> ▪ Added ICD-10 codes: G51.31, G51.32, G51.33. ▪ Removed ICD-10 code: G51.3.
	Updated References section.
11-20-2018	Updated Description section.
	In Policy section: <ul style="list-style-type: none"> ▪ In Item A 9, added "in patients unresponsive to or intolerant of" and removed "that is inadequately controlled with" to read, "Urinary incontinence due to detrusor overreactivity associated with neurogenic causes (eg, spinal cord injury, multiple sclerosis) in patients unresponsive to or intolerant of anticholinergics." ▪ In Item B 11, removed "(ICD-10 F95.1)" and "(ICD-10 F95.2)" to read, "Chronic motor tic disorder, and tics associated with Tourette's syndrome (motor tics).
	Updated Rationale section.
	In Coding section: <ul style="list-style-type: none"> ▪ Removed coding bullets.
	Updated References section.

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