OnabotulinumtoxinA

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Link to Codes

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Clinical Indications

- OnabotulinumtoxinA may be indicated for **1 or more** of the following(1)(2)(3)(4)(5)(6)(7):
  - Achalasia, as indicated by **1 or more** of the following(88):N
    - Initial course, as indicated by **ALL** of the following:
      - Achalasia confirmed by esophageal manometry
      - Failure of or patient not candidate for pneumatic dilation or surgical myotomy (eg, elderly patient)(91)(93)
      - No response to pharmacologic treatment (eg, long-acting nitrates, calcium channel antagonists)
      - Other causes of dysphagia (eg, peptic stricture, carcinoma, lower esophageal ring or extrinsic compression) ruled out by upper gastrointestinal endoscopy
      - Progressive dysphagia for liquids and solids
    - Subsequent course, with favorable response to prior administration of onabotulinumtoxinA
  - Anal fissure, as indicated by **1 or more** of the following(94)(95)(96):N
    - Initial course, as indicated by **ALL** of the following:

- At least 2 months of symptoms, including **1 or more** of the following:
  - Nocturnal pain and bleeding
  - Postdefecation pain
- Failure of or intolerance to topical nitrates or topical calcium channel blockers
- Patient not surgical candidate or has refused surgery

- Subsequent course, with favorable response to prior administration of onabotulinumtoxinA

Blepharospasm, as indicated by **1 or more** of the following(100)(101)(102)(103):N

- Initial course, as indicated by **ALL** of the following:
  - Age 12 years or older
  - Blepharospasm, as indicated by **1 or more** of the following:
    - Benign essential blepharospasm
    - Blepharospasm associated with dystonia
    - Blepharospasm associated with facial nerve (cranial nerve VII) disorder such as Bell palsy
  - No infection at proposed injection site
  - No neuromuscular disease (eg, myasthenia gravis)
- Subsequent course, as indicated by **ALL** of the following:
  - Age 12 years or older
  - Favorable response to prior administration of onabotulinumtoxinA

Cervical dystonia (spasmodic torticollis), as indicated by **1 or more** of the following(100)(102)(107)(108)(109)(110):N

- Initial course, as indicated by **ALL** of the following:
  - Age 16 years or older
  - Neck pain or abnormal head position causing adverse effect on daily functioning
  - No fixed contractures causing decreased neck range of motion
  - No infection at proposed injection site
  - No neuromuscular disease (eg, myasthenia gravis)
- Subsequent course, as indicated by **ALL** of the following:
  - Age 16 years or older
  - Favorable response to prior administration of onabotulinumtoxinA

Hemifacial spasm, as indicated by **1 or more** of the following(102)(103)(120)(121)(122):N

- Initial course
- Subsequent course, with favorable response to prior administration of onabotulinumtoxinA

Hyperhidrosis (axillary), as indicated by **1 or more** of the following[A](126)(127)(128)(130)(131)(132)(133)(134):N

- Initial course, as indicated by **ALL** of the following:
  - Age 18 years or older
  - Axillary hyperhidrosis, with Hyperhidrosis Disease Severity Scale (HDSS) score of 2 or more[B]
  - Inadequate response to 1 or more months of topical treatment (eg, aluminum chloride), as evidenced by no improvement in HDSS score, or patient intolerant to topical treatment due to unacceptable skin irritation[C]
  - No infection at proposed injection site
  - Secondary causes of hyperhidrosis (eg, hyperthyroidism) have been evaluated and, if necessary, treated.(143)
  - Significant effect of hyperhidrosis upon daily activities
- Subsequent course, with favorable response to prior administration of botulinum toxin A

- Laryngeal dystonia (ie, adductor spasmodic dysphonia), as indicated by **1 or more** of the following(112)(144)(145):
  - Initial course, as indicated by **ALL** of the following:
    - Adductor-type spasmodic dysphonia confirmed by fiberoptic laryngoscopy
    - Moderate to severe difficulty in phonation
  - Subsequent course, with favorable response to prior administration of onabotulinumtoxinA
- Migraine headache prophylaxis needed, as indicated by **1 or more** of the following(152)(153)(154)(155)(156)(157):
  - Initial course, as indicated by **ALL** of the following:
    - Age 18 years or older
    - Headaches occurring 15 or more days per month with 8 or more migraine days per month for 3 or more months(175)
    - Migraine headache lasting 4 hours to 72 hours, as indicated by 5 or more attacks with **ALL** of the following(175)(176):
      - Headache symptoms, as indicated by **2 or more** of the following:
        - Aggravation by or causing avoidance of routine physical activity
        - Moderate or severe pain intensity
        - Pulsating quality
        - Unilateral location
      - Migraine-associated symptoms, as indicated by **1 or more** of the following:
        - Nausea or vomiting
        - Photophobia and phonophobia
      - Other potential causes of headaches have been excluded.
    - Use of preventive medication (eg, calcitonin gene-related peptide monoclonal antibody, beta-blocker, tricyclic antidepressant, antiseizure medication) has been ineffective or not tolerated for trial of at least 3 months.(173)(177)(178)(179)(180)
    - No neuromuscular disease (eg, myasthenia gravis)
  - Subsequent course, as indicated by **ALL** of the following:
    - Age 18 years or older
    - Favorable response to prior administration of onabotulinumtoxinA
- Motor tics, as indicated by **1 or more** of the following(181)(182):
  - Initial course, as indicated by **ALL** of the following:
    - Age 16 years or older
    - Patient unable to adequately suppress tics
    - Tics causing interference with daily functioning
  - Subsequent course, as indicated by **ALL** of the following:
    - Age 16 years or older
    - Favorable response to prior administration of onabotulinumtoxinA
- Overactive bladder with or without urgency urinary incontinence, as indicated by **1 or more** of the following(184)(185)(186)(187)(188)(189):
  - Initial course, as indicated by **ALL** of the following:
    - Age 18 years or older
    - Failure of, intolerance to, or contraindication to pharmacologic therapy (eg, anticholinergic medication, beta-3 adrenergic agonist)
    - No acute urinary retention
    - No acute urinary tract infection
  - Subsequent course, as indicated by **ALL** of the following:
    - Age 18 years or older
    - Favorable response to prior administration of onabotulinumtoxinA

- Sialorrhea (excessive salivation), as indicated by **1 or more** of the following(128)(205)(206)(207)(208)(209)(210):N
  - Initial course
  - Subsequent course, with favorable response to prior administration of onabotulinumtoxinA
- Spasticity, as indicated by **1 or more** of the following(221)(222)(223)(224)(225)(226):N
  - Initial course, as indicated by **1 or more** of the following:
    - Child with cerebral palsy receiving rehabilitation(228)(245)(252)(253)
    - Upper or lower extremity spasticity in individual age 2 years or older(254)(255)(256)
  - Subsequent course, with favorable response to prior administration of onabotulinumtoxinA
- Strabismus, as indicated by **1 or more** of the following(257)(258):N
  - Initial course, as indicated by **ALL** of the following:
    - Age 12 years or older
    - Deviation of 50 prism diopters or less
    - No infection at proposed injection site
    - Strabismus not due primarily to Duane syndrome with lateral rectus weakness
    - Strabismus not due primarily to restrictive strabismus
    - Strabismus not due primarily to secondary strabismus caused by prior surgical over-recession of antagonist muscle
  - Subsequent course, as indicated by **ALL** of the following:
    - Age 12 years or older
    - Favorable response to prior administration of onabotulinumtoxinA
- Upper extremity focal dystonia (eg, writer's cramp), as indicated by **1 or more** of the following(112)(144)(263)(264):N
  - Initial course, as indicated by **ALL** of the following:
    - Age 16 years or older
    - Extremity pain or abnormal hand or forearm position causing adverse effect on daily functioning
    - No infection at proposed injection site
    - No prior surgical treatment
  - Subsequent course, as indicated by **ALL** of the following:
    - Age 16 years or older
    - Favorable response to prior administration of onabotulinumtoxinA
- Urinary incontinence due to neurogenic detrusor overactivity, as indicated by **1 or more** of the following(186)(187)(266):
  - Adult and **1 or more** of the following(267):N
    - Initial course, as indicated by **ALL** of the following:
      - Age 18 years or older
      - Condition secondary to spinal cord injury, spinal dysraphism, or neurologic disease (eg, multiple sclerosis)(276)(277)
      - Failure of or intolerance to pharmacologic therapy including anticholinergic medication
      - No acute urinary retention unless patient receiving regular clean intermittent catheterization
      - No acute urinary tract infection
    - Subsequent course, as indicated by **ALL** of the following:
      - Age 18 years or older
      - Favorable response to prior administration of onabotulinumtoxinA
  - Child or adolescent and **1 or more** of the following(278):N
    - Initial course, as indicated by **ALL** of the following:
      - Age 5 years to younger than 18 years

- Condition secondary to spinal cord injury, spinal dysraphism, or transverse myelitis
- Failure of or intolerance to pharmacologic therapy including anticholinergic medication
- No acute urinary tract infection

- Subsequent course, as indicated by **ALL** of the following:
  - Age 5 years to younger than 18 years
  - Favorable response to prior administration of onabotulinumtoxinA

Evidence Summary

Background

OnabotulinumtoxinA is a purified form of botulinum toxin A, prepared by extraction of the toxin from cultures of the type A strain of *Clostridium botulinum*.(1) **(EG 2)** Botulinum toxins are potent neurotoxins; injection into striated muscles results in paralysis within 2 to 5 days, lasting for 2 to 3 months. Botulinum toxin has inhibiting effects on dystonia and spasticity, and it blocks autonomic activity to smooth muscle and exocrine glands. There are 7 different serotypes (A to G), each with varying potencies and characteristics of action.(8) **(EG 2)** OnabotulinumtoxinA has been the most-studied agent; other commercially available products include 5 botulinum toxin A agents (abobotulinumtoxinA, incobotulinumtoxinA, daxibotulinumtoxinA, prabotulinumtoxinA, and letibotulinumtoxinA) and rimabotulinumtoxinB (purified botulinum toxin B).(9)(10)(11)(12)(13)(14) **(EG 1)** The commercially available agents differ in synthesis and purification processes, potency, duration of action, and tendency toward clinically relevant systemic spread due to migration from the injection site.(2)(8)(14)(15)(16)(17)(18) **(EG 2)**

Criteria

The evidence for the clinical indications found in this guideline includes 238 published peer reviewed articles, 16 specialty society or other evidence-based guidelines, and 22 Cochrane systematic reviews.

For achalasia, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** Review articles have reported that studies of endoscopic injection of botulinum toxin A into the lower esophageal sphincter demonstrated symptomatic benefit that diminishes over time, with sustained response in approximately 32% of patients at 12 months and nearly universal relapse at 2 years.(89)(90) **(EG 2)** Additional reviews have also concluded that botulinum toxin A may be an effective therapeutic option for patients who are not candidates for or who have failed pneumatic dilation or surgical myotomy.(88)(91) **(EG 1)** A specialty society guideline recommends botulinum toxin injections for patients with achalasia who are unable to undergo definitive treatment (eg, pneumatic dilation, laparoscopic Heller myotomy), but notes that the duration of symptom relief associated with botulinum toxin treatments is limited.(92) **(EG 2)**

For anal fissure, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** Systematic reviews and meta-analyses of randomized trials have concluded that medical therapy, including botulinum toxin A, is less effective than surgical sphincterotomy, which has higher healing rates and lower rates of recurrence.(94)(97)(98) **(EG 1)** Botulinum toxin may be an effective treatment option for patients who fail topical nitrate therapy and for whom surgery presents a high risk for incontinence.(95)(96)(99) **(EG 2)**

For blepharospasm, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** A systematic review and meta-analysis of 3 randomized placebo-controlled trials concluded that botulinum toxin A treatment was associated with improvements in blepharospasm-specific severity and disability.(104) **(EG 1)** A split-face, double-blind, randomized controlled trial comparing incobotulinumtoxinA with onabotulinumtoxinA in 48 patients with benign essential blepharospasm found no significant differences in subjective and objective outcome measures between the 2 treatments.(105) **(EG 1)** Expert evidence reviews on the use of botulinum toxin in movement disorders found high-level evidence supporting use of onabotulinumtoxinA for blepharospasm.(101)(106) **(EG 2)** A specialty society technology assessment report concluded that onabotulinumtoxinA was effective for treating benign essential blepharospasm.(103) **(EG 2)**

For cervical dystonia (spasmodic torticollis), evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** A systematic review of 9 randomized controlled trials with 1144 patients found that a single treatment session of botulinum toxin A injections yielded significant and clinically relevant improvements in cervical dystonia pain, disability, and severity, as compared with placebo; onabotulinumtoxinA was used in 2 trials with 225 patients, while abobotulinumtoxinA and incobotulinumtoxinA were used in the other 7 trials.(111) **(EG 1)** Expert evidence-based guidelines and a network meta-analysis concluded that all 4 botulinum toxins included in the studies were effective as first-line treatment for this condition.(112)(113)(114)(115) **(EG 1)** Systematic and other reviews of long-term case series of patients with cervical dystonia reported sustained benefit of botulinum toxin A over the course of multiple treatment sessions without serious adverse events.(116)(117)(118) **(EG 2)** A systematic review of 3 randomized studies with 270 patients found that there is low-quality evidence that botulinum toxin A and botulinum toxin B have comparable efficacy for cervical dystonia.(119) **(EG 1)**

For hemifacial spasm, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** A systematic review did not identify any randomized controlled trials evaluating botulinum toxin A for hemifacial spasm that met the study's inclusion criteria but noted that observational studies suggest that botulinum toxin A is associated with symptom improvements in hemifacial spasm and is safe.(123) **(EG 1)** An expert evidence-based review and case series have found that onabotulinumtoxinA and abobotulinumtoxinA are possibly effective, with minimal side effects and possible equivalence in efficacy.(120)(121)(122)(124)(125) **(EG 2)** A specialty society technology assessment report concluded that onabotulinumtoxinA was effective for treating hemifacial spasm.(103) **(EG 2)**

For hyperhidrosis (axillary), evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** A systematic review and meta-analysis of 23 studies found moderate-quality evidence to support botulinum toxin injections to control symptoms of axillary hyperhidrosis for up to 16 weeks compared with placebo.(131) **(EG 1)** Review articles and observational studies support the use of botulinum toxin A for the treatment of axillary hyperhidrosis if a trial of a topical agent (eg, aluminum chloride) is unsuccessful.(126)(127)(128)(129)(130)(132)(135)(136)(137)(138) **(EG 2)**

For laryngeal dystonia (ie, adductor spasmodic dysphonia), evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** A randomized double-blind placebo-controlled trial including 22 patients with adductor spasmodic dysphonia found that a single injection of onabotulinumtoxinA into the thyroarytenoid muscle was associated with improvements in speech production accuracy at 4 weeks of follow-up compared with placebo.(146) **(EG 1)** A systematic review and meta-analysis of 17 studies (3 clinical trials and 14 cohort studies) evaluating voice-related quality of life after botulinum toxin injection for adductor spasmodic dysphonia reported improvements in Voice Health Index voice-related quality-of-life scores after botulinum toxin therapy.(147) **(EG 1)** Expert consensus guidelines and review articles indicate that botulinum toxin is effective for treating this disorder based on limited evidence from randomized controlled trials.(112)(148)(149)(150) **(EG 2)** A retrospective analysis of 548 patients concluded that onabotulinumtoxinA injections into the thyroarytenoid or lateral cricoarytenoid muscle complex was an effective treatment for adductor spasmodic dysphonia, lateral laryngeal tremor, or a combination of these vocal disorders, with the greatest effectiveness noted in patients with tremor-free adductor spasmodic dysphonia.(151) **(EG 2)**

For migraine headache prophylaxis, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** A systematic review and meta-analysis of 28 randomized controlled trials (4190 patients) concluded that prophylaxis treatment with botulinum toxin A, as compared with placebo, was associated with 2 fewer migraine days per month in patients with chronic migraines (15 or more headache days per month with 8 or more of those days being migraine days). Botulinum toxin A was not associated with fewer episodic migraines (fewer than 15 headache days per month), and the evidence was considered inadequate in this population.(158) **(EG 1)** A randomized controlled study with 904 patients suggests that onabotulinumtoxinA may also be effective in limiting medication overuse in chronic migraine patients.(159) **(EG 1)** A prospective observational study including 197 patients with chronic migraine (defined by the International Classification of Headache Disorders (ICHD-3) criteria) found, at 2-year follow-up, that participants who had received at least one injection of onabotulinumtoxinA (184 patients) reported improved quality of life (as measured by the Migraine-Specific Quality of Life Questionnaire), fewer headache days per month, and fewer headache-related emergency department visits and inpatient admissions.(160)(161) **(EG 2)** Observational studies and review articles support the use of onabotulinumtoxinA for migraine prophylaxis in appropriately selected patients with chronic migraine headaches.(162)(163)(164)(165)(166)(167)(168) **(EG 2)** An industry-sponsored, double-blind, randomized, placebo-controlled trial including 125 adolescents age 12 to 18 years with chronic migraine found that treatment with onabotulinumtoxinA was not associated with reductions in the frequency of headache days or severe headache days at 12 weeks post treatment, as compared with placebo. The authors note that the study may have been underpowered

and that additional studies in the pediatric population are needed.(169) **(EG 1)** A specialty society guideline recommends the use of onabotulinumtoxinA for chronic migraine prophylaxis, as it was found to be established and effective in increasing headache-free days and probably effective in improving health-related quality of life.(170) **(EG 2)** A practice guideline recommends botulinum toxin type A for the prophylaxis of headache in adults with chronic migraines (defined as at least 15 days of headache per month and at least 8 days of migraine) who have not responded to at least 3 prior pharmacologic prophylaxis therapies and whose condition is appropriately managed for medication overuse.(171) **(EG 2)** A specialty society guideline recommends that for chronic migraines, patients should have tried 2 to 3 other migraine prophylactics before initiating treatment with onabotulinumtoxinA.(172) **(EG 2)** An international specialty society guideline considers onabotulinumtoxinA to be first-line therapy for patients with chronic migraine (15 or more headache days per month and 8 or more migraine days per month).(173) **(EG 2)** An expert consensus guideline supports the use of onabotulinumtoxinA injections for prevention of chronic migraines but makes a weak recommendation against the use of onabotulinumtoxinA injections for prevention of episodic migraines.(174) **(EG 2)**

For motor tics, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** A systematic review found one very low-quality randomized controlled trial employing onabotulinumtoxinA injections in 18 patients with muscle tics; the review authors were unable to conclude if the active treatment offered any therapeutic benefit as compared with placebo.(183) **(EG 1)** A specialty society guideline indicates that onabotulinumtoxinA injections are a treatment option for reducing tic severity in adolescents and adults.(181)(182) **(EG 2)**

For overactive bladder with or without urgency urinary incontinence, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** A randomized placebo-controlled dose-ranging study of 313 patients reported improvement in urinary incontinence with onabotulinumtoxinA as compared with placebo.(190) **(EG 1)** Another randomized placebo-controlled trial of 240 women with refractory detrusor overactivity reported higher rates of urinary continence with onabotulinumtoxinA therapy; however, urinary tract infection and voiding difficulties requiring self-catheterization were more common.(191) **(EG 1)** A randomized trial comparing onabotulinumtoxinA with anticholinergic therapy in 249 women reported that the group receiving onabotulinumtoxinA was more likely to have complete resolution of urgency urinary incontinence but had higher rates of transient urinary retention and urinary tract infections.(192) **(EG 1)** An industry-sponsored, randomized, double-blind, placebo-controlled trial including 250 adult patients with overactive bladder refractory to anticholinergics and/or beta-3 adrenergic agonists found that, at 12 weeks post treatment, onabotulinumtoxinA was associated with a greater decrease in daily urinary incontinence episodes compared with placebo.(193) **(EG 1)** A systematic review and meta-analysis of 7 randomized controlled trials and 2 retrospective studies (1649 patients) comparing onabotulinumtoxinA with sacral neuromodulation found that patients receiving onabotulinumtoxinA were more likely to have a reduction in urgency urinary incontinence but had higher rates of urinary tract infections.(194) **(EG 1)** A randomized study of 557 patients with overactive bladder and urinary incontinence found that onabotulinumtoxinA decreased the daily frequency of incontinence episodes and improved health-related quality-of-life scores as compared with placebo.(195) **(EG 1)** A randomized study of 28 patients with overactive bladder and urgency incontinence after prostate surgery found significant improvement in quality of life after administration of botulinum toxin A.(196) **(EG 1)** A systematic review and network meta-analysis concluded that onabotulinumtoxinA provided the greatest relief of overactive bladder symptoms compared with oral or transdermal anticholinergic medications, mirabegron, and placebo.(197) **(EG 1)** A systematic review and network meta-analysis of 19 trials concluded that botulinum toxin A was associated with fewer incontinence episodes and fewer micturitions per 24 hours as compared with mirabegron. However, botulinum toxin A was associated with a greater risk of urinary tract infections than mirabegron.(198) **(EG 1)** A specialty society guideline and review articles support the use of onabotulinumtoxinA due to significant improvement in measured frequency, urgency, and incontinence in the management of lower urinary tract disorders for patients who have failed to improve with conservative or oral medical therapy.(185)(199)(200)(201)(202)(203) **(EG 2)** In pediatric patients, a randomized double-blind trial of 55 patients age 12 to 17 years with overactive bladder and urinary incontinence (all inadequately managed with at least one anticholinergic agent) compared 3 doses of intradetrusor onabotulinumtoxinA (25 units, 50 units, or 100 units) and found, at 12 weeks post treatment, that only patients in the highest dose group demonstrated a significant improvement from baseline in frequency of daily urinary incontinence episodes. The authors noted that the study was limited by premature termination because of low enrollment and baseline between-group differences in the frequency of urinary incontinence episodes.(204) **(EG 1)**

For sialorrhea, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** Systematic reviews of randomized controlled trials and noncomparative studies investigating sialorrhea in children with cerebral palsy reported that all trials of intrasalivary injection of botulinum toxin demonstrated a statistically significant reduction in drooling; however, authors have concluded that there was insufficient evidence to fully inform clinical practice for this condition.(211)(212)(213) **(EG 1)** A prospective single-center cohort study of 483 pediatric patients referred to a multidisciplinary saliva control clinic for sialorrhea found, at 3-month follow-up, that onabotulinumtoxinA injections (207 patients) resulted in the

greatest improvement in Drooling Impact Scale (DIS) scores compared with other interventions (duct transpositional surgery, oral anticholinergics, inhaled ipratropium bromide, oromotor programs).(214) **(EG 2)** Expert reviews and consensus guidelines recommend intrasalivary injection of botulinum toxin, primarily botulinum toxin type A, to reduce drooling in patients with cerebral palsy, Parkinson disease,(207)(215)(216)(217) amyotrophic lateral sclerosis, and other neurodegenerative conditions.(209)(218)(219)(220) **(EG 2)**

For spasticity, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** Systematic reviews and meta-analyses have found evidence in support of botulinum toxin A for the management of spasticity when it is administered with concomitant rehabilitation therapy,(222) particularly in children.(227)(228)(229) **(EG 1)** A systematic review and meta-analysis of 31 randomized trials evaluating type A botulinum neurotoxins for lower limb spasticity in children with cerebral palsy found moderate-quality evidence that type A botulinum neurotoxin improves gait scores in the short term and medium term, compared with placebo or sham treatment, and low-quality evidence that type A botulinum neurotoxin improves gait scores and functioning in the medium term, compared with usual care or physical therapy.(230) **(EG 1)** A phase III randomized controlled trial of 235 patients (age 2 to 17 years) with single-arm upper limb spasticity due to cerebral palsy compared treatment with occupational therapy combined with either onabotulinumtoxinA (at 1 of 2 doses) or placebo and found, at 4-week and 6-week follow-up, that both doses of onabotulinumtoxinA were associated with greater improvements from baseline in spasticity in the affected limb (measured with the Modified Ashworth Scale-Bohannon score) compared with placebo.(231) **(EG 1)** A similarly designed phase III randomized controlled trial of 384 patients (age 2 to 17 years) with lower limb spasticity due to monoplegic or hemiplegic cerebral palsy compared treatment with physical therapy combined with either onabotulinumtoxinA (at 1 of 2 doses) or placebo and found, at 4-week and 6-week follow-up, that both doses of onabotulinumtoxinA were associated with greater improvements from baseline in ankle spasticity (measured by the Modified Ashworth Scale-Bohannon score at the ankle) compared with placebo.(232) **(EG 1)** An open-label extension study that included 580 patients from the previous 2 randomized controlled trials found, at 60-week follow-up, that improvements in spasticity scores were stable over time in patients treated with onabotulinumtoxinA.(233) **(EG 2)** Guidelines recommend botulinum toxin A for treating children with spasticity due to cerebral palsy.(224)(234)(235)(236)(237) **(EG 2)** However, a systematic review indicates that industry-sponsored studies of cerebral palsy patients are significantly more likely to have favorable conclusions as compared with nonsponsored studies.(238) **(EG 1)** A systematic review of use in children younger than 2 years indicates that evidence is lacking with regard to improvement in general motor development, even though there appears to be an advantage in avoiding contractures, reducing spasticity, and delaying need for surgery.(239) **(EG 1)** An industry-sponsored systematic review and network meta-analysis of studies evaluating type A botulinum neurotoxins for lower limb spasticity in children reported that, compared with placebo, onabotulinumtoxinA was associated with improved scores on some spasticity scales, depending on the dose used. However, the study did not find improvements in functional goal attainment with onabotulinumtoxinA. The authors noted that a sparsity of studies and small sample sizes impacted the reliability of the conclusions.(240) **(EG 2)** Systematic reviews and meta-analyses have concluded that botulinum toxin A is effective for treatment of upper extremity spasticity in adults due to stroke, with improvement in functionality.(221)(241) **(EG 1)** A multicenter randomized controlled trial of 333 patients reported that the addition of botulinum toxin to an upper limb therapy program did not improve active upper limb function; however, significant differences were seen in favor of the intervention group for basic functional tasks involving hand hygiene and facilitation of dressing.(242) **(EG 1)** With regard to lower extremity functional improvement in patients with stroke, a meta-analysis and systematic review found that studies on the injection of botulinum toxin A into the rectus femoris, while associated with significant improvement in knee flexion, have yet to confirm significant improvement in functional outcomes.(243) **(EG 1)** In a randomized study of 273 poststroke patients with focal or multifocal upper or lower limb spasticity, administration of botulinum toxin A along with standard rehabilitation care was not associated with significant improvement in patients' principal and secondary active functional goals, as compared with placebo and standard care.(244) **(EG 1)** A randomized double-blind study of 52 adults with spastic pes equinovarus after stroke, traumatic brain injury, or diffuse hypoxia compared treatment with botulinum toxin A or placebo and found, at 24-week follow-up, that the botulinum toxin A group had decreased muscle tone, as measured by the Modified Ashworth score.(245) **(EG 1)** A 12-week, double-blind, randomized, placebo-controlled trial with 450 patients, followed by a 48-week open-label extension study with 413 patients, found that onabotulinumtoxinA significantly improved symptoms of poststroke ankle spasticity during both phases of the trial.(246) **(EG 1)** An expert consensus guideline on rehabilitation after stroke suggests botulinum toxin for patients with focal spasticity.(247) **(EG 2)** Systematic and expert evidence-based reviews have found that botulinum toxin A is effective in improving muscle tone and range of motion in patients with spasticity due to multiple sclerosis and other neurologic conditions; however, the authors noted that evidence confirming active functional improvement has not yet been demonstrated.(248)(249)(250)(251) **(EG 2)**

For strabismus, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** A systematic review comparing extraocular muscle botulinum toxin A injection with eye muscle surgery in nonparalytic, nonrestrictive horizontal strabismus identified 13 studies of onobotulinumtoxinA (only 2 of which were randomized controlled trials) and concluded that botulinum

toxin A is associated with a similar rate of successful motor outcomes compared with surgery for small-angle to moderate-angle strabismus, although multiple treatments may be required.(259) **(EG 1)** A systematic review found comparable success rates between surgery and use of botulinum toxin A, with the advantage that adverse effects such as diplopia and ptosis are short-lived in the latter scenario.(257) **(EG 2)** A systematic review evaluating the efficacy of botulinum toxin A for congenital and acquired strabismus included 4 randomized trials comparing botulinum toxin A with corrective surgery and found, at 12-month follow-up, that treatment with botulinum toxin A did not improve strabismus or binocular single vision compared with surgery.(260) **(EG 1)** Review articles support the use of botulinum toxin A as either the primary treatment or as an adjunct to surgery for strabismus.(261)(262) **(EG 2)**

For upper extremity focal dystonia (ie, writer's cramp, other occupational hand dystonias, non-task-specific hand dystonia), evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** A randomized controlled trial of 30 patients with focal brachial dystonia with dystonic tremor compared treatment with either onabotulinumtoxinA or placebo and found, at 6-week and 12-week follow-up, that onobotulinumtoxinA was associated with lower tremor severity (measured by the Fahn-Tolosa-Marin Tremor Rating Scale) compared with placebo.(265) **(EG 1)** Expert evidence-based guidelines recommend that botulinum toxin A formulations should be considered as a treatment option for this condition.(112) **(EG 2)**

For urinary incontinence due to neurogenic detrusor overactivity in adults, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** Systematic reviews and randomized controlled trials concluded that cystoscopically guided injection of the detrusor with onabotulinumtoxinA improved quality-of-life scores(268)(269)(270) and daily urinary incontinence frequency,(269)(271) as well as catheter use and bladder pressures.(270)(271)(272) **(EG 1)** Practice guidelines and review articles recommend bladder wall injection of botulinum toxin A for patients with symptomatic neurogenic bladder unresponsive to antimuscarinic medication.(248)(266)(267)(273)(274)(275)(276) **(EG 2)**

For urinary incontinence due to neurogenic detrusor overactivity in children and adolescents, evidence demonstrates an incomplete assessment of net benefit vs harm; the drug is currently approved by a federal regulatory agency. **(RG A3)** An industry-sponsored randomized trial of 114 patients age 5 to 17 years with urinary incontinence related to detrusor overactivity due to spinal cord injury, spinal dysraphism, or transverse myelitis (all with symptoms inadequately controlled with anticholinergic agents) compared intra-detrusor injections of onabotulinumtoxinA at 3 doses (50 units, 100 units, or 200 units) and found, at 6 weeks of follow-up, that patients in all 3 groups had improvement from baseline in the number of daytime urinary incontinence episodes, with no significant difference seen between groups. Adverse events occurred in 58% of patients over 12 weeks of follow-up, including urinary tract infections in 19.5% of all patients.(279) **(EG 1)** A systematic review of 12 studies (293 patients) evaluating intra-detrusor botulinum toxin A in pediatric patients with spina bifida and neurogenic detrusor overactivity found resolution of incontinence in 23% to 100% of patients. The authors noted that the small number of patients, short-term follow-up, and lack of placebo control in the included studies limited the results.(280) **(EG 1)** A retrospective cohort study of 53 patients age 16 years or younger with spina bifida and detrusor overactivity or poor bladder compliance found that 30% of patients had global success (as defined by both urodynamic improvement and clinical improvement, including no incontinence episodes between clean intermittent catheterizations, fewer than 8 clean intermittent catheterizations per 24 hours, and absence of urinary urgency) after one intra-detrusor botulinum toxin A injection.(281) **(EG 2)** A specialty society guideline states that intra-detrusor botulinum toxin may improve urodynamic parameters in children with neurogenic bladder and detrusor overactivity.(282) **(EG 2)**

Inconclusive or Non-Supportive Evidence

For anal sphincter achalasia, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A meta-analysis of 16 nonrandomized studies of patients with internal anal sphincter achalasia reported that after botulinum toxin A injection, rates of transient fecal incontinence, nonresponse, and subsequent surgical procedures were significantly higher as compared with patients who underwent myectomy.(19) **(EG 2)**

For back pain, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review found only 3 randomized trials, with significant heterogeneity present, and concluded that current evidence does not support the use of botulinum toxin for low back pain and sciatica.(20) **(EG 1)**

For benign prostatic hyperplasia with lower urinary tract symptoms, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A review article found studies suggesting efficacy of either abobotulinumtoxinA or onabotulinumtoxinA for treatment of male lower urinary tract symptoms, but the author concluded that the overall level of evidence is low, and additional clinical trials are required.(21) **(EG 2)** A systematic review and meta-analysis of 3 randomized controlled trials with 522 patients with benign prostatic hyperplasia found that treatment with botulinum toxin A produced a slightly greater improvement in International Prostate Symptom Scores when compared with placebo; however, there were no differences in maximum urinary flow, prostate volume, and postvoid residual volume between the botulinum toxin A and placebo groups. The authors concluded that these trials did not support the use of botulinum toxin A for men with lower urinary tract symptoms due to benign prostatic hyperplasia.(22) **(EG 1)**

For chronic idiopathic constipation in children, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A randomized trial assigned 42 patients to onabotulinumtoxinA or to myectomy of the internal anal sphincter and reported comparable improvement after 1 year in both groups; however, larger randomized studies are needed.(23) **(EG 1)** A retrospective study of 141 children with severe constipation unresponsive to medication management found that treatment with botulinum toxin injections into the internal anal sphincter was associated with a decrease in defecatory pain or an increase in frequency of bowel movements in 70% of patients. The authors note that a prospective randomized placebo-controlled trial is needed.(24) **(EG 2)** A retrospective cohort study of 196 pediatric patients with treatment-refractory chronic functional constipation who were treated with botulinum toxin A injection (abobotulinumtoxinA or onabotulinumtoxinA) into the external anal sphincter reported, at 4 months and 16 months post injection, improvements from baseline in symptom severity scores; however, the authors noted that the number of patients available for longer-term follow-up was limited.(25) **(EG 2)**

For chronic pain, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review and meta-analysis of randomized controlled trials found preliminary but not confirmatory evidence that either abobotulinumtoxinA or onabotulinumtoxinA may be effective for a variety of painful conditions, as well as convincing evidence of lack of effectiveness for myofascial pain syndrome.(26) **(EG 1)** Systematic reviews of randomized trials reported that evidence is inconclusive to support the use of botulinum toxin for myofascial pain.(27)(28)(29) **(EG 1)** Systematic reviews and meta-analyses of randomized controlled trials found that intra-articular injections of botulinum toxin A significantly improved joint pain; however, the clinical effect was small, and the authors recommended further studies assessing the benefit of this therapy.(30)(31) **(EG 1)** A systematic review and meta-analysis of 10 randomized placebo-controlled trials (2 of which were unpublished) including 530 patients evaluated botulinum toxin A for neuropathic pain and found, at 1-month and 3-month follow-up, that botulinum toxin A was associated with improvement in visual analog scale pain scores. However, the results were limited by small study sizes and variability in botulinum toxin A used, doses, and areas of the body treated.(32) **(EG 1)** A multicenter double-blind trial randomly allocated 176 patients with nociceptive pain from knee osteoarthritis to treatment with a single intra-articular injection of onabotulinumtoxinA (at 2 different doses) or saline. At 8-week follow-up, all 3 groups noted significant pain relief that was sustained throughout the 24-week study; however, there were no between-group differences when comparing onabotulinumtoxinA vs placebo.(33) **(EG 1)** For various types of chronic pain, including inflammatory pain, musculoskeletal pain, neuropathic pain, and postoperative pain, evidence-based reviews (involving primarily onabotulinumtoxinA) reported that the role of this therapy is not well established.(34)(35) **(EG 2)** A randomized placebo-controlled trial with 30 patients with postherpetic neuralgia found that botulinum toxin A was significantly more effective than placebo in reducing postherpetic pain over a period of 16 weeks, but the authors indicated that further confirmatory studies are needed.(36) **(EG 1)** Review articles on evidence for the effectiveness of botulinum toxin A for various types of neuropathic pain found 2 randomized studies supporting use for postherpetic neuralgia; however, one study involved a formulation not available in the United States, and the second had only 15 patients per treatment arm with 24-week follow-up.(37)(38)(39) **(EG 2)** A specialty society guideline states that botulinum toxin A may be considered as a third-line treatment option for patients with spinal cord injury who have neuropathic pain that is refractory to medical therapy; the authors note that the supporting evidence is weak.(40) **(EG 2)**

For chronic pelvic pain in men, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review of interventions for chronic prostatitis and chronic pelvic pain in men identified 3 studies evaluating botulinum toxin A. The authors concluded that there is low-quality evidence that intraprostatic botulinum toxin A injection may be associated with reduction of prostatitis symptoms, while pelvic floor muscle botulinum toxin A injection was not associated with symptom reduction in men.(41) **(EG 1)** A double-blind randomized controlled trial of 64 patients with chronic scrotal pain and an incomplete response to prior therapies compared further treatment with local anesthetic alone or combined with onabotulinumtoxinA and found, 1 month after injection, no significant difference in patient-reported scrotal pain between groups.(42) **(EG 1)**

For clubfeet, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review of interventions for congenital clubfoot found insufficient evidence to draw conclusions about the incremental efficacy of adding botulinum toxin A to serial manipulation and casting. The review identified one randomized study of 20 newborns with 32 clubfeet who received onabotulinumtoxinA or placebo in addition to standard serial manipulation or casting; no significant incremental benefit was demonstrated for onabotulinumtoxinA in terms of reducing cast time, need for tenotomy, or risk for relapse.(43) **(EG 1)** A double-blind randomized controlled trial of 62 infants with congenital idiopathic clubfoot who were treated at the time of hindfoot stall found no difference in response rates (defined as obtaining 15 degrees or more of dorsiflexion) between treatment with onabotulinumtoxinA and placebo at 6 weeks after the injection.(44) **(EG 1)** A retrospective case series of 361 affected feet in 239 eligible patients younger than 2 years found that botulinum toxin appeared to be safe, but the authors cautioned that properly controlled prospective outcome studies are necessary to better assess efficacy.(45) **(EG 2)**

For depression, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A randomized double-blind crossover study of 30 patients with depression followed over 24 weeks found significant improvement in depressive symptoms with botulinum toxin A, but the authors stated that larger confirmatory studies with longer-term follow-up are essential.(46) **(EG 1)** In a randomized controlled study, 74 patients with major depression received onabotulinumtoxinA or placebo injections in corrugator and frown muscles. After 6 weeks, 52% of actively treated patients, as compared with 15% of those receiving placebo, achieved at least 50% improvement in a major depression rating scale; the authors indicated that larger, longer-term study is needed.(47) **(EG 1)**

For essential tremor, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A randomized controlled trial of 117 patients with essential head tremor (with or without limb tremor) compared treatment with either a series of 2 onabotulinumtoxinA injections 12 weeks apart or placebo injections and found, at 18 weeks of follow-up, that onabotulinumtoxinA was associated with more patients achieving at least a 2-point improvement on the Clinical Global Impression of Change (CGI) scale compared with placebo; 47% of patients who received onabotulinumtoxinA had an adverse event (eg, local pain, neck weakness, dysphagia), compared with 16% of patients who received placebo. The authors noted that the use of a subjective measure (CGI) as a primary endpoint and between-group differences in rates of study discontinuation between the first and second injections limited the results.(48) **(EG 1)** Expert evidence-based reviews found limited evidence to suggest that botulinum toxins may be helpful for disabling essential tremor of the hands in those patients who fail treatment with oral agents and prior to consideration of thalamic deep brain stimulation; however, existing evidence was insufficient to draw a conclusion on the use of botulinum toxins in the treatment of head and voice tremor.(49)(50)(51)(52)(53)(54) **(EG 2)**

For focal dystonias of the lower extremity, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A review and specialty society guideline summary indicated that evidence for effectiveness of botulinum toxin in focal lower limb dystonia is at the lowest level of consideration.(55) **(EG 1)** A review article on use of botulinum toxin for treatment of primary focal dystonias makes no recommendations for use in lower limb dystonias.(56) **(EG 2)**

For gastroparesis, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review and review articles have concluded that there is no evidence of effectiveness of botulinum toxin for this condition.(57)(58)(59) **(EG 2)** Expert consensus guidelines on the management of gastroparesis state that additional randomized controlled trials evaluating intrapyloric botulinum toxin for gastroparesis are needed.(60)(61) **(EG 2)**

For gustatory sweating (Frey syndrome), evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review found only uncontrolled case series and concluded that there is insufficient evidence to support the use of botulinum toxin for this condition.(62) **(EG 1)**

For idiopathic toe walking, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review of conservative and surgical treatments for idiopathic toe walking in children identified a single randomized controlled trial in 47 children with idiopathic toe walking that showed no significant improvement in parent-reported toe walking time with below-the-knee walking casts with botulinum toxin A injected into the calf muscles, as compared with casting alone.(63) **(EG 1)**

For masseter hypertrophy, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review found a lack of relevant randomized controlled trials or other robust evidence to support or refute the effectiveness of botulinum toxins for treatment of masseter hypertrophy.(64) **(EG 1)**

For obesity, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review and meta-analysis of 4 randomized controlled trials with 108 obese patients concluded that gastric injections of botulinum toxin A were not effective for reducing weight.(65) **(EG 1)**

For Parkinson disease tremor, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A randomized trial compared the effects of onabotulinumtoxinA injection vs placebo in 12 patients with limb pain and advanced Parkinson disease and found no significant differences between the 2 treatments.(66) **(EG 1)**

For pelvic floor pain syndrome, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review of 16 studies evaluating botulinum toxin A for chronic pelvic pain (ie, bladder pain syndrome, gynecologic pain syndrome, prostate pain syndrome, chronic anal pain, and myofascial pelvic pain) included 4 studies (194 patients) of onabotulinumtoxinA for gynecologic pelvic pain and one study (59 patients) of onabotulinumtoxinA for myofascial pelvic pain. In a pooled analysis, onabotulinumtoxinA was not associated with significant improvement in pain scores at 6-month follow-up compared with placebo; reporting on quality-of-life and functional outcomes was limited. In a single randomized placebo-controlled trial, onabotulinumtoxinA was not associated with significant improvements in pain scores at 3-month follow-up compared with placebo. The authors noted that the included studies were at high risk of bias and confounding and stated that additional multicenter trials evaluating botulinum toxin A for chronic pelvic pain are needed.(67) **(EG 1)** A systematic review of 24 studies (5 of which were randomized trials) evaluating botulinum toxin for pelvic floor tension myalgia and persistent pelvic pain (1133 patients total) reported that, although observational studies found improvements in patient-reported outcomes after botulinum toxin treatment, a meta-analysis of data from the 4 randomized controlled trials with adequate data for analysis found no significant differences between botulinum toxin-treated and placebo-treated patients in outcomes related to vaginal pressure or patient-reported pain or sexual function.(68) **(EG 1)** A randomized trial of 94 women with chronic pelvic pain and increased pelvic floor muscle tension refractory to pelvic floor muscle therapy compared treatment with either botulinum toxin A or placebo injections into the pelvic floor muscles and found, at 26-week follow-up, no between-group differences in the proportion of patients reaching at least a 33% reduction in average pain score.(69) **(EG 1)** A systematic review concluded that significantly more study is needed to evaluate the effectiveness of botulinum toxin A for anismus.(70) **(EG 1)**

For plantar fasciitis, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review evaluating minimally invasive nonsurgical management of plantar fasciitis included 3 randomized controlled trials (144 patients) comparing botulinum toxin A injection with placebo or corticosteroids and found that botulinum toxin A was associated with improved patient-reported visual analog scale pain scores compared with other interventions. However, the authors noted that heterogeneity among included studies limited the results, and further studies were recommended.(71) **(EG 1)** A randomized controlled trial of 71 patients with plantar fasciitis compared treatment with injected anesthetic (ropivacaine), corticosteroid, or botulinum toxin A and found, at 24-week follow-up, that all groups had improvement in patient-reported visual analog scale pain scores and Maryland Foot Score results, as well as improvement in ultrasound-measured plantar fascia thickness, with no differences seen between treatment groups.(72) **(EG 1)**

For postnatal brachial plexus injury, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review of studies including use of either abobotulinumtoxinA or onabotulinumtoxinA found only a low level of promising but not confirmatory evidence, and the authors indicated that multicenter randomized trials are needed.(73) **(EG 2)**

For refractory interstitial cystitis (ie, bladder pain syndrome), evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review of 16 studies evaluating botulinum toxin A for chronic pelvic pain (ie, bladder pain syndrome, gynecologic pain syndrome, prostate pain syndrome, chronic anal pain, and myofascial pelvic pain) identified 7 studies (374 patients) of botulinum toxin A for bladder pain syndrome (interstitial cystitis), including 2 studies evaluating onabotulinumtoxinA, one study each evaluating abobotulinumtoxinA and

incobotulinumtoxinA, and 3 studies evaluating unspecified botulinum toxin A. The review found that, although half of the included studies reported significant improvements in pain at 3 to 12 months post treatment, the available evidence was limited by heterogeneity in intervention and control treatments, including the type and dose of botulinum toxin A, sites of injection, outcome measures, and follow-up periods. The authors stated that additional multicenter trials evaluating botulinum toxin A for chronic pelvic pain are needed.(67) **(EG 1)** A systematic review and network meta-analysis of 16 randomized controlled trials concluded that among 7 intravesical treatments for refractory interstitial cystitis, botulinum toxin A had the highest probability of being the best in terms of global response assessment and improved bladder capacity; however, the authors suggested further research to improve understanding of the disease and its treatment.(74) **(EG 1)** A randomized trial of 58 female patients with interstitial cystitis/bladder pain syndrome compared treatment with either a single intradetrusor injection of onabotulinumtoxinA or 6 weekly bladder instillations of lidocaine, heparin, and sodium bicarbonate and found, at 2 months post treatment, that onabotulinumtoxinA was associated with lower Interstitial Cystitis Symptom Index (ICSI) scores compared with bladder instillation; at 6 to 9 months post treatment, no difference was seen between groups, and urinary retention requiring self-catheterization had occurred in 8% of patients who received onabotulinumtoxinA. The authors noted that the study was underpowered due to loss of patients in the instillation group.(75) **(EG 1)** An expert consensus statement suggests that botulinum toxin injections be considered for patients with primary bladder pain syndrome that is refractory to intravesical therapies but notes that there is limited evidence demonstrating their benefit.(76) **(EG 2)** A specialty society guideline includes intradetrusor onabotulinumtoxinA as a treatment option for patients with interstitial cystitis/bladder pain syndrome but states that the evidence is limited by variability in injection protocols and few prospective trials.(77) **(EG 2)**

For shoulder pain, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** Systematic reviews and meta-analyses found some evidence that intramuscular botulinum toxin A injection may reduce pain, but due to small sample sizes and significant study heterogeneity, the authors cautioned that more study is needed.(78)(79) **(EG 1)**

For thoracic outlet syndrome, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A meta-analysis and systematic review stated that there is moderate evidence suggesting that botulinum toxin injections to the scalene muscles for treatment of thoracic outlet syndrome resulted in no greater improvement than placebo injection of saline.(80) **(EG 1)**

For trigeminal neuralgia, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A meta-analysis of 4 randomized controlled trials (178 patients) found that treatment with botulinum toxin A had a favorable effect on pain compared with placebo in patients with trigeminal neuralgia; the authors cautioned that the findings should be interpreted with caution due to the limited number of patients and trials and the need for longer follow-up. The authors recommended future randomized controlled trials to evaluate this intervention.(81) **(EG 1)** An uncontrolled study of 87 patients with trigeminal neuralgia showed that injection of botulinum toxin in the pain area had an effective rate of 48% at 1 week and 80% at 8 weeks.(82) **(EG 2)** Review articles of the use of botulinum toxin A for trigeminal neuralgia found evidence consisting only of small studies with limited follow-up; some studies suggested a possible favorable response, but the authors indicated that larger, randomized studies are needed.(37)(83)(84) **(EG 2)** A specialty society guideline notes that botulinum toxin A may have an effect as adjunctive therapy for treating patients with trigeminal neuralgia, acknowledging that the evidence supporting this conclusion is of very low quality.(85) **(EG 2)**

For upper esophageal sphincter dysfunction, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review to assess the efficacy and safety of botulinum toxin for improving upper esophageal sphincter dysfunction in patients with dysphagia did not identify any relevant randomized controlled trials and stated that there was insufficient evidence to inform clinical practice.(86) **(EG 1)** A subsequent systematic review found only case series describing the use of botulinum toxin for cricopharyngeal dysfunction; the authors noted that the treatment appears to be associated with a high recurrence rate but may be suitable in patients who have multiple comorbidities or are elderly, and they recommended future studies to better evaluate the efficacy of this intervention.(87) **(EG 1)**

Rationale

Use of this MCG care guideline helps the clinician determine if a particular treatment, medication, or service might be appropriate for a specific patient, taking into account their unique health complexities.

Use of these evidence-based clinical criteria to support decision making benefits the patient by identifying patient-specific complex clinical factors and conditions, promoting personalized treatment. Utilizing evidence-based clinical criteria promotes patient safety by helping ensure that potential patient benefits outweigh the risks. In addition, the use of evidence-based guidelines can increase consistency in treatment thresholds, leading to less variation in care and promoting equitable treatment among patients.

Related CMS Coverage Guidance

This guideline supplements but does not replace, modify, or supersede existing Medicare regulations or applicable National Coverage Determinations (NCDs) or Local Coverage Determinations (LCDs).

Code of Federal Regulations (CFR): 42 CFR 419.22(283); 42 CFR 422.101(284)

Internet-Only Manual (IOM) Citations: CMS IOM Publication 100-02, Medicare Benefit Policy Manual, Chapter 14 - Medical Devices(285); CMS IOM Publication 100-02, Medicare Benefit Policy Manual, Chapter 15 - Covered Medical and Other Health Services(286); CMS IOM Publication 100-02, Medicare Benefit Policy Manual, Chapter 16 - General Exclusions from Coverage(287)

Medicare Coverage Determinations: Medicare Coverage Database(288)

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Footnotes

[A] For axillary hyperhidrosis, botulinum toxin A is administered intradermally into affected areas as determined by standard iodine-starch testing. Repeated doses may be administered when the clinical effectiveness of the most recent dose has diminished.(126)(127)(128)(129)(130) [A in Context Link 1]

[B] The Hyperhidrosis Disease Severity Scale (HDSS) is used to evaluate the severity of hyperhidrosis and how it affects the individual's daily activities and is based on the patient answering a single statement. A score of 1 reflects mild disease severity, while a score of 2 reflects moderate disease severity. A score of 3 or 4 reflects severe disease severity.(127)(129)(139) [B in Context Link 1]

[C] Topical aluminum chloride hexahydrate may initially be applied using a concentration of 10% to 12% to minimize skin irritation; a concentration of 35% may be required to achieve euhidrosis.(138)(140)(141)(142) [C in Context Link 1]

Codes

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