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Drug Class Update: Botulinum Toxins

Date of Review: May 2018 **Date of Last Review:** May 2014

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
Review evidence for uses of botulinum toxin and funding for these indications under the Oregon Health Plan (OHP) Prioritized List of Health Services.

Research Questions:
1. Are there differences in efficacy/effectiveness between botulinum toxin (BoNT) therapy to support choosing a specific BoNT based on indication?
2. Are there differences in harms between BoNT therapy to support restricting use of a specific BoNT based on indication?
3. Are there subpopulations based on demographic characteristics (i.e., age, gender, comorbid conditions) in which certain BoNT therapies may be more effective or safer than others?

Conclusions:
- Six new high quality systematic reviews of BoNT treatment for conditions funded under the OHP were identified. These reviews focused on the efficacy of BoNT treatment for limb spasticity, symptomatic benign prostatic hyperplasia (BPH), strabismus, and cervical dystonia. The American Academy of Neurology (AAN) also published a practice guideline update on BoNT treatment for blepharospasm, cervical dystonia, adult spasticity, and headache.
- A systematic review with meta-analyses evaluated efficacy of BoNT type A (BoNTA) treatment on improving 'ease of care' for patients the upper and lower limb spasticity. A meta-analysis of BoNTA for 4 to 12 weeks for treatment of upper limb spasticity demonstrated a statistically significant effect for all outcomes in favor of BoNTA based moderate quality evidence (standardized mean difference [SMD] 0.80; 95% confidence interval [CI], 0.55 to 1.06; p<0.001).[9] The relative risk for the global assessment of benefit measures was 2.21 (95% CI, 1.67 to 2.93; p<0.0001, number needed to treat [NNT]=5) if rated by patients and 2.51 (95% CI, 1.21 to 5.20, p=0.01, NNT=6) if rated by the clinician.[9] A meta-analysis of upper limb outcomes for 12 to 24 weeks demonstrated a continued statistically significant effect in favor of BoNTA for individual outcomes (SMD 0.48; 95% CI, 0.34 to 0.62; p<0.001).[9] For lower limb studies, both the patient- and clinician-rated scores failed to demonstrate a significant effect and were rated as low to insufficient evidence.[9]
- Another systematic review examined the efficacy of BoNTA on improving activity restriction (i.e., active function) of the upper and lower limbs and quality of life in patients with spasticity. Active range of motion in the upper limb was examined in 8 studies using stroke patients but nearly all of them found no statistically significant difference between BoNTA and placebo.[10] Only one of 3 studies found statistically significant improvement of active range of motion in lower limbs.[10] No statistically significant differences were found in 7 studies that evaluated timed walk tests.[10] Overall evidence for these

outcomes was insufficient to low quality primarily due to lack of study directness and small sample sizes.[10] Data were insufficient to assess effect of BoNTA on quality of life.[10]

- A systematic review was performed to assess the overall treatment efficacy and safety of BoNTA for benign prostatic hyperplasia (BPH) with lower urinary tract symptoms (LUTS). The pooled overall SMD in the mean change in International Prostate Symptom Score (IPSS) from baseline for BoNTA versus the placebo group was −1.02 (95% CI −1.97, −0.07).[11] Overall, there is low quality evidence that BoNTA for BPH with LUTS is not more efficacious than placebo and that there are no differences in adverse events.[11]
- The Cochrane collaboration examined the efficacy of BoNT in the treatment of strabismus. The systematic review with meta-analyses found insufficient evidence for effect of BoNT on reducing visual symptoms in acute sixth nerve palsy, poor response in people with horizontal strabismus without binocular vision, similar or slightly reduced achievement of successful ocular alignment in children with esotropia and potential increased achievement of successful ocular alignment where surgery and BoNT are combined.[12] High quality trials using robust methodologies are required to compare the clinical efficacy of various formulations of BoNT, to compare BoNT with and without adjuvant solutions, and to compare BoNT to alternative surgical interventions in strabismus cases with and without potential for binocular vision.[12]
- The Cochrane collaboration updated a 2003 review that compared efficacy of BoNTA versus BoNT type B (BoNTB) for cervical dystonia.[13] All trials evaluated the effect of a single BoNT treatment session, and not repeated treatment sessions, using doses from 100 units to 250 units of BoNTA (all onabotulinumtoxinA [onaBoNTA] formulations) and 5,000 units to 10,000 units of BoNTB (rimabotulinumtoxinB [rimaBoNTB]).[13] The meta-analysis found no difference between the 2 types of BoNT in terms of overall efficacy, with a mean difference of -1.44 (95% CI -3.58 to 0.70) points lower on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) for BoNTB-treated participants, measured at 2 to 4 weeks after injection. The proportion of patients with adverse events was also not different between BoNTA and BoNTB (BoNTB vs. BoNTA: RR 1.40; 95% CI 1.00 to 1.96). Overall, they found low quality evidence that a single treatment of onaBoNTA and a single treatment of rimaBoNTB are equally effective and safe in the treatment of adults with certain types of cervical dystonia.[13]
- Based on evidence reviewed by the AAN, either onaBoNTA or incobotulinumtoxinA (incoBoNTA) are recommended (Level B), and abobotulinumtoxinA (aboBoNTA) may be considered (Level C), as treatment options for blepharospasm; onaBoNTA should be offered as a treatment option to patients with chronic migraine to increase the number of headache-free days (Level A) and should be considered to reduce headache impact on health-related quality-of-life (Level B); aboBoNTA and rimaBoNTB should be offered (Level A), and onaBoNTA and incoBoNTA should be considered (Level B), as options for the treatment of cervical dystonia; for focal manifestations of adult spasticity involving the upper limb, aboBoNTA, incoBoNTA, and onaBoNTA should be offered (Level A), and rimaBoNTB should be considered (Level B), as treatment options; and for focal manifestations of adult spasticity involving the lower limb that warrant treatment, onaBoNTA and aboBoNTA should be offered (Level A) as treatment options.[16]
- IncoBoNTA (Xeomin) received an indication in December 2015 for the improvement of adult patients with upper limb spasticity.[17]
- AboBoNTA (Dysport) received an indication in July 2016 for the treatment of lower limb spasticity in pediatric patients 2 years of age and older and an indication in June 2017 for treatment of lower limb spasticity in adult patients.[1]

Recommendations:

- Update current clinical prior authorization criteria to reflect current coverage and guidelines in the OHA Prioritized List of Health Services.

Previous Conclusions:

- There is moderate quality evidence that BoNTA is recommended first-line for cervical dystonias due to increased efficacy compared to standard therapies. BoNTB is recommended for BoNTA-resistant dystonias. There is low quality evidence of no difference between aboBoNTA and onaBoNT in the treatment of cervical dystonia.
- There is low quality evidence demonstrating efficacy of BoNTA for the treatment of blepharospasm. However, open-label studies have demonstrated a significant effect size and clinical practice guidelines recommend BoNT as a treatment option for blepharospasm. There is low quality evidence of no difference between aboBoNTA and onaBoNTA and no difference between aboBoNTA and incoBoNTA in the treatment of blepharospasm.
- There is moderate quality evidence that aboBoNTA, onaBoNTA and rimaBoNTB reduces muscle tone and improves passive function for upper limb spasticity and low-quality evidence for lower limb spasticity. There is insufficient evidence for an effect on active function.
- There is low quality evidence that unspecified BoNTA products may be associated with benefit in the prophylaxis of chronic migraine headaches (≥15 days a month), but results are inconsistent. In addition, the clinical significance remains uncertain, as the absolute reduction in the number of headaches is only 2 to 3 headaches per month. There is moderate quality evidence of no benefit of prophylaxis with BoNTA in patients with intermittent migraine attacks (less than 15 headache days per month) or chronic tension type headache.
- There is high quality evidence of no difference between BoNT injections and placebo in neck pain. There is insufficient evidence to support the use of BoNT injections to improve pain or function in patients with lower back pain.
- There is low quality and inconsistent evidence for the use of BoNT for increasing healing of anal fissure and appears less effective than sphincterotomy.
- In the treatment of strabismus, there is low quality evidence that BoNT may be as effective as surgery for retreatment of acquired or infantile esotropia but does not appear effective for acute 6th nerve palsy or adult horizontal strabismus.
- There is low quality evidence of clinical efficacy of BoNT in the treatment of axillary hyperhidrosis and palmar hyperhidrosis. There is insufficient comparative evidence. Aluminum chloride preparations are the most widely used first-line agents.
- There is moderate quality evidence that BoNTA injections in the detrusor are the most effective minimally invasive treatment to reduce urinary incontinence in patients with neurogenic detrusor over activity that is unresponsive to more conservative therapies.
- There is moderate to high quality evidence that pneumatic dilation and surgical myotomy are more effective on long term remission that BoNT for the treatment of achalasia. BoNT is effective short term, but response diminishes at 2 years. It is a reasonable treatment approach for patients who are not candidates for surgical therapy.
- There is insufficient evidence to make conclusions on the use of BoNT to treat neurogenic dysphagia. A recent systematic review identified no randomized controlled trials that met inclusions criteria and an overall lack of evidence to demonstrate efficacy.
- There is insufficient evidence demonstrating long term efficacy of BoNT for the treatment of laryngeal dysphonia or spasmotic dysphonia.

Previous Recommendations:

- Implement prior authorization criteria to limit use to diagnoses supported by evidence.

Background:

Acetylcholine is an important neurotransmitter in the parasympathetic, and to some degree, in the sympathetic autonomic nervous system.[2] Several autonomic disorders arise from over-activity of acetylcholine. For example, cholinergic over-activity occurs at the neuromuscular junction in overactive bladder or at the neurosecretory junction in hypersecretory disorders.[2] The ability of BoNTs to block release of acetylcholine at neuromuscular junctions accounts for

its therapeutic action to relieve dystonia, spasticity, and other related disorders.[3] Both the direct and indirect actions of the toxin are largely or completely reversible.[3]

BoNT drugs are comprised of the botulinum toxin component, formed by botulinum neurotoxin and non-toxic complexing proteins, and excipients.[4] When BoNT is injected into tissue, it binds with high affinity to glycoprotein structures located on the cholinergic nerve terminal.[4] BoNT inhibits release of acetylcholine at presynaptic cholinergic nerve terminals of the peripheral nervous system and at ganglionic nerve terminals of the autonomic nervous system.[5] Muscle tissue is unable to contract with disruption of neurotransmission of acetylcholine, causing paralysis.[5] Depending on the target tissue, BoNT can block the cholinergic neuromuscular transmission, but also the cholinergic autonomic innervation of sweat, tear and salivary glands and smooth muscles.[5] Recovery of neuromuscular activity occurs through regeneration of axonal sprouts and motor end plates which limits the duration of activity of BoNT to a few months.[5] In general, the effects of BoNT are first observed after 2 to 3 days, with maximal effect after about 2 weeks, and prolonged effects for 2 to 3 months before the effect begins to wear off.[4] The time course of this effect is remarkably reproducible over time without evidence of tachyphylaxis.[4]

Adverse effects associated BoNT generally fall into 3 broad categories. First, diffusion of the toxin from the intended sites of action can lead to unwanted inhibition of transmission at neighboring nerve endings.[3] Second, sustained blockade of transmission can produce effects similar to anatomic denervation, including muscle atrophy.[3] Third, neutralizing antibodies can be formed against all the foreign protein within the BoNT which can result in therapy failure.[3]

Currently, there are 3 BoNTA products (aboBoNTA [Dysport®]; incoBoNTA (Xeomin®); onaBoNTA (Botox®; Botox® Cosmetic) and one BoNTB product (rimaBoNTB [Myobloc®]) available commercially in the United States. Indications and off-label uses for each of these products are listed in **Tables 1 and 2**. These preparations are not interchangeable; assay methods used to determine potency of botulinum toxins are specific to each individual manufacturer and formulation.[6]

Table 1. Indications for Botulinum Toxins Approved by the U.S. Food and Drug Administration.

Botulinum toxin type A:

- AbobotulinumtoxinA (DYSPORT):
  - The treatment of adults with cervical dystonia
  - The 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
  - The treatment of spasticity in adults
  - The treatment of lower limb spasticity in pediatric patients ≥2 years of age
- IncobotulinumtoxinA (XEOMIN):
  - Upper limb spasticity in adults
  - Cervical dystonia in adults
  - Blepharospasm in adults with prior treatment of onabotulinumtoxinA (Botox®)
  - Temporary improvement in the appearance of moderate to severe glabellar lines with corrugator and/or procerus muscle activity in adults
- OnabotulinumtoxinA (BOTOX; BOTOX COSMETIC):
  - 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 over-activity 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
Botulinum toxin type B: * RimabotulinumtoxinB (MYOBLOC): ○ Management of cervical dystonia (spasmodic torticollis) to decrease severity of associated abnormal head position and neck pain in adults

Table 2. Off-label Clinical Uses of Botulinum Toxins.[4]

Ophthalmology • Protective ptosis *(a procedure to close the upper eyelid to facilitate healing of severe corneal infections)* • Entropion *(inversion of the lower eyelid producing painful corneal irritation)* **Neurology** • Dystonias ○ Focal: oromandibular dystonia, lingual dystonia, Meige syndrome (blepharospasm with oromandibular and lingual dystonia), tardive dystonia, bruxism (forceful closure of jaws), occupational dystonias (writer's cramp, musician's cramp) ○ Segmental dystonia ○ Hemidystonia ○ Axial dystonia ○ Generalized dystonia ○ Symptomatic dystonias: Hallervorden-Spatz syndrome, etc. • Spasticity ○ Focal; leg ○ Non-focal: hemispasticity (arm and leg), paraspasticity (both legs), tetraspasticity (high spinal/supraspinal processes) • Hemifacial spasm (synchronous unilateral muscles contractions innervated by facial nerve)	**Urology** • Detrusor sphincter dyssynergia (dyscoordination of the detrusor and the sphincter bladder muscles that result in UTIs from residual urine) • Urinary retention • Bladder pain syndrome • Pelvic floor spasms • Benign prostate hyperplasia • Anal fissures **Otorhinolaryngology** • Laryngeal dystonia (spasmodic dysphonia) • Pharyngeal dystonia • Gustatory sweating (sweating while eating) • Crocodile's tears (uncontrolled flow of tears during eating in patients with facial nerve impairment) • Chronic rhinitis **Pediatrics** • Infantile cerebral palsy (produces complex movement disorders with paresis, spasticity, ataxia and apraxia) **Gastroenterology** • Achalasia (aperistalsis and reduced relaxation of the lower esophageal sphincter)

• Reinnervation synkinesias (involuntary facial contractions producing eyelid closure when perioral movements are intended, and perioral movements when eyelid closure is intended)
• Tics (involuntary muscle contractions results in disinhibited movement of any body region, but usually of the face or shoulder muscles)
• Cerebral palsy
• Hyperhidrosis (excessive sweating)
  ○ Focal: palmar, plantar
  ○ Diffuse
• Sialorrhea (drooling, typically from Parkinsonian syndromes, motor neuron disease)
• Tremor (mostly of the neck)
• Muscular Pain
  ○ Muscular dystonia, spasticity, piriformis syndrome, thoracic outlet syndrome, epicondylitis lateralis (tennis elbow)
• Raynaud phenomenon
• Untreatable focal seizures
	• Cricipharyngeal achalasia (upper esophageal sphincter affected)
	• Unspecific esophageal spasms
	• Gastroparesis
	• Sphincter Oddi spasms

BoNT has been studied and used for several different hypersecretory disorders.[2] Primary focal hyperhidrosis is a chronic idiopathic disorder of excessive sweating which most often affects the axillae, palms, soles, and forehead.[2] Drooling may be a disabling problem in parkinsonian syndromes, amyotrophic lateral sclerosis (ALS), and cerebral palsy.[2] Of these conditions, BoNT is established as safe and effective for the treatment of axillary hyperhidrosis and is probably safe and effective for palmar hyperhidrosis and in drooling in patients with Parkinson's Disease.[2] There is insufficient evidence to support the effectiveness of BoNT in hyperlacrimation. There are no head-to-head studies that have compared BoNT with other treatment options in hyperhidrosis or drooling, but BoNT is typically reserved until other treatments have been exhausted.[2] In neurodegenerative disorders such as ALS, BoNT should be used with caution as dysphagia or worsening weakness may occur.[2]

BoNT has been studied and used for some neurologic disorders. Patients with neurogenic bladder suffer from detrusor over-activity (detrusor hyperreflexia), which may be combined with detrusor sphincter dyssynergia (DSD; uncoordinated voiding).[2] Both conditions cause high intravesical pressure and can lead to upper urinary tract damage.[2] Treatment for both DSD and detrusor over-activity include pharmacologic therapy, catheterization or surgery.[2] BoNT is established as safe and effective for the treatment of neurogenic detrusor over-activity in adults, but evidence for management of DSD is conflicting.[2] BoNT is probably safe and effective for the treatment of DSD in patients with spinal cord injury but lacks benefit for the treatment of DSD in patients with MS.[2]

BoNT has been extensively studied for migraine headache.[2] BoNT has not shown to be effective for episodic migraine based on available studies.[2] Chronic daily headache (CDH) is a headache that occurs more than 15 days out of a month, and it may be a migraine or tension headache.[2] The primary outcome measure for all CDH studies was the mean change in headache-free days per month.[2] Based on inconsistent results from studies, there is insufficient evidence to support or refute a benefit of BoNT for the treatment of chronic daily headache.[2] BoNT injection is probably ineffective for patients with chronic tension-type headaches based available study results.[2]

BoNT is effective for treatment of adult spasticity of the upper or lower limb by reducing muscle tone and improving passive function.[3] Treatment aims to increase range of motion (passive and/or active), reduce pain, or achieve other functional goals (e.g., hygiene/ease of dressing).[7] However, there is lack of consensus on what constitutes meaningful functional gain following treatment for spasticity. There is insufficient evidence in controlled trials to support use of BoNT in adults to improve active (voluntary) function.[3] There are no controlled studies comparing BoNT to other treatment modalities for adult spasticity.

BoNT is now standard clinical practice for the treatment of many disorders of excess motor activity, including numerous forms of dystonia and spasticity.[3] However, treatment response varies widely within and among indications.[3] Future studies should investigate factors that predict which patient subgroups have optimal response.[3] A major limitation in published clinical trials of BoNT is the lack of standardized rating tools for many clinical indications (e.g., spasticity or focal hand dystonia).[3] Furthermore, there is often disagreement among investigators, clinicians, patients, and regulatory agencies as to what constitutes functional improvement.[3] Future studies would benefit from the development of validated scales applicable across the spectrum of tasks eliciting the abnormal movements and sensitive to changes with focal treatment such as BoNT.[3]

Cerebral palsy is a movement and posture disorder that appears in early childhood. Muscle hypertonia can lead to fixed contractures, torsional deformities of long bones, and joint instability as the child grows.[3] Treatment options for childhood cerebral palsy include physical and occupational therapy, splinting/casting, surgical approaches, and BoNT.[3] As in adult spasticity, there is lack of consensus on what constitutes meaningful functional gain following treatment for spasticity.[3] Nonetheless, BoNT injection of the gastrocnemius-soleus muscles is established as effective in the treatment of spastic equinus in patients with cerebral palsy.[3] In patients with adductor spasticity, BoNT is probably effective in improving adductor spasticity and range of motion, as well as postoperative pain in children undergoing adductor muscle lengthening surgery.[3] In patients with upper extremity symptoms, BoNT is probably effective in improving spasticity and range of motion.[3] BoNT of the calf muscles should be offered as a treatment option for equinus varus deformity in children with cerebral palsy.[3] BoNT should be considered as a treatment option for treatment of adductor spasticity and for pain control in children undergoing adductor-lengthening surgery.[3] BoNT should be considered as a treatment option in children with upper extremity spasticity.[3]

Blepharospasm is a focal dystonia characterized by involuntary contraction of orbicularis oculi, causing involuntary closure of the eye.[8] Blepharospasm was one of the first indications studied for BoNT treatment. The evidence supporting BoNT use in blepharospasm is limited. The large magnitude of benefits in the initial open label studies and the lack of other effective therapy likely have discouraged efforts to study BoNT in larger and more properly controlled clinical trials.[8] OnaBoNTA received an FDA indication for blepharospasms in 1989, although incoBoNTA also has an indication and likely has similar efficacy.[8]

Hemifacial spasm is characterized by a combination of unilateral clonic and tonic spasms of the muscles innervated by the facial nerve. Treatment options include carbamazepine, baclofen, or a benzodiazepine, with limited efficacy, or microvascular decompression of the facial nerve.[8] BoNT injection can also be considered as a treatment option, but evidence is limited to 2 studies which showed possible effectiveness with aboBoNTA and onaBoNTA. It is not known how BoNT compares to standard oral drug treatments.

Spasmodic torticollis, more commonly known as cervical dystonia, is a focal dystonia causing involuntary activation of the muscles of the neck and shoulders resulting in abnormal, sustained, and painful posturing of the head, neck, and shoulders.[8] BoNT has longstanding and widespread use in the treatment of cervical dystonia as there are no effective alternative medical therapies. [8] There are no data to compare BoNT with surgical treatment of cervical dystonia.

BoNT is probably effective for the treatment of focal upper extremity limb dystonia. Focal hand dystonia is a common form, which usually refers to “writer’s cramp” and other occupational hand dystonias.[8] For these conditions, BoNT presents risk for causing excessive muscle weakness.[8] The pattern of limb dystonia varies widely among patients, and there are currently no effective alternative medical or well-established surgical therapies for these conditions.[8]

Laryngeal dystonia (spasmodic dysphonia) generally presents as adductor type (ADSD) and less frequently as abductor type of spasmodic dysphonia (ABSD).[8] ADSD is characterized by a “strain-strangle” voice, while ABSD produces a breathy and hypophonic voice.[8] There are no effective alternative medical or surgical therapies for spasmodic dysphonia.[8] However, BoNT is probably effective for the treatment of ADSD, although evidence to support its use in ADSD is limited.[8] There is insufficient evidence to support use of BoNT in ABSD.[8]

Tics are relatively brief, intermittent movements (motor tics) or sounds (vocal or phonic tics), usually associated with Tourette syndrome.[8] Oral anti-dopaminergic drugs (e.g., second-generation antipsychotics) are often used to treat troublesome multifocal tics.[8] BoNT is possibly effective for the treatment of motor tics based off of a single study, but there is insufficient data to use BoNT in phonic tics.[8] There are no studies to compare the efficacy of BoNT and oral agents in the treatment of tic disorders.

Oral agents and deep brain stimulation are alternative treatments for essential tremor.[8] BoNT is probably effective at reducing the tremor amplitude in patients with essential hand tremor and should be considered as a treatment in those patients who fail treatment with oral agents.[8] However, evidence is insufficient to draw conclusions regarding BoNT for treatment of head and voice tremor.[8] No studies have compared the efficacy of BoNT to oral agents or deep brain stimulation.[8] The benefits must be considered in conjunction with the common adverse effect of muscle weakness associated with BoNT injection.[8]

The Health Evidence Review Commission (HERC) Prioritized List of Health Services funds treatment of BoNT for following conditions:[9]

- Chemodenervation with BoNT (CPT 64642-64647) is funded on line 292 for treatment of upper and lower limb spasticity (ICD-10-CM codes G24.02, G24.1, G35, G36.0, I69.03- I69.06 and categories G71, and G80-G83).
- Chemodenervation with BoNT (CPT 67345) is funded on lines 351 and 393 for the treatment of strabismus due to other neurological disorders (ICD-10 H50.89).
- Chemodenervation with BoNT (CPT 64612, 64616) is funded on line 362 only for treatment of blepharospasm (ICD-10-CM G24.5), spasmodic torticollis (ICD-10-CM G24.3), and other fragments of torsion dystonia (ICD-10-CM G24.9).
- Chemodenervation with BoNT (CPT 43201) is funded on line 378 for treatment of achalasia (ICD-10 K22.0).

Chemodenervation with BoNT (CPT 64650, 64653) is not funded for the treatment of axillary hyperhidrosis and palmar hyperhidrosis (ICD-10 L74.52, R61) because these conditions fall below the funding line on line 515.[9]

The HERC updated treatment guidelines within the Prioritized List of Health Services for use of chemodenervation for chronic migraine and for over-active bladder.[9] Specifically, the guideline notes address continuing funding only for positive response from BoNT therapy for these conditions. Details are highlighted below:

GUIDELINE NOTE 42, CHEMODENERVATION FOR CHRONIC MIGRAINE [9]
Line 409
Chemodenervation for treatment of chronic migraine (CPT 64615) is included on this line for prophylactic treatment of adults who meet all of the following criteria:

1. have chronic migraine defined as headaches on at least 15 days per month of which at least 8 days are with migraine;
2. has not responded to or have contraindications to at least 3 prior pharmacological prophylaxis therapies (beta-blocker, calcium channel blocker, anticonvulsant or tricyclic antidepressant); and
3. treatment is administered in consultation with a neurologist or headache specialist.

Treatment is limited to 2 injections given 3 months apart. Additional treatment requires documented positive response to therapy. Positive response to therapy is defined as a reduction of at least 7 headache days per month compared to baseline headache frequency.

GUIDELINE NOTE 45, CHEMODENERVATION OF THE BLADDER [9]
Line 327
Chemodenervation of the bladder (CPT 52287) is included on this line only for treatment of idiopathic detrusor over-activity or neurogenic detrusor over-activity (ICD-10-CM N32.81) in patients who have not responded to or been unable to tolerate at least 2 urinary incontinence antimuscarinic therapies (e.g. fesoterodine, oxybutynin, solifenacin, darifenacin, tolterodine, trospium). Treatment is limited to 90 days, with additional treatment only if the patient shows documented positive response. Positive response to therapy is defined as a reduction of urinary frequency of 8 episodes per day or urinary incontinence of 2 episodes per day compared to baseline frequency.

In addition, Guideline Note 37 does not permit use of BoNT for conditions of the back and spine due to lack of evidence of effectiveness for the treatment of conditions on lines 346 and 527, including cervical, thoracic, lumbar and sacral conditions.[9]

Prior authorization criteria for botulinum toxins was first approved by the Oregon Pharmacy & Therapeutics Committee in September 2014.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Limb Spasticity: Ease of Care

A systematic review evaluated efficacy of BoNTA on improving ease of care in patients with upper and lower limb spasticity.[10] Tasks performed for the patient by a caregiver or by the patient's unaffected limb are often referred to as passive function or self-care activities.[10] Limitation to passive function or self-care activities can lead to increased caregiver burden, complications of spasticity, and soft tissue changes, such as skin breakdown, malodor, and difficulty washing and dressing the limb.[10] Studies were included in the review if they were RCTs, included the use of BoNTA versus a placebo control group, on either upper or lower limb in adult inpatients or outpatients, with outcome measures relating to ease of care.[10] Muscle spasticity of any origin was considered. The outcomes considered were passive range of movement, global assessment of benefit scales (also called clinical global impression, global assessment scale), disability assessment scale, caregiver burden scales and goals/goal attainment scale.[10] Evidence quality was assessed by the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach.[10]

In the upper limb, 14 trials looked at passive range of movement, 4 at the disability assessment scale, 9 at the global assessment of benefit, 6 at caregiver burden scales and 6 at goal-setting. The majority of trials used stroke patients with a few including acquired brain injury or using mixed neurological diagnoses.[10] The Disability Assessment Scale was the most consistently applied tool.[10] Goal-setting in particular was often poorly explained, making it difficult to ascertain the nature of the goals.[10] Only 2 studies used the validated Goal Attainment Scale.[10] Statistically significant improvement for treatment groups was found for all studies using the global assessment of benefit and the disability assessment scale, in 8 trials that used passive range of movement, and 3 trials that used caregiver burden scales.[10] Both trials using the Goal Attainment Scale found statistically significant improvements with BoNTA.[10]

In the lower limb, 5 trials examined passive range of movement, 7 trials measured global assessment of benefit, 2 trials looked at caregiver burden with the hygiene score and only one trial set goals.[10] Treatment was either aimed at the hip adductors or the triceps.[10] Results were less notable for the treatment groups in the lower limb: 2 trials found improvements in passive range of movement but failed to reach significance, and 4 trials found statistically significant improvements in global assessment of benefit.[10]

A meta-analysis of the upper limb results for weeks 4 to 12 demonstrated a statistically significant effect for all outcomes in favor of BoNTA with moderate quality evidence (SMD 0.80; 95% CI, 0.55 to 1.06; $p<0.001$).[10] The relative risk for the global assessment of benefit measures was 2.21 (95% CI, 1.67 to 2.93; $p<0.0001$, NNT=5) if patient-rated, and was 2.51 (95% CI, 1.21 to 5.20, $p=0.01$, NNT=6) if clinician-rated.[10] A meta-analysis of upper limb outcomes for weeks 12 to 24 demonstrated a continued significant effect in favor of BoNT for individual outcomes (SMD 0.48; 95% CI, 0.34 to 0.62; $p<0.001$).[10] For lower limb studies, both the patient- and clinician-rated scores failed to demonstrate a significant effect and were rated as low and very low quality evidence, respectively.[10]

Limb Spasticity: Activity Restriction and Quality of Life

A systematic review examined the efficacy of BoNTA on improving activity restriction (i.e., active function) of the upper and lower limbs and quality of life using the GRADE system in patients with spasticity.[11] Studies were eligible for inclusion if they were RCTs, included the use of BoNTA versus placebo or control group on either the upper or lower limb in adult inpatients or outpatients, and evaluated outcomes measures related to active function or quality of life.[11] Studies were chosen for meta-analysis if they provided sufficient data as a group in either dichotomous form (when data allowed results to be divided into improved versus no change/worse) or as means and standard deviations. Data were used from between 1 and 6 months post-intervention; results were then analyzed for 4 to 12 weeks (to analyze the effect over the active time for BoNTA) and for 12 to 24 weeks (to gauge any significant lasting effects of treatment). Dichotomous data were analyzed using the Mantel-Haenszel method to provide risk ratios (RR). Continuous data were analyzed using the inverse-variance

method to give a weighted mean difference for individual outcome measures where possible. The standardized mean difference was used to pool the results of all outcome measures together as it allows for a variety of measurement methods. Random effects models were used in the presence of significant unexplained heterogeneity. Twenty-five studies were included: 18 on the upper limb, 6 on the lower limb and one on both the upper and lower limb. Eight studies used quality of life outcome measures and 22 measured active function outcomes.[11]

In general, all studies used varied measuring techniques, which were not always fully described or objective.[11] The level of function in subjects also varied greatly with only one study stipulating appropriate inclusion criteria for existing active function. In addition, quality of life issues were not stipulated in the inclusion criteria for any study.[11] Additional methodological weaknesses for the studies using quality of life measures were the lack of proven specificity and sensitivity of the scales for problems caused by spasticity. Active range of motion in the upper limb was examined in 8 studies using stroke patients, but nearly all studies found no statistically significant difference between placebo and treatment groups.[11] Only one of 3 studies found statistically significant improvement of active range of motion in lower limb studies.[11] All 3 studies that used the Action Research Arm Test, which assesses changes in limb function in patients with history of stroke resulting in hemiplegia, found significant improvements in scores for the treatment groups; however, the one study that examined stroke only found a statistically significant improvement in a subgroup of patients who had no arm function at the start of the study.[11] Seven studies used the Barthel Index, which is a generic global scale rating 10 items of activities of daily living and mobility.[11] All but one study evaluated stroke patients. Two of 6 studies that performed gait analysis found a significant difference in favor of BoNTA.[11] No statistically significant differences were found in 7 studies that evaluated timed walk tests (5 studies used a 10-minute walk test; one a 6-minute walk test, and one a 2-minute walk test).[11] Overall evidence for these outcomes was insufficient to low quality primarily due to lack of study directness and small sample sizes.[11] Data were insufficient to assess effect of BoNTA on quality of life.[11]

Benign Prostatic Hyerplasia

Benign prostatic hyperplasia (BPH) with LUTS is a common clinical complaint in adult men, and the risk of developing BPH increases with age. A systematic review was performed to assess the overall treatment efficacy and safety of BoNTA compared with placebo.[12] This meta-analysis was guided by the standard PRISMA protocol (preferred reporting items for systematic reviews and meta-analyses) and methods proposed by the Cochrane Collaboration.[12] Randomized controlled trials with intention-to-treat (ITT) analysis of patients diagnosed with BPH and LUTS were included.[12] Diagnostic tools included the International Prostate Symptom Score (IPSS), maximal urinary flow rate (Qmax), post-void residual volume (PVR), rectal examination, and ultrasonography-confirmed prostate volume (PV) increase.[12] The experimental group received BoNT-A 200 units injection, and the control group received placebo injection.[12] No other doses were included because of insufficient data for doses other than 200 units.[12] Outcome measures included changes in IPSS, Qmax, PV, and PVR from baseline in patients receiving BoNT-A versus placebo.[12] The primary outcome was change in IPSS.[12] Statistical heterogeneity was assessed by the Cochran's Q test and the I^2 statistic.[12] Either the Cochran's Q statistic ($p<0.1$) or I^2 statistic (>50%) indicated the existence of significant heterogeneity between studies.[12]

Only 3 studies from 55 citations met inclusion criteria, which included 531 patients (265 patients in the BoNTA group and 266 patients in the placebo group).[12] The duration of treatment ranged from 8 to 24 weeks.[12] The route of administration was transperineal and transrectal, and the injection sites were the transition zone and lobe of the gland.[12] The pooled overall SMD in the mean change in IPSS from baseline for the BoNTA group versus the placebo group was −1.02 (95% CI −1.97, −0.07).[12] Heterogeneity test produced a $p<0.01$, and the I^2 was 94.5%.[12] No statistically significant results were found with the secondary endpoints: the pooled overall SMD in the mean change in Qmax from baseline for the BoNTA group versus the placebo group was 0.78 (95% CI −0.13, 1.69); the pooled overall SMD in the mean change in PV from baseline for the BoNTA group versus the placebo group was −0.76 (95% CI −1.69, 0.18); and the pooled overall SMD in the mean change in PVR from baseline for the BoNTA group versus the placebo group was −0.63 (95% CI −1.54, 0.28).[12] The most frequent adverse events were hematuria (11.3% and 9.8%) and hematospermia (7.2% and 8.6%) in the BoNTA and placebo groups, respectively.[12] There was

no significant difference in all reported adverse events between the 2 groups.[12] The investigators concluded from the meta-analysis that BoNTA injection for BPH with LUTS is not more efficacious than placebo and that there are no differences in procedure-related adverse events.[12]

Strabismus

The use of BoNT as a treatment modality for strabismus is well reported, but it is unclear how effective it is in compared to other treatment options for strabismus. The primary objective of a Cochrane review was to examine the efficacy of BoNT in the treatment of strabismus, focused on types of strabismus that particularly benefit from BoNT (such as small angle strabismus or strabismus with binocular potential, i.e. the potential to use both eyes together as a pair), compared with alternative conservative or surgical treatment options.[13]

Six RCTs evaluating use of BoNT for treatment of strabismus were eligible for inclusion. The studies were judged to be a mixture of low, unclear and high risk of bias; however, none of the studies had low risk of bias for all domains.[13] Two trials conducted in Spain (102 patients, number of eyes not specified) compared BoNT with surgery in children that required retreatment for acquired or infantile esotropia.[13] These two studies provided low-quality evidence that children who received BoNT may have a similar or slightly reduced chance of achieving ocular alignment (RR 0.91, 95% CI 0.71 to 1.16), binocular single vision (RR 0.88, 95% CI 0.63 to 1.23), sensory fusion (RR 0.88, 95% CI 0.63 to 1.23) and stereopsis (RR 0.86, 95% CI 0.59 to 1.25) compared with children who received surgery.[13] One trial from Canada compared BoNT with surgery in 30 adult patients (30 eyes) with horizontal strabismus and reported a reduced chance of ocular alignment with BoNT (RR 0.38, 95% CI 0.17 to 0.85; low-quality evidence).[13] One trial in the UK (n=47) suggested that BoNT may result in a similar or slightly improved chance of ocular alignment in patients with acute onset sixth nerve palsy compared with observation (RR 1.19, 95% CI 0.96 to 1.48; low-quality evidence).[13] Low-quality evidence from one trial from Brazil (n=23) was not able to show that adjuvant BoNT in strabismus surgery increases the chances of ocular alignment compared with strabismus surgery alone (RR 1.83, 95% CI 0.41 to 8.11).[13] One trial from China (47 patients; 94 eyes) suggested that patients receiving BoNT combined with sodium hyaluronate may have a similar or slightly reduced chance of achieving ocular alignment compared with BoNT alone (RR 0.81, 95% CI 0.36 to 1.82; low-quality evidence).[13] Reported complications in people given BoNT in the included trials included ptosis (range 9% to 42%) and vertical deviation (range 8% to 19%).[13] Ptosis occurred less frequently in patients treated with BoNT combined with sodium hyaluronate compared to BoNT alone.[13] The authors concluded there is a lack of evidence for effect of BoNT on reducing visual symptoms in acute sixth nerve palsy, poor response in people with horizontal strabismus without binocular vision, similar or slightly reduced achievement of successful ocular alignment in children with esotropia and potential increased achievement of successful ocular alignment where surgery and BoNT are combined.[13] High quality trials using robust methodologies are required to compare the clinical efficacy of various formulations of BoNT, to compare BoNT with and without adjuvant solutions, and to compare BoNT to alternative surgical interventions in strabismus cases with and without potential for binocular vision.[13]

Cervical Dystonia

The Cochrane Collaboration updated a 2003 review that compared efficacy of BoNTA versus BoNTB for cervical dystonia.[14] Cervical dystonia is the most common form of focal dystonia and is a disabling disorder characterized by painful involuntary head posturing.[14] Although BoNTA is considered the first-line therapy for cervical dystonia and BoNTB is considered an alternative option, there is no compelling theoretical reason to consider BoNTB less effective than BoNTA. Of note, a separate Cochrane review found that BoNTB is associated with statistically significant and clinically relevant reduction in cervical dystonia impairment including severity, disability and pain, and is well tolerated, when compared to placebo.[15] For this review, double-blind, parallel, placebo-controlled RCTs that compared BoNTA versus BoNTB in adults with cervical dystonia were included.[14] Two independent authors identified and selected eligible studies, extracted data, and evaluated the risk of bias. Meta-analyses were performed using the random-effects model to compare BoNTA versus BoNTB to estimate pooled effects and corresponding 95% CI. The primary efficacy outcome was improvement on any validated symptomatic rating scale (e.g., Tsui scale,

Toronto Western Spasmodic Torticollis Rating Scale, and Cervical Dystonia Severity Scale), measured between weeks 3 and 6 post-injection.[14] The primary safety endpoint was the proportion of participants with any adverse event, measured at any point during study follow-up.[14]

Since the 2003 review was published, 3 additional RCTs were identified. Two studies exclusively enrolled participants with a known positive response to BoNTA treatment. The Cochrane investigators were concerned that may result in bias by population enrichment, with a higher probability of participants who benefit from BoNTA treatment.[14] In addition, the Cochrane investigators found that none of the trials were free of for-profit bias, nor did they provide information regarding registered study protocols.[14] All trials evaluated the effect of a single BoNT treatment session, and not repeated treatment sessions, using doses from 100 units to 250 units of BoNTA (all onaBoNTA formulations) and 5,000 units to 10,000 units of BoNTB (rimaBoNTB). The investigators found no difference between the two types of BoNT in terms of overall efficacy, with a mean difference of -1.44 (95% CI -3.58 to 0.70) points lower on the Toronto Western Spasmodic Torticollis Rating Scale (assess severity of spasm, disability and pain; range 0-85) for BoNTB-treated patients, measured at 2 to 4 weeks after injection. The proportion of patients with adverse events was also not different between BoNTA and BoNTB (BoNTB vs. BoNTA: RR 1.40; 95% CI 1.00 to 1.96). However, BoNTB was associated with an increased risk of treatment-related sore throat/dry mouth (BoNTB 46.7% vs. BoNTA 10.5%: RR 4.39; 95% CI 2.43 to 7.91). Treatment-related dysphagia (swallowing difficulties) was not different between BoNTA and BoNTB (RR 2.89; 95% CI 0.80 to 10.41). According to the investigators, the two types of BoNT were otherwise clinically non-distinguishable in all the remaining outcomes.[14] Overall, they found low quality evidence that a single treatment of onaBoNTA and a single treatment of rimaBoNTB are equally effective and safe in the treatment of adults with certain types of cervical dystonia. Treatment with BoNTB appears to present an increased risk of sore throat/dry mouth, but overall, there is no clinical evidence to support or contest the preferential use of one form of BoNT over the other.[14]

Lateral Epicondylitis
A systematic review recently assessed the effectiveness of BoNT compared with non-surgical treatments in patients with lateral epicondylitis (tennis elbow); however, the study will not be further reviewed here because this condition is not funded under the OHP.[16]

New Guidelines:
American Academy of Neurology
The American Academy of Neurology (AAN) published a practice guideline update on BoNT for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache.[17] In 2008, the AAN published their original guideline for use of BoNT. Since then, new research on use of BoNT for these indications prompted the update.

The guideline panel was comprised of specialists with experience in the therapeutic use of BoNT for the indications under consideration or with expertise in guideline methodology.[17] The AAN claims to be committed to producing independent and critical clinical practice guidelines.[17] According to the AAN, significant efforts are made to minimize the potential for conflicts of interest to influence recommendations.[17] To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the guidelines and the developers of the guidelines.[17] Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to the project.[17] The AAN forbids commercial participation in, or funding of, guideline projects.[17] Drafts of the guideline were reviewed by at least 3 AAN committees, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields.[17] Detailed methods to AAN guideline development are available online.[18] The articles were classified as Class I (e.g., high quality RCT) through Class IV (non-controlled study or case report) using the AAN guideline process.[18] Please see http://tools.aan.com/globals/axon/assets/9023.pdf for more information on guideline methodology and classification of evidence.

Blepharospasm

BoNT is considered the first-line treatment of blepharospasm by most movement disorder specialists.[17] The 2008 guideline concluded that BoNT as a class is probably safe and effective for treatment of blepharospasm on the basis of 2 studies comparing onaBoNTA with placebo, one study comparing onaBoNTA with aboBoNTA, and one study comparing onaBoNTA with incoBoNTA.[8] The AAN concluded from the evidence that onaBoNTA and incoBoNTA are probably safe and effective, and aboBoNTA is possibly effective, for treating blepharospasm.[8]

Since the 2008 AAN guideline reviewed the evidence of BoNT for blepharospasm,[8] one class I double-blinded RCT found that incoBoNTA (doses of up to 50 units/eye) was superior to placebo; a class II placebo-controlled RCT found that aboBoNT (40 units, 80 units or 120 units) improved disability in a dose-related manner based on the Blepharospasm Disability Index (minimum clinically important difference [MCID] was not identified); and a class I double-blinded RCT and class II double-blinded RCT both found comparable magnitude and duration of benefit between onaBoNTA and incoBoNTA.[17] Commonly reported adverse events with BoNT injections included periorbital hematoma (25%), ptosis (range of risk differences [RDs] 13%– 54%), dry eyes (range of RDs 7.1%–13%), and blurred vision (RD 42%).[17] Four class IV observational studies reported long-term outcomes, which showed sustained benefit from aboBoNTA or onaBoNTA for at least 15 years and incoBoNTA for at least 5 years.[17]

The AAN concluded onaBoNTA (2 class II studies from 2008 guideline) and incoBoNTA (1 class I study) are probably safe and effective, and aboBoNTA (1 Ccass II study) is possibly effective, for treating blepharospasm.[17] There is insufficient evidence to determine the efficacy of rimaBoNTB.[17] In addition, incoBoNTA and onaBoNTA (1 class I comparative effectiveness study from the 2008 guideline and 2 more recent comparative effectiveness studies [class I and class II]) are equivalent in efficacy for treating blepharospasm.[17] AboBoNTA and onaBoNTA (1 class II study from the 2008 guideline) are possibly equivalent for treating blepharospasm.[17] Based on these conclusions, the AAN recommends either onaBoNTA or incoBoNTA be considered (Level B), and aboBoNTA may be considered (Level C), as treatment options for blepharospasm.[17]

Cervical Dystonia

BoNT is accepted as first-line treatment for cervical dystonia.[17] The 2008 guideline concluded that BoNT is established as safe and effective for treatment of cervical dystonia on the basis of one class I trial of onaBoNTA, 2 class I trials of aboBoNTA, and 3 class I trials of rimaBoNTB.[8] In addition, on the basis of a single class I study that compared aboBoNTA with trihexyphenidyl, the guideline concluded that BoNT is probably more efficacious and better tolerated than trihexyphenidyl for cervical dystonia.[8]

Since the 2008 AAN guideline reviewed the evidence of BoNT for cervical dystonia,[8] a placebo-controlled class I RCT found that incoBoNTA (120 units and 240 units) significantly improved Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total scores (and severity, disability and pain subscores) from baseline to week 4.[17] A 12-point change is the minimal clinically important change after treatment using TWSTRS as endpoint for an average trial population.[19] A second placebo-controlled class II RCT found onaBoNTA produced greater improvements in the Cervical Dystonia Severity Scale and Global Assessment Scale.[17] The studies found rhinitis and treatment-related dysphagia were more frequent with onaBoNTA than placebo.[17] Five studies compared different formulations of BoNT: 2 class I studies found similar TWSTRS scores at 4 weeks between onaBoNTA (150-250 units) or rimaBoNTB (10,000 units); one class I study found onaBoNTA (70-240 units) resulted in similar Tsui scores at 4 weeks compared to aboBoNTA (240-720 units); a double-blind class II, non-inferiority, cross-over RCT also found similar Tsui scores from baseline to 4 weeks after injection, as well as similar TWSTRS, global impression and frequency of adverse effects from baseline to 4 weeks after injection, when aboBoNTA was compared to onaBoNTA (2.5:1 dose ratio); and a class II double-blind, crossover RCT of onaBoNTA versus aboBoNTA (1:3 dosing ratio) showed similar benefit at week 4, but there was a significant shorter duration and lower efficacy of onaBoNTA at

week 12 as assessed by reduction in TWSTRS total score, suggesting the 1:3 dose ratio is suboptimal for dose conversions.[17] Three long-term, prospective, open-label studies (class IV) evaluated the clinical response of repeated injections of onaBoNTA and found persistent benefit for up to 2 years.[17]

The AAN concluded aboBoNTA (2 class I studies reviewed in the 2008 guideline) and rimaBoNTB (3 class I studies reviewed in the 2008 guideline) are established as safe and effective for the treatment of cervical dystonia; onaBoNTA (one class I study reviewed in the 2008 guideline, one more recent class II study) and incoBoNTA (one more recent class I study) are probably safe and effective for the treatment of cervical dystonia; and rimaBoNTB and onaBoNTA (2 class I comparative effectiveness studies) are equivalent in efficacy for treating cervical dystonia.[17] AboBoNTA and onaBoNTA (1 class I study) are probably equivalent for treating cervical dystonia.[17] Based on these conclusions, the AAN recommends aboBoNTA and rimaBoNTB be offered (Level A), and onaBoNTA and incoBoNTA should be considered (Level B), as options for the treatment of cervical dystonia.[17]

Adult Spasticity

The 2008 guideline concluded BoNT is established as effective in the treatment of adult spasticity in the upper extremity on the basis of 6 class I studies of aboBoNTA, 4 class I studies of onaBoNTA, and one class I study of rimaBoNTB.[3] The guideline also concluded that BoNT is effective in treating lower limb spasticity on the basis of 2 class I studies of aboBoNTA and 1 class I study of onaBoNTA. Studies demonstrated that BoNT is effective for reducing muscle tone and improving passive function (e.g., improved range of motion) and is probably effective for improving active function (1 class I study of aboBoNTA).[3]

Since the 2008 AAN guideline reviewed the evidence of BoNT for upper limb spasticity,[3] 4 new class I trials investigating aboBoNTA demonstrated significant reductions in upper limb tone as measured by the modified Ashworth scale (MCID not established); 4 studies (3 class I, 1 class II) demonstrated consistent efficacy in tone reduction in the upper limb from onaBoNTA; one class I comparative study found onaBoNTA was superior to tizanidine for improving wrist and finger flexor tone, whereas tizanidine showed no benefit over placebo but was associated with significant adverse effects; 2 new class I trials showed significant improvement in tone reduction with incoBoNTA; and one class I study did not find a significant difference between rimaBoNTB and placebo in improvement in upper elbow extension as measured by the Modified Frenchay Scale.[17]

The guideline concluded from the overall evidence for these agents in upper limb spasticity that aboBoNTA, incoBoNTA, and onaBoNTA are established as safe and effective for the reduction of adult upper limb spasticity and improvement of passive function (multiple class I studies for all preparations).[17] RimaBoNTB is probably safe and effective for the reduction of adult upper limb spasticity (1 class I study).[17] In addition, onaBoNTA is probably superior to tizanidine for reducing upper extremity tone in adult spasticity.[17] Data are inadequate to determine the efficacy of aboBoNTA, onaBoNTA, incoBoNTA, or rimaBoNTB for improvement of active function associated with adult upper limb spasticity (class I studies, inconsistent results dependent on active functional outcome).[17] Based on these conclusions, the AAN recommends for focal manifestations of adult spasticity involving the upper limb, aboBoNTA, incoBoNTA, and onaBoNTA should be offered (Level A), and rimaBoNTB should be considered (Level B), as treatment options.[17] OnaBoNTA should be considered before tizanidine for treatment of upper extremity spasticity (Level B).[17]

Since the 2008 AAN guideline reviewed the evidence of BoNT for lower limb spasticity,[3] one placebo-controlled class I trial evaluated aboBoNTA use in multiple sclerosis with reduced pain in both legs in patients randomized to aboBoNTA.[17] Three class I studies of onaBoNTA in the treatment of adult lower limb spasticity demonstrated significant reduction in tone but found inconsistent results in regard to functional measures.[17] No studies met inclusion criteria addressing the efficacy of incoBoNT-A or rimaBoNTB for adult lower limb spasticity.[17]

The guideline concluded from the overall evidence for these agents in lower limb spasticity that aboBoNTA and onaBoNTA are established as safe and effective for the reduction of adult lower limb spasticity (multiple class I studies); data are inadequate to determine the efficacy of incoBoNTA or rimaBoNTB for improvement of active function in adult lower limb spasticity; and data are inadequate to determine the efficacy of aboBoNTA, onaBoNTA, incoBoNTA, or rimaBoNTB for improvement of active function associated with adult lower-limb spasticity (no studies available or inconsistent results dependent on specific outcome from multiple class I studies).[17] Based on these conclusions, the AAN recommends for focal manifestations of adult spasticity involving the lower limb that warrant treatment, onaBoNTA and aboBoNTA should be offered (Level A) as treatment options.[2] There is insufficient evidence to support or refute a benefit of incoBoNTA or rimaBoNTB for treatment of adult lower limb spasticity.[17]

Headache

Chronic migraine refers to migraine attacks that occur 15 days or more per month for at least 3 months, with attacks lasting 4 hours or more.[17] The 2008 guideline found inconsistent results from 4 class II studies that compared onaBoNTA with placebo, resulting in insufficient evidence for use of BoNT for treatment of chronic migraine.[2] Since then, 2 class I placebo-controlled studies have been published that met inclusion criteria for the 2016 guideline. In one study, onaBoNTA was ineffective at reducing total headache episodes (the primary endpoint) but was effective at reducing total headache days/28 days by a mean difference of 1.4 days (95% CI, -2.4 to -0.40).[17] In the second study, onaBoNTA reduced headache days/28 days from baseline to weeks 21-24 posttreatment by 9 days versus 6.7 fewer headache days with placebo (indicating a high placebo response).[17] The guideline also identified a class III study which showed similar efficacy between onaBoNTA and topiramate in chronic migraine.[17] The magnitude of benefit onaBoNTA demonstrated from these 2 studies was small (1.7 and 2.4 more headache-free days).[17] Pooled analysis from the 2 studies also showed improvement in health-related quality of life after 24 weeks with onaBoNT-A.[17]

The AAN guideline concluded from the overall evidence that onaBoNTA is established as safe and effective at reducing the number of headache days in patients from chronic migraine (2 class I studies) and probably effective at improving health-related quality-of-life (1 class I study).[17] Based on these conclusions, the AAN recommends onaBoNTA should be offered as a treatment option to patients with chronic migraine to increase the number of headache-free days (Level A) and should be considered to reduce headache impact on health-related quality-of-life (Level B).

OnaBoNTA is ineffective for the treatment of episodic migraines based on evidence from 3 class I studies and should not be offered as a treatment option for this type of migraine (Level A).[17]

New Formulations or Indications:

IncoBoNTA (Xeomin) received an indication in December 2015 for the improvement of adult patients with upper limb spasticity.[20] The efficacy of incoBoNTA for this indication is based on two placebo-controlled, double-blind, multi-centered RCTs in patients with post-stroke spasticity of the upper limb.[20] Study 1 (n=317) included the main 12-week double-blinded phase followed by three 12-week open-label extension treatment cycles (total duration 48 weeks).[20] Patients received incoBoNTA 400 units or placebo administered intramuscularly during the main phase and incoBoNTA 400 units every 12 weeks for the extension study.[20] In Study 1, one co-primary efficacy variable was the change from baseline in Ashworth Scale (AS) score of the primary target clinical pattern determined by the investigator at the week 4 visit.[20] The AS is a clinical measure (scores range from 0-4; MCID not established) of the severity of spasticity by judging resistance to passive movement.[20] The spasticity of the elbow flexors, wrist flexors, finger flexors, and thumb muscles as well as the forearm pronators was assessed on the 0 to 4-point AS at each visit.[20] At week 4, mean AS scores decreased by -0.9 points for incoBoNTA and -0.5 points for placebo based on last observation carried forward for the intention-to-treat population.[20] This difference was statistically significant. The other co-primary efficacy variable of Study 1 was the Investigator's Global Impression of Change Scales (GICS) after 4 Weeks of treatment with incoBoNTA or placebo.[20] The GICS is a global

measure of a subject's functional improvement.[20] Investigators were asked to evaluate the subject's global change in spasticity of the upper limb due to treatment, compared to symptoms before the last injection.[20] The response was assessed using a 7-point Likert scale that ranges from -3 (very much worse) to +3 (very much improved).[20] A greater percentage of incoBoNTA-treated subjects (40%) than placebo-treated subjects (22%) reported 'much improved' in their spasticity.[20] Only 4 patients reported 'very much improved' (3 with incoBoNTA and 1 with placebo).[20] The efficacy of incoBoNTA based from the second study is not described.

AboBoNTA (Dysport) received an indication in July 2016 for the treatment of lower limb spasticity in pediatric patients 2 years of age and older.[1] The efficacy of aboBoNTA for this indication is based from one double-blind, placebo-controlled multi-centered trial in patients 2 to 17 years of age with lower limb spasticity because of cerebral palsy resulting in dynamic equinus foot deformity.[1] Pediatric patients (n=235) with a Modified Ashworth Score (MAS) score 2 or higher (score 0-4, with higher scores indicating increase muscle tone and rigidity) at the ankle plantar flexor were enrolled to aboBoNTA 10 units/kg/leg, 15 units/kg/leg or placebo injected into the gastrocnemius and soleus muscles.[1] The co-primary endpoints were the mean change from baseline in MAS in ankle plantar flexor at week 4 and the mean Physician's Global Assessment (PGA) score at week 4.[1] At week 4, least square mean MAS scores decreased by -1.0, -0.9 and -0.5 points for aboBoNTA 15 units/kg/leg, aboBoNTA 10 units/kg/leg and placebo, respectively.[1] The MAS differences between either dose of aboBoNTA and placebo were statistically significant.[1] Least square mean PGA response to treatment increased by 1.5, 1.5 and 0.7 points for aboBoNTA 15 units/kg/leg, aboBoNTA 10 units/kg/leg and placebo, respectively.[1] The PGA differences between either dose of aboBoNTA and placebo were statistically significant.[1]

AboBoNTA (Dysport) received an indication in June 2017 for the treatment of lower limb spasticity in adult patients.[1] The efficacy of aboBoNTA for this indication is based on one double-blind, placebo-controlled, multi-center trial in patients with lower limb spasticity who were at least 6 months post-stroke or post-traumatic brain injury.[1] Patients (n=381) had a Modified Ashworth Scale (MAS) score of 2 or higher in the affected ankle joint for toxin naïve patients or MAS score of 3 or greater in affected ankle joint for toxin non-naïve patients.[1] The primary endpoint was muscle tone as assessed by the MAS at the ankle joint at week 4.[1] At week 4, the least square mean MAS scores decreased by 0.6, 0.8, and 0.5 points for aboBoNTA 1000 units, aboBoNTA 1500 units, and placebo, respectively.[1] The MAS difference between aboBoNTA 1500 units and placebo was statistically significant but the difference between the aboBoNTA 1000 unit dose and placebo was not.[1]

OnaBoNTA (Botox Cosmetic) received an indication in October 2017 for temporary improvement in the appearance of moderate to severe forehead lines associated with frontalis muscle activity.[21] This indication is not funded by the OHP.

New FDA Safety Alerts:
None identified.

Randomized Controlled Trials:
A total of 224 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical, not funded under OHP).

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Appendix 1: Current Preferred Drug List

GENERIC NAME	BRAND NAME	FORM	PDL STATUS
ABOBOTULINUMTOXINA	DYSPORT	VIAL	
INCOBOTULINUMTOXINA	XEOMIN	VIAL	
ONABOTULINUMTOXINA	BOTOX	VIAL	
ONABOTULINUMTOXINA	BOTOX COSMETIC	VIAL	
RIMABOTULINUMTOXINB	MYOBLOC	VIAL	

Botulinum Toxins

Goal(s):
- Approve botulinum toxins for funded OHP conditions supported by evidence of benefit.
- Require positive response to therapy for use in chronic migraine headaches or overactive bladder.

Length of Authorization:
- From 90 days to 12 months

Requires PA:
- Use of botulinum toxins without associated dystonia or neurological disease diagnosis in last 12 months.

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization for management of migraine headache or detrusor over-activity (e.g., overactive bladder)?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code	
3. Is botulinum toxin treatment for any of the following? a. Upper or lower limb spasticity (G24.02, G24.1, G35, G36.0, I69.03- I69.06 and categories G71, and G80-G83); b. Strabismus due to a neurological disorder (H50.89); c. Blepharospasm (G24.5); d. Spasmodic torticollis (G24.3); e. Torsion dystonia (G24.9); or f. Achalasia (K22.0).	**Yes:** Approve for up to 12 months	**No:** Go to #4

Approval Criteria		
4. Is botulinum toxin treatment for chronic migraine, with ≥15 headache days per month, of which ≥8 days are with migraine?	**Yes:** Go to #5	**No:** Go to #7
5. Is the botulinum toxin administered by, or in consultation with, a neurologist or headache specialist?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Has the patient had an inadequate response, or has contraindications, to ≥1 drugs from at least 3 of the following drug classes? • Beta-blockers: (propranolol; metoprolol; atenolol; nadolol; or timolol) • Tricyclic antidepressants: (nortriptyline or amitriptyline) • Anticonvulsants: (divalproex sodium/valproic acid; carbamazepine; topiramate; or gabapentin) • Calcium channel blockers (diltiazem; verapamil; or nimodipine)	**Yes:** • Baseline headaches/month: _____. Approve no more than 2 injections given ≥3 months apart. Additional treatment requires documented positive response to therapy from baseline (see Renewal Criteria).	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of preferred alternatives at www.orpdl.org/drugs/
7. Is botulinum toxin treatment for idiopathic or neurogenic detrusor over-activity (ICD10-CM N32.81)?	**Yes:** Go to #8	**No:** Pass to RPh. Go to #9
8. Has the patient had an inadequate response to, or is intolerant of, ≥2 incontinence anti-muscarinic drugs (e.g., fesoterodine, oxybutynin, solifenacin, darifenacin, tolterodine, or trospium)?	**Yes:** • Baseline urine frequency/day: _____. • Baseline urine incontinence episodes/day: _____. Approve for up to 90 days. Additional treatment requires documented positive response to therapy from baseline (see Renewal Criteria).	**No:** Pass to RPh. Deny; medical appropriateness.

9. RPh only: Medical literature with evidence for use in funded conditions must be submitted and determined to be appropriate for use before approval is granted.

Deny for the following conditions; not funded by the OHP
Axillary hyperhidrosis and palmar hyperhidrosis (ICD-10 L74.52, R61) Neurologic conditions with none or minimally effective treatment or treatment not necessary (G244; G2589; G2581; G2589; G259); Facial nerve disorders (G510-G519); Spastic dysphonia (J387); Anal fissure (K602); Disorders of sweat glands (e.g., focal hyperhidrosis) (L301; L740-L759; R61); Other disorders of cervical region (M436; M4802; M530; M531; M5382; M5402; M5412; M542; M6788); Acute and chronic disorders of the spine without neurologic impairment (M546; M545; M4327; M4328; M532X7; M532X8; M533; M438X9; M539; M5408; M545; M5430; M5414-M5417; M5489; M549); Disorders of soft tissue (M5410; M609; M790-M792; M797); Headaches (G44209; G44009; G44019; G44029; G44039; G44049; G44059; G44099; G44209; G44219; G44221; G44229; G44309; G44319; G44329; G4441; G4451-G4453; G4459; G4481-G4489; G441; R51); Gastroparesis (K3184) Lateral epicondylitis (tennis elbow)) (M7710-M7712)
Deny for medical appropriateness because evidence of benefit is insufficient

Dysphagia (R130; R1310-R1319);
Other extrapyramidal disease and abnormal movement disorders (G10; G230-GG238; G2401; G244; G250-G26);
Other disorders of binocular eye movements (e.g., esotropia, exotropia, mechanical strabismus, etc.) (H4900-H518);
Tics (F950-F952; F959);
Laryngeal spasm (J385);
Spinal stenosis in cervical region or brachial neuritis or radiculitis NOS (M4802; M5412-M5413);
Spasm of muscle in absence of neurological diagnoses (M6240-M62838);
Contracture of tendon (sheath) in absence of neurological diagnoses (M6240; M62838);
Amyotrophic sclerosis (G1221);
Clinically significant spinal deformity or disorders of spine with neurological impairment (M4800; M4804; M4806; M4808; M5414-M5417);
Essential tremor (G25.0)
Hemifacial spasm (G513)
Occupational dystonias (e.g., “Writer’s cramp”) (G248, G249)
Hyperplasia of the prostate (N400-403; N4283)
Conditions of the back and spine for the treatment of conditions on lines 346 and 527, including cervical, thoracic, lumbar and sacral conditions. See Guideline Note 37.

Renewal Criteria		
1. Is this a request for renewal of a previously approved prior authorization for management of migraine headache?	**Yes:** Go to #2	**No:** Go to #3
2. Is there documentation of a reduction of ≥7 headache days per month compared to baseline headache frequency?	**Yes:** Approve no more than 2 injections given ≥3 months apart. Baseline:____ headaches/month Current:____ headaches/month	**No:** Pass to RPh. Deny; medical appropriateness
3. Is this a request for renewal of a previously approved prior authorization for management of idiopathic or neurogenic detrusor over-activity?	**Yes:** Go to #4	**No:** Go to Approval Criteria
4. Is there a reduction of urinary frequency of ≥8 episodes per day or urinary incontinence of ≥2 episodes per day compared to baseline frequency?	**Yes:** Approve for up to 12 months • Baseline:____ urine frequency/day • Current:____ urine frequency/day -or- • Baseline:____ urine incontinence episodes/day • Current:____ urine incontinence episodes/day	**No:** Pass to RPh. Deny; medical appropriateness

P&T / DUR Review: *5/18 (AG); 11/15; 9/14; 7/14*
Implementation: *6/18/18; 10/13/16; 1/1/16*