

# Botulinum Toxins A and B

Policy Number: CS2021D0017AC  
Effective Date: April 1, 2021

[Instructions for Use](#)

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Related Community Plan Policy
• <a href="#">Occipital Neuralgia and Headache Treatment</a>
Commercial Policy
• <a href="#">Botulinum Toxins A and B</a>

## Application

This Medical Benefit Drug Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Florida	Refer to the state’s Medicaid clinical policy
Indiana	<a href="#">Botulinum Toxins A and B (for Indiana Only)</a>
Kansas	Refer to the state’s Medicaid clinical policy
Kentucky	<a href="#">Botulinum Toxins A and B (for Kentucky Only)</a>
Louisiana	<a href="#">Botulinum Toxins A and B (for Louisiana Only)</a>
North Carolina	None
Pennsylvania	Refer to the state’s Medicaid clinical policy

## Coverage Rationale

This policy refers to the following Botulinum toxin type A and B drug products:

- [Dysport® \(abobotulinumtoxinA\)](#)
- [Xeomin® \(incobotulinumtoxinA\)](#)
- [Botox® \(onabotulinumtoxinA\)](#)
- [Myobloc® \(rimabotulinumtoxinB\)](#)

### The Following Information Pertains to Medical Necessity Review

#### *General Requirements (Applicable to All Medical Necessity Requests)*

- For initial therapy, both of the following:
  - Diagnosis; and
  - Medical records documenting both of the following:
    - History and physical examination documenting the severity of the condition; and
    - Laboratory results or diagnostic evidence supporting the indication for which botulinum toxin is requested

- and
- Botulinum toxin administration is no more frequent than every 12 weeks, regardless of diagnosis
- For continuation of therapy, both of the following:
  - Documentation of positive clinical response to botulinum toxin therapy; and
  - Statement of expected frequency and duration of proposed botulinum toxin treatment
- and
- Botulinum toxin administration is no more frequent than every 12 weeks, regardless of diagnosis

## Diagnosis-Specific Requirements

The information below indicates additional requirements for those indications having specific medical necessity criteria in the list of proven indications.

Dysport (abobotulinumtoxinA) is medically necessary in the treatment of the following conditions:

- Achalasia<sup>81</sup>

Dysport is medically necessary for the treatment of achalasia when all of the following criteria are met:

  - Diagnosis of achalasia as confirmed by esophageal manometry; and
  - Patient has failed or is not a candidate for pneumatic dilation or myotomy; and
  - History of failure, contraindication, or intolerance to one of the following:
    - Calcium channel blocker
    - Long-acting nitrate;
  - and
  - Other causes of dysphagia (e.g., peptic stricture, carcinoma, extrinsic compression) ruled out by upper gastrointestinal endoscopy
- Anal fissures, chronic<sup>7,8,81</sup>

Dysport is medically necessary for the treatment of chronic anal fissures when all of the following criteria are met:

  - Diagnosis of chronic anal fissure; and
  - At least 2 months of symptoms including one of the following:
    - Nocturnal pain and bleeding
    - Post-defecation pain
  - and
  - History of failure, contraindication, or intolerance to one of the following conventional therapies:
    - Topical nitrate
    - Topical calcium channel blocker (e.g., diltiazem, nifedipine)
- Blepharospasm associated with dystonia<sup>10,81</sup>
- Cervical dystonia (also known as spasmodic torticollis)<sup>10,19,81,83,84</sup>

Dysport is medically necessary for the treatment of cervical dystonia when both of the following criteria are met:

  - Diagnosis of cervical dystonia; and
  - Symptoms including both of the following:
    - Sustained head tilt or abnormal posturing resulting in pain and/or functional impairment
    - Recurrent involuntary contraction of one or more muscles of the neck (e.g., sternocleidomastoid, splenius, trapezius, posterior cervical)
- Detrusor overactivity (also known as detrusor hyperreflexia) or detrusor-sphincter dyssynergia due to spinal cord injury or disease<sup>15,17,18,53,54,63,81</sup>

Dysport is medically necessary when both of the following criteria are met:

  - One of the following:
    - Diagnosis of detrusor overactivity
    - Diagnosis of detrusor-sphincter dyssynergia due to spinal cord injury or disease;
  - and
  - History of failure, contraindication, or intolerance to two anticholinergic medications (e.g., oxybutynin, trospium, darifenacin, tolterodine)

- Hand dystonia (writer's, musician's or typist's cramp)<sup>19,81,83</sup>
- Hand tremor<sup>19,81</sup>
- Hemifacial spasm (seventh cranial nerve disorders)<sup>19,81</sup>
- Hyperhidrosis<sup>1,15,81</sup> including gustatory sweating (Frey's Syndrome)<sup>9,15,38</sup>
- Oromandibular dystonia
- Sialorrhea<sup>15,57,81</sup>
- Spasmodic dysphonia (laryngeal dystonia)<sup>3,19</sup>
- Spasticity associated with cerebral palsy; multiple sclerosis; neuromyelitis optica (NMO); stroke; or other injury, disease, or tumor of the brain or spinal cord<sup>1,6,39,81</sup>
- Strabismus<sup>1,19,81</sup>
- Tongue dystonia
- Torsion dystonia
- Voice tremor<sup>4</sup>

Xeomin (incobotulinumtoxinA) is medically necessary in the treatment of the following conditions:

- Blepharospasm associated with dystonia<sup>70,76</sup>
- Cervical dystonia (spasmodic torticollis)<sup>70,76,83,4</sup>  
Xeomin is medically necessary for the treatment of cervical dystonia (spasmodic torticollis) when both of the following criteria are met:
  - Diagnosis of cervical dystonia; and
  - Symptoms including both of the following:
    - Sustained head tilt or abnormal posturing resulting in pain and/or functional impairment
    - Recurrent involuntary contraction of one or more muscles of the neck (e.g., sternocleidomastoid, splenius, trapezius, posterior cervical)
- Sialorrhea<sup>70</sup>
- Spasticity associated with cerebral palsy; multiple sclerosis; neuromyelitis optica (NMO); stroke; or other injury, disease, or tumor of the brain or spinal cord<sup>65-6,70,76</sup>

Botox (onabotulinumtoxinA) is medically necessary in the treatment of the following conditions:

- Achalasia<sup>80</sup>  
Botox is medically necessary for the treatment of achalasia when all of the following criteria are met:
  - Diagnosis of achalasia as confirmed by esophageal manometry; and
  - Patient has failed or is not a candidate for pneumatic dilation or myotomy; and
  - History of failure, contraindication, or intolerance to one of the following:
    - Calcium channel blocker
    - Long-acting nitrate
 and
  - Other causes of dysphagia (e.g., peptic stricture, carcinoma, extrinsic compression) ruled out by upper gastrointestinal endoscopy
- Anal fissures, chronic<sup>8,80</sup>  
Botox is medically necessary for the treatment of chronic anal fissures when all of the following criteria are met:
  - Diagnosis of chronic anal fissure; and
  - At least 2 months of symptoms including one of the following:
    - Nocturnal pain and bleeding
    - Post defecation pain
 and
  - History of failure, contraindication, or intolerance to one of the following conventional therapies:
    - Topical nitrates
    - Topical calcium channel blockers (e.g., diltiazem, nifedipine)
- Blepharospasm associated with dystonia<sup>1,19,80</sup>

- Cervical dystonia (also known as spasmodic torticollis)<sup>1,10,80,83-4</sup>  
Botox is medically necessary for the treatment of cervical dystonia when both of the following criteria are met:
  - Diagnosis of cervical dystonia; and
  - Symptoms including both of the following:
    - Sustained head tilt or abnormal posturing resulting in pain and/or functional impairment
    - Recurrent involuntary contraction of one or more muscles of the neck (e.g., sternocleidomastoid, splenius, trapezius, posterior cervical)
- Detrusor overactivity (also known as detrusor hyperreflexia) or detrusor-sphincter dyssynergia due to spinal cord injury or disease<sup>15,17,18,53,54,63,80</sup>  
Botox is medically necessary when both of the following criteria are met:
  - One of the following:
    - Diagnosis of detrusor overactivity
    - Diagnosis of detrusor-sphincter dyssynergia due to spinal cord injury or disease
 and
  - History of failure, contraindication, or intolerance to two anticholinergic medications (e.g., oxybutynin, trospium, darifenacin, tolterodine)
- Hand dystonia (writer's, musician's or typist's cramp)<sup>19,80,83</sup>
- Hand tremor<sup>19,80</sup>
- Hemifacial spasm (seventh cranial nerve disorders)<sup>19,80</sup>
- Hyperhidrosis<sup>1,80</sup> including gustatory sweating (Frey's Syndrome)<sup>9,15,38</sup>
- Migraine headache, chronic<sup>1,71,80</sup>  
Botox is medically necessary for the prophylaxis of chronic migraine when all of the following criteria are met:
  - Diagnosis of chronic migraine, defined by all of the following:
    - Greater than or equal to 15 headache days per month
    - Greater than or equal to 8 migraine days per month
    - Headaches last 4 hours per day or longer;
 and
  - History of failure (after a trial of at least two months), contraindication, or intolerance to prophylactic therapy with one agent from two of the following therapeutic classes:
    - Antidepressant [i.e., Elavil (amitriptyline), Effexor (venlafaxine)]
    - Antiepileptic drug [i.e., Depakote/Depakote ER (divalproex sodium), Topamax (topiramate)]
    - Beta blocker [i.e., atenolol, Inderal (propranolol), nadolol, timolol, Toprol XL (metoprolol extended-release)]
 and
  - Botox dose does not exceed 155 units administered intramuscularly divided over 31 injection sites divided across 7 head and neck muscles every 12 weeks
- Oromandibular dystonia
- Overactive bladder<sup>1,80</sup>  
Botox is medically necessary for the treatment of overactive bladder when all of the following criteria are met:
  - Diagnosis of overactive bladder; and
  - One of the following symptoms:
    - Urge urinary incontinence
    - Urgency
    - Frequency
 and
  - History of failure, contraindication, or intolerance to two anticholinergic medications (e.g., oxybutynin, trospium, darifenacin, tolterodine); and
  - Botox dose does not exceed 100 units divided over 20 injection sites every 12 weeks
- Sialorrhea<sup>15,57,80</sup>
- Spasmodic dysphonia (laryngeal dystonia)<sup>3,5,19,80</sup>

- Spasticity associated with cerebral palsy; multiple sclerosis; neuromyelitis optica (NMO); stroke; or other injury, disease, or tumor of the brain or spinal cord<sup>1,6,39,80</sup>
- Strabismus<sup>1,19,80</sup>
- Tongue dystonia<sup>80</sup>
- Torsion dystonia<sup>80</sup>
- Voice tremor<sup>4</sup>

Myobloc (rimabotulinumtoxinB) is medically necessary in the treatment of the following conditions:

- Cervical dystonia (also known as spasmodic torticollis)<sup>2,83-4</sup>

Myobloc is medically necessary for the treatment of cervical dystonia when both of the following criteria are met:

- Diagnosis of cervical dystonia; and
- Symptoms including both of the following:
  - Sustained head tilt or abnormal posturing resulting in pain and/or functional impairment
  - Recurrent involuntary contraction of one or more muscles of the neck (e.g., sternocleidomastoid, splenius, trapezius, posterior cervical)

- Detrusor overactivity (also known as detrusor hyperreflexia)<sup>15,18</sup>

Myobloc is medically necessary when both of the following criteria are met:

- Diagnosis of neurogenic detrusor overactivity; and
- History of failure, contraindication, or intolerance to two anticholinergic medications (e.g., oxybutynin, trospium, darifenacin, tolterodine)

- Sialorrhea<sup>15,56-7</sup>

- Spasticity associated with cerebral palsy; multiple sclerosis; neuromyelitis optica (NMO); stroke; or other injury, disease, or tumor of the brain or spinal cord<sup>89</sup>

## Unproven

Dysport, Myobloc, and Xeomin are unproven and not medically necessary for the treatment of chronic migraine headache.<sup>14,15,24,25-6,64,75,81</sup>

Botox, Dysport, Myobloc, and Xeomin are unproven and not medically necessary for the treatment of the following conditions:

- Acquired nystagmus
- Anismus (pelvic floor dyssynergia)<sup>16</sup>
- Benign prostatic hyperplasia<sup>13,18,33,68,80,81</sup>
- Brachial plexus palsy<sup>46,80,81</sup>
- Chronic daily headache<sup>15,36,80,81</sup>
- Chronic low back pain<sup>36,80</sup>
- Chronic prostatic pain<sup>18</sup>
- Cricopharyngeal dysphagia<sup>20-23</sup>
- Epiphora following salivary gland transplantation
- Esophageal spasm<sup>37</sup>
- Gastroparesis (including diabetic gastroparesis)<sup>58-62,90-91</sup>
- Gustatory epiphora (crocodile tears)
- Head tremor
- Lateral epicondylitis (tennis elbow)<sup>51,52</sup>
- Lichen simplex
- Lower urinary tract (voiding) dysfunction<sup>11,18</sup>
- Motor tics
- Myofascial pain syndrome<sup>45,72,81</sup>
- Nasal hypersecretion<sup>50,67</sup>
- Pain and/or wound healing after hemorrhoidectomy
- Pancreas divisum
- Pelvic floor spasticity (and associated pain conditions)<sup>18</sup>
- Piriformis syndrome<sup>49</sup>
- Post-parotidectomy sialoceles
- Post-thoracotomy pseudoangina
- Proctalgia fugax<sup>18</sup>
- Severe bruxism<sup>41-42</sup>
- Severe paradoxical vocal cord movement<sup>40</sup>
- Sphincter of Oddi dysfunction<sup>12</sup>
- Stiff-person syndrome
- Temporomandibular disorders<sup>43-44,48</sup>
- Tension headache<sup>15,27,78</sup>
- Thyroid associated ophthalmopathy<sup>47</sup>
- Tourette's syndrome<sup>55</sup>
- Traumatic sixth nerve palsy
- Trigeminal neuralgia<sup>32,73-4</sup>
- Trismus and stridor in amyotrophic lateral sclerosis

## Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J0585	Injection, onabotulinumtoxinA, 1 unit
J0586	Injection, abobotulinumtoxinA, 5 units
J0587	Injection, rimabotulinumtoxinB, 100 units
J0588	Injection, incobotulinumtoxinA, 1 unit

Diagnosis Code	Description
G04.1	Tropical spastic paraplegia
G11.4	Hereditary spastic paraplegia
G24.09	Other drug induced dystonia
G24.1	Genetic torsion dystonia
G24.2	Idiopathic nonfamilial dystonia
G24.3	Spasmodic torticollis
G24.4	Idiopathic orofacial dystonia
G24.5	Blepharospasm
G24.8	Other dystonia
G24.9	Dystonia, unspecified
G25.89	Other specified extrapyramidal and movement disorders
G36.0	Neuromyelitis optica
G43.701	Chronic migraine without aura, not intractable, with status migrainosus
G43.709	Chronic migraine without aura, not intractable, without status migrainosus
G43.711	Chronic migraine without aura, intractable, with status migrainosus
G43.719	Chronic migraine without aura, intractable, without status migrainosus
G51.0	Bell's palsy
G51.1	Geniculate ganglionitis
G51.2	Melkersson's syndrome
G51.31	Clonic hemifacial spasm, right
G51.32	Clonic hemifacial spasm, left
G51.33	Clonic hemifacial spasm, bilateral
G51.39	Clonic hemifacial spasm, unspecified
G51.4	Facial myokymia
G51.8	Other disorders of facial nerve
G51.9	Disorder of facial nerve, unspecified
G80.0	Spastic quadriplegic cerebral palsy
G80.1	Spastic diplegic cerebral palsy
G80.2	Spastic hemiplegic cerebral palsy
G80.3	Athetoid cerebral palsy

Diagnosis Code	Description
G80.4	Ataxic cerebral palsy
G80.8	Other cerebral palsy
G80.9	Cerebral palsy, unspecified
G81.10	Spastic hemiplegia affecting unspecified side
G81.11	Spastic hemiplegia affecting right dominant side
G81.12	Spastic hemiplegia affecting left dominant side
G81.13	Spastic hemiplegia affecting right nondominant side
G81.14	Spastic hemiplegia affecting left nondominant side
G83.4	Cauda equina syndrome
H50.89	Other specified strabismus
H51.0	Palsy (spasm) of conjugate gaze
J38.5	Laryngeal spasm
K11.7	Disturbances of salivary secretion
K22.0	Achalasia of cardia
K59.4	Anal spasm
K60.1	Chronic anal fissure
K60.2	Anal fissure, unspecified
L74.510	Primary focal hyperhidrosis, axilla
L74.511	Primary focal hyperhidrosis, face
L74.512	Primary focal hyperhidrosis, palms
L74.513	Primary focal hyperhidrosis, soles
L74.519	Primary focal hyperhidrosis, unspecified
L74.52	Secondary focal hyperhidrosis
N31.0	Uninhibited neuropathic bladder, not elsewhere classified
N31.1	Reflex neuropathic bladder, not elsewhere classified
N31.9	Neuromuscular dysfunction of bladder, unspecified
N32.81	Overactive bladder
N36.44	Muscular disorders of urethra
N39.41	Urge incontinence
N39.46	Mixed incontinence
R25.0	Abnormal head movements
R25.1	Tremor, unspecified
R25.2	Cramp and spasm
R25.3	Fasciculation
R25.8	Other abnormal involuntary movements
R25.9	Unspecified abnormal involuntary movements
R29.891	Ocular torticollis
R49.0	Dysphonia
R49.9	Unspecified voice and resonance disorder
S04.50XA	Injury of facial nerve, unspecified side, initial encounter
S04.51XA	Injury of facial nerve, right side, initial encounter
S04.52XA	Injury of facial nerve, left side, initial encounter



## Background

There are seven serologically distinct forms of botulinum toxin, A through G. All seven neurotoxins share a common structure consisting of one heavy chain and one light chain. They all inhibit acetylcholine release at the neuromuscular junction via the enzymatic inactivation of a protein that is required for the docking and fusion process involved in the release of acetylcholine. Each neurotoxin works at a distinct site. Botulinum toxin type A cleaves the protein SNAP-25 and botulinum toxin type B cleaves synaptobrevin, both of these proteins are part of a protein complex necessary for proper docking and fusion.<sup>1,2,10,70</sup>

The potency units of botulinum toxins are specific to the preparation and assay method utilized. They are not interchangeable and, therefore, the units of biological activity cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method.<sup>1,2,10,70</sup>

## Clinical Evidence

### Proven

#### *Cervical Dystonia*

In a randomized, double-blind, multicenter, non-inferiority, two-period crossover study, Yun et al compared the efficacy and safety of Dysport and Botox at a 2.5:1 ratio in the treatment of cervical dystonia (CD).<sup>14</sup> The lower ratio than 3:1 was suggested as a more appropriate conversion ratio, due to the higher efficacy of Botox and more frequent incidence of adverse effects in CD and other focal movement disorders. Patients who were over 20 years old and have experienced CD for at least 18 months were eligible and were allowed to continue on a stable dose of medications for CD for the duration of the trial. Both products were diluted so that the 2.5:1 ratio resulted in the same volume to be administered. The patients received either Dysport or Botox and were followed monthly for the first 16 weeks. After the 4-week washout period, each group was crossed over to receive the other product, respectively. Patients were also followed up with monthly for 16 weeks in the second period. Results from both periods were merged and compared according to the two different products. The primary efficacy outcome was the change in the Tsui scale between the baseline value and that at 1 month after each injection (peak effect). One hundred and two patients enrolled in the study. Patients were allocated 49 and 53 to two different arms of the trial. Arm 1 received Dysport during the first phase and Botox during the crossover phase. Arm 2 received Botox during the first phase and Dysport during the second phase. Only 94 of the 102 patients completed the entire study and were included in the final analysis. Mean changes in the Tsui scale between baseline and 4 weeks after each injection trended to favor Botox, however, this was not statistically significant ( $4.0 \pm 3.9$  points Dysport vs.  $4.8 \pm 4.1$  points for Botox; 95% CI, -0.1 – 1.7;  $p = 0.091$ ). The mean change of the Toronto western spasmodic torticollis rating scale score, the proportion of improvement in clinical global impression and patient global impression, and the incidences of adverse events were not significantly different between the two treatments. The authors concluded that, in terms of efficacy and safety, Dysport at a ratio of 2.5:1 to Botox was not inferior to Botox in patients with CD.

#### *Detrusor Overactivity*

In a prospective, long-term (3 year), multicenter, open-label extension study following a 52-week, phase III trial of onabotulinumtoxinA, patients were treated on an “as needed” basis with intradetrusor onabotulinumtoxinA (200U or 300U) for urinary incontinence (UI) due to neurogenic detrusor overactivity.<sup>94</sup> Patients received treatment  $\geq 12$  weeks since the previous treatment and a UI episode threshold. The primary efficacy endpoint was the change from study baseline in UI episodes/day at week 6 after each treatment. Additional efficacy measurements included: percent change in UI episodes, the proportions of patients with  $\geq 50\%$  and  $100\%$  reductions from baseline in UI episodes/day, changes from baseline in volume/void and Incontinence Quality of Life (I-QOL) total summary scores, IQOL responder rates (proportion of patients achieving a  $\geq 11$ -point increase from baseline in I-QOL total score, which is defined as the minimally important difference for I-QOL in NDO), and duration of treatment effect (time to patient request for retreatment). OnabotulinumtoxinA 200U consistently reduced UI episodes/day; reductions from baseline ranged from -3.2 to -4.1 across six treatments. Volume/void consistently increased, nearly doubling after treatment. I-QOL improvements were consistently greater than twice the minimally important difference (+11 points). Overall median duration of effect was 9.0 months (200U). Results were similar for onabotulinumtoxinA 300U. Most common AEs were urinary tract infections and urinary retention. De novo CIC rates were 29.5, 3.4, and 6.0% (200U), and 43.0, 15.0, and 4.8% (300U) for treatments 1–3, respectively; de novo CIC rates were 0% for treatments 4–6. The authors concluded



that OnabotulinumtoxinA treatments consistently improve UI, volume/void, and QOL in patients with UI due to NDO in this 4-year study, with no new safety signals.

## ***Migraine Headache***

OnabotulinumtoxinA is beneficial for the prophylaxis of chronic migraine headaches based upon FDA approval, published practice guidelines, professional society evidence reviews, randomized controlled clinical trials, and smaller randomized exploratory studies.<sup>15,24,25-6</sup>

Aurora et al performed a secondary analysis of the data to assess patients who received all five treatment cycles and completed the PREEMPT-1 and PREEMPT-2 trials. Both studies were 24 week double-blind, placebo controlled, parallel-group phase, with a 32-week open-label phase, that evaluated the efficacy and safety of onabotulinumtoxinA (BoNT-A). Out of a total of 1,384 total patients, 1,005 received all five treatment cycles and were included in the analysis. Of these, 513 received all 5 cycles with BTA, whereas 492 underwent 2 cycles of placebo followed by 3 cycles of BoNT-A treatment. After 56 weeks of treatment, significant between group differences were found favoring BoNT-A treatment vs. placebo, even after those receiving placebo switching to BoNT-A. The following headache symptoms were evaluated: mean change in frequency of headache days (-12.0 vs -11.0,  $p=0.035$ ); total migraine days (-11.6 vs -10.7,  $p=0.038$ ), and moderate/severe headache days (-11.0 vs -10.1  $n=0.042$ ). There were also large mean improvements from baseline in the following measures: cumulative hours of headache on headache days, frequency of headache episodes, percentage with severe Headache Impact Test (HIT)-6 scores, and total HIT-6 and Migraine-Specific Quality of Life Questionnaire scores). The percent of patients with a  $\geq 50\%$  reduction from baseline in frequency of headache days was significantly greater for the BoNT-A only group at week 56 (69.6% vs 62.8%,  $p = 0.023$ ). Treatment-related adverse event rates were 28.5% for the BoNT-A group vs. 12.4% for the placebo group during the double-blind phase of the trials. The most frequently reported treatment related adverse events were neck pain (4.3%), muscular weakness (1.6%), injection site pain (2.1%), and eyelid ptosis (1.9%). This data supports the use of onabotulinumtoxinA for the treatment of migraine headaches.

In a follow up analysis of the PREEMPT clinical trials, Lipton et al., assessed the effects of treatment with onabotulinumtoxinA on health-related quality of life (HRQoL) and headache impact in adults with chronic migraine.<sup>28</sup> In the PREEMPT trials, Headache Impact Test (HIT)-6 scores were obtained at baseline and every 4 weeks. In terms of change in total HIT-6 scores, a negative value reflects reduced headache impact and an improvement in the patient's functionality. HRQoL was measured by the Migraine-Specific Quality of Life Questionnaire (MSQ v2.1). This score was obtained at baseline and every 12 weeks. A positive change in MSQ v2.1 scores reflects improvement in HRQoL during the PREEMPT study. An analysis of the combined data looked at 688 subjects who received treatment with Botox vs. 696 who received saline placebo injections. Baseline mean total HIT-6 and MSQ v2.1 scores were comparable between groups; 93.1% were severely impacted based on HIT-6 scores  $\geq 60$ . At 24 weeks, in comparison with placebo, Botox treatment significantly reduced HIT-6 scores at all time periods during the double-blind phase of the trials ( $p \leq 0.014$ ). Additionally, HIT-6 measures of headache impact scores showed significant benefit for the Botox group at 24 weeks of treatment ( $p < 0.001$ ). Botox treatment significantly improved all domains of the MSQ v2.1 at 24 weeks ( $p < 0.001$ ). There was also a significant benefit shown for the Botox group compared to placebo with regard to the proportion of subjects who received clinically meaningful reduction in the number of headache days at all time points in the double-blind study periods ( $p \leq 0.025$ ). The authors concluded that Botox treatment reduces headache impact and improves HRQoL.

The pooled results of two phase 3, randomized, double-blind, multicenter, placebo controlled trials addressing the use of botulinum toxin for the treatment of chronic migraine headaches were reported by Dodick et al., in 2010.<sup>29-31</sup> These studies were from the Phase III REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) clinical program, involving a 24 week randomized, double-blind phase followed by a 32 week open-label phase. Subjects were randomized (1:1) to receive either 155 units of onabotulinumtoxinA (BoNT-A) or placebo injections every 12 weeks. A total of 1384 adult patients were randomized to onabotulinumtoxinA ( $n=688$ ) or placebo ( $n=696$ ), with study visits every 4 weeks. Both studies were identical in design, with the exception being the designation of the primary (mean change from baseline in frequency of headache days for the 28-day period ending with week 24) and secondary endpoints (frequency of migraine days, number of cumulative hours of headache on headache days, proportion of patients with severe HIT-6 score, and others). Injections of BoNT-A or placebo were injected as 31 fixed-sites, fixed-dose injections across 7 specific head/neck muscle areas. A discretionary 40 units could be administered using a "follow-the-pain" strategy, resulting in 195 units over 39 sites. Pooled analyses demonstrated a large mean decrease from baseline in frequency of headache days, with statistically significant between-group differences favoring onabotulinumtoxinA over placebo at week 24 (-8.4 vs. -6.6;  $p < 0.001$ ) and at all other time points. Significant differences favoring onabotulinumtoxinA were also observed for all secondary efficacy variables at all time points, including frequency of headache

days, cumulative headache hours, and the proportion of subjects with severe headaches. No significant difference was noted in the frequency of acute headache pain medication taken. There was a significantly greater proportion of experimental group subjects that had a greater than 50% decrease from baseline in headache days. Adverse events occurred in 62.4% of experimental group subjects and 51.7% of placebo subjects, with a greater than 5% incidence of neck pain and muscular weakness in the experimental group. The authors concluded that the use of onabotulinumtoxinA treatment for chronic migraine was effective, safe, and well tolerated.

### ***Overactive Bladder***

Nitti et al examined the efficacy and safety of onabotulinumtoxinA for the treatment of overactive bladder and urinary incontinence (UI) in a phase 3, randomized, multicenter, placebo controlled trial.<sup>93</sup> Adult patients (18 years or older) with idiopathic overactive bladder who experienced 3 or more urgency UI episodes in a 3-day period and an average of 8 or more micturitions per day were enrolled in the study. Patients were randomized 1:1 to either receive onabotulinumtoxinA 100 U or placebo over 20 evenly distributed intradetrusor injections. Co-primary end points were the change from baseline in the number of urinary incontinence episodes per day and the proportion of patients with a positive response on the treatment benefit scale at posttreatment week 12. Secondary end points included other overactive bladder symptoms and health related quality of life. OnabotulinumtoxinA significantly decreased the daily frequency of urinary incontinence episodes vs placebo (-2.65 vs -0.87,  $p < 0.001$ ) and 22.9% vs 6.5% of patients became completely continent. A larger proportion of onabotulinumtoxinA than placebo treated patients reported a positive response on the treatment benefit scale (60.8% vs 29.2%,  $p < 0.001$ ). All other overactive bladder symptoms improved vs placebo ( $p < 0.05$ ). OnabotulinumtoxinA improved patient health related quality of life across multiple measures ( $p < 0.001$ ). Uncomplicated urinary tract infection was the most common adverse event. A 5.4% rate of urinary retention was observed. The authors concluded that OnabotulinumtoxinA showed significant, clinically relevant improvement in all overactive bladder symptoms and health related quality of life in patients inadequately treated with anticholinergics and was well tolerated.

### ***Spasticity (Associated with Cerebral Palsy)***

In a global, randomized, placebo-controlled study, the efficacy and safety of abobotulinumtoxinA was evaluated for the treatment of spasticity in cerebral palsy children with dynamic equinus foot deformity.<sup>95</sup> Two hundred and forty-one patients were randomized 1:1:1 to receive either abobotulinumtoxinA 10 U/kg/leg, 15 U/kg/leg, or placebo injections into the gastrocnemius-soleus complex of either one or both legs. The primary endpoint was the demonstration of benefit for each dose over placebo on the Modified Ashworth Scale from baseline to week 4. Secondary endpoint includes the change of the Physician's Global Assessment at week 4 from baseline. Two hundred and twenty-six patients completed the study. At week 4, Modified Ashworth Scale scores significantly improved with abobotulinumtoxinA; mean (95% confidence interval) treatment differences versus placebo were -0.49 (-0.75 to -0.23;  $P = 0.0002$ ) for 15 U/kg/leg and -0.38 (-0.64 to -0.13;  $P = 0.003$ ) for 10 U/kg/leg. The Physician's Global Assessment treatment differences versus placebo of 0.77 (0.45 to 1.10) for 15 U/kg/leg and 0.82 (0.50 to 1.14) for 10 U/kg/leg were also significant (both  $P$ s  $< .0001$ ). The most common treatment-related adverse event was muscular weakness (10 U/Kg/leg = 2; placebo = 1). The authors concluded that treatment with abobotulinumtoxinA improves muscle tone in children with dynamic equinus resulting in an improved overall clinical impression and is well tolerated.

An additional subgroup analysis was conducted on the same two-hundred and forty-one patients examined in the above study. Delgado et al. found that abobotulinumtoxin A was similarly effective in treating spasticity in cerebral palsy children with dynamic equinus foot deformity in both children who had not received botulinum toxin before and children who had previously received botulinum toxin. Of the 241 patients examined, 113 had received botulinum toxin treatment before participating in the study. Previous botulinum toxin treatment also had no effect on safety outcomes between the two groups.<sup>97</sup>

## **Unproven**

### ***Benign Prostatic Hyperplasia***

The efficacy and tolerability of botulinum toxin A (BoNT-A) for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (LUTS/BPH) was evaluated in a randomized placebo controlled trial involving 315 subjects assigned to either 200 U of BoNT-A (Botox) ( $n = 157$ ) or placebo ( $n = 156$ ).<sup>33</sup> Patients with International Prostate Symptom Score (I-PSS) 14 or greater, with peak urinary flow rate 4 to 15 ml per second and total prostate volume 30 to 80 ml were randomized 1:1 to a single intraprostatic injection of BoNT-A or placebo. A single-blind sham procedure followed by a 4-week run in was included to minimize potential placebo effect. The primary endpoint from baseline is total I-PSS at week 12. Additional endpoints assessed

at weeks 6, 12, and 24 were peak urinary flow rate (Qmax), total prostate volume (TPV), and post-void residual urine volume (PVR). At all-time points there was no difference in I-PSS between the BoNT-A and placebo groups, included at the primary time point at 12 weeks, however both groups experienced a decrease (-6.3 vs -5.6 points,  $p < 0.001$ ). There were no differences between treatment groups for TPV, PSA, or PVR at 12 or 24 weeks. The authors concluded that BoNT-A is unlikely to be a therapy for male LUTS/BPH.

In an additional phase III clinical trial completed in 2018, BoNT-A was tested against optimized oral medications in treating lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia. Four months after BoNT-A injection, most of the patients who received BoNT-A were able to interrupt LUTS-related medical treatments, but this study's design did not allow for a conclusion that this improvement was related to the study drug rather than a sustained placebo effect.<sup>98</sup>

### ***Chronic Daily Headache***

Four studies were published in the American Academy of Neurology's 2008 assessment of botulinum neurotoxin for pain disorders.<sup>15</sup> Each of the studies specifically referenced chronic daily headache (CDH) and had a large population of patients with transformed migraine. The primary outcome measure for all the studies was mean change in headache-free days per month. The first study, which used a technique of modifying injection site based on location of pain, showed a significant benefit (11 days vs. 8 days) in the BoNTA treated population. The second study, the largest of patients with CDH, was a randomized, double-blind, placebo-controlled, phase II study, enrolling 702 patients. This trial used a fixed-site strategy. Eligible patients were injected with BoNTA at 225 U, 150 U, 75 U, or placebo and returned for additional masked treatments at day 90 and day 180. Patients were assessed every 30 days for 9 months. The primary efficacy end point was the mean change from baseline in the frequency of headache-free days at day 180 for the placebo nonresponder group. The primary efficacy end point was not met. Mean improvements from baseline at day 180 of 6.0, 7.9, 7.9, and 8.0 headache-free days per month were observed with BoNTA at 225 U, 150 U, 75 U, or placebo, respectively ( $p = 0.44$ ). However, a priori-defined analysis of headache change from baseline in headache frequency revealed that the 225 U and 150 U Botox A groups had statistically significant greater reductions in headache frequency compared with placebo at day 240 ( $p = 0.03$ ). In conclusion, BoNTA was safe and well tolerated. Although the primary efficacy end point was not met, all groups responded to treatment. The 225 U and 150 U groups experienced a greater decrease in headache frequency than the placebo group at day 240, but the placebo response was higher than expected. The third study was a subgroup of patients not taking prophylactic medications from a larger overall study. Only this subgroup showed a significant mean increase in headache-free days although there was a decrease in the frequency per 30 days. An additional study evaluated 82 patients with chronic daily headache treated with botulinum neurotoxin A.<sup>36</sup> 76.1% of the chronic migraine patients and 36.4% of the chronic tension-type headache patients were considered responders. Because studies of botulinum A for the prevention of chronic daily headache show mixed results, further studies are recommended.

### ***Tension Headache***

Four studies of patients with tension-type headache were reviewed in the American Academy of Neurology's 2008 assessment of botulinum neurotoxin for pain disorders.<sup>15</sup> Patients in these studies were randomized to either botulinum neurotoxin (BoNT) or placebo. After 6 weeks, the first study ( $n = 112$ ) showed no significant difference compared to a baseline 6-week period in the primary outcome measure of area under the headache curve in the subjects' headache diary. In another of the studies, both the BoNT and the placebo group showed improvement in the primary outcome of mean change from baseline in number of headache-free days from 30 to 60 after injection, but BoNT was not more beneficial and a power analysis was not provided. A third study showed no significant benefit of BoNT after 12 weeks for decrease of headache, intensity on visual analog scale, mean number of headache days, headache hours per day, days on which symptomatic treatment was taken, number of analgesics taken per day, or patient's assessment of improvement.<sup>5</sup> The fourth study, a smaller trial, included 16 patients in a prospective double-blind, placebo-controlled crossover study and thirty patients in an open-label long-term study. These patients showed reduction in headache severity and pericranial muscle tenderness, and increased headache-free days with botulinum treatment.

Additional small randomized controlled trials have found conflicting results similar to those presented above.<sup>27</sup> Until larger randomized trials are conducting showing a beneficial effect of BTX-A, its use in tension headache is unproven.

### ***Miscellaneous***

Botulinum toxin A has been studied in a number of other disorders including: cricopharyngeal dysphagia,<sup>20,23</sup> gustatory epiphora (crocodile tears), Sphincter of Oddi dysfunction,<sup>12</sup> pancreas divisum, anismus,<sup>16</sup> lower urinary tract dysfunction,<sup>11,18</sup>

pelvic floor spasticity,<sup>18</sup> chronic prostatic pain,<sup>18</sup> severe paradoxical vocal cord movement,<sup>40</sup> post-parotidectomy sialoceles, severe bruxism,<sup>41-42</sup> temporomandibular disorders,<sup>43-44,48</sup> myofascial pain syndrome,<sup>45,72,81</sup> brachial plexus palsy,<sup>46,80,81</sup> thyroid associated ophthalmopathy,<sup>47</sup> esophageal spasm,<sup>37</sup> post-thoracotomy pseudoangina, epiphora following salivary gland transplantation, trigeminal neuralgia,<sup>32,73-74</sup> trismus and stridor in amyotrophic lateral sclerosis, proctalga fugax, nasal hypersecretion,<sup>50,67</sup> gastroparesis (including diabetic gastroparesis),<sup>58-62,80,90-91</sup> Lichen simplex, lateral epicondylitis,<sup>51,52</sup> Stiff-person syndrome, traumatic sixth nerve palsy, Tourette's syndrome,<sup>55</sup> chronic scrotal pain,<sup>99</sup> and pain and/or wound healing after hemorrhoidectomy. The studies in these disorders have been small and/or uncontrolled open-label trials. Larger, well-designed studies must occur to demonstrate the effectiveness of botulinum toxin in the treatment of these conditions.

## Technology Assessments

### *Achalasia*

A 2014 Cochrane review was published evaluating and comparing endoscopic pneumatic dilation (PD) versus botulinum toxin injection in the management of primary achalasia.<sup>34</sup> Seven studies involving 178 participants were included. Two studies were excluded from the meta-analysis of remission rates on the basis of clinical heterogeneity of the initial endoscopic protocols. There was no significant difference between PD or botulinum treatment in remission within four weeks of the initial intervention; with a risk ratio of remission of 1.11 (95% CI 0.97 to 1.27). There was also no significant difference in the mean esophageal pressures between the treatment groups; with a weighted mean difference for PD of -0.77 (95% CI -2.44 to 0.91, P = 0.37). Data on remission rates following the initial endoscopic treatment were available for three studies at six months and four studies at 12 months. At six months 46 of 57 PD participants were in remission compared to 29 of 56 in the botulinum group, giving a risk ratio of 1.57 (95% CI 1.19 to 2.08, P = 0.0015); whilst at 12 months 55 of 75 PD participants were in remission compared to 27 of 72 botulinum participants, with a risk ratio of 1.88 (95% CI 1.35 to 2.61, P = 0.0002). No serious adverse outcomes occurred in participants receiving botulinum, while PD was complicated by perforation in three cases. The authors concluded that PD is the more effective endoscopic treatment in the long term (greater than six months) for patients with achalasia.

### *Cervical Dystonia*

An update of a Cochrane review from 2005 was published in 2017 to compare the efficacy, safety, and tolerability of botulinum toxin type A (BtA) versus placebo in people with cervical dystonia.<sup>100</sup> The authors included eight randomized controlled trials (RCTs) of moderate overall risk of bias, including 1010 participants with cervical dystonia. Six studies excluded participants with poorer responses to BtA treatment, therefore including an enriched population with a higher probability of benefiting from this therapy. Only one trial was independently funded. All RCTs evaluated the effect of a single BtA treatment session, using doses from 150 U to 236 U of onabotulinumtoxinA (Botox), 120 U to 240 U of incobotulinumtoxinA (Xeomin), and 250 U to 1000 U of abobotulinumtoxinA (Dysport). BtA was associated with a moderate-to-large improvement in the participant's baseline clinical status as assessed by investigators, with reduction of 8.06 points in the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS total score) at week 4 after injection (95% CI 6.08 to 10.05; I<sub>2</sub> = 0%) compared to placebo, corresponding on average to a 18.7% improvement from baseline. The mean difference (MD) in TWSTRS pain subscore at week 4 was 2.11 (95% CI 1.38 to 2.83; I<sub>2</sub> = 0%). Overall, both participants and clinicians reported an improvement of subjective clinical status. There were no differences between groups regarding withdrawals due to adverse events. However, BtA treatment was associated with an increased risk of experiencing an adverse event (risk ratio (RR) 1.19; 95% CI 1.03 to 1.36; I<sub>2</sub> = 16%). Dysphagia (9%) and diffuse weakness/tiredness (10%) were the most common treatment-related adverse events (dysphagia: RR 3.04; 95% CI 1.68 to 5.50; I<sub>2</sub> = 0%; diffuse weakness/tiredness: RR 1.78; 95% CI 1.08 to 2.94; I<sub>2</sub> = 0%). Treatment with BtA was associated with a decreased risk of participants withdrawing from trials. We have moderate certainty in the evidence across all of the aforementioned outcomes. The authors found no evidence supporting the existence of a clear dose-response relationship with BtA, nor a difference between BtA formulations, nor a difference with use of EMG-guided injection. Due to clinical heterogeneity, the authors did not pool data regarding health-related quality of life, duration of clinical effect, or the development of secondary non-responsiveness. The authors stated that they have moderate certainty in the evidence that a single BtA treatment session is associated with a significant and clinically relevant reduction of cervical dystonia-specific impairment, including severity, disability, and pain, and that it is well tolerated, when compared with placebo. There is also moderate certainty in the evidence that people treated with BtA are at an increased risk of developing adverse events, most notably dysphagia and diffuse weakness. There are no data from RCTs evaluating the effectiveness and safety of repeated BtA injection cycles. There is no evidence from RCTs to allow us to draw definitive conclusions on the optimal treatment intervals and doses, usefulness of guidance techniques for injection, the impact on quality of life, or the duration of treatment effect.



## ***Chronic and Episodic Migraine Headache***

A 2018 Cochrane review was published evaluating the effects of botulinum toxins versus placebo or active treatment for the prevention or reduction in frequency of chronic or episodic migraine in adults.<sup>75</sup> Twenty-eight studies involving 4,190 participants were eligible for inclusion. The longest treatment duration was three rounds of injections with three months between treatments, so the authors could not analyze long-term effects. For the primary analyses, the authors pooled data from both chronic and episodic participant populations. Where possible, the authors also separated data into chronic migraine, episodic migraine and 'mixed group' classification subgroups. Most trials (21 out of 28) were small (fewer than 50 participants per trial arm). The risk of bias for included trials was low or unclear across most domains, with some trials reporting a high risk of bias for incomplete outcome data and selective outcome reporting. Twenty-three trials compared botulinum toxin with placebo. Botulinum toxin may reduce the number of migraine days per month in the chronic migraine population by 3.1 days (95% confidence interval (CI)-4.7 to -1.4, 4 trials, 1497 participants, low-quality evidence). This was reduced to -2 days (95% CI -2.8 to -1.1, 2 trials, 1384 participants; moderate-quality evidence) when the authors removed small trials. A single trial of people with episodic migraine (N = 418) showed no difference between groups for this outcome measure (P = 0.49). In the chronic migraine population, botulinum toxin reduces the number of headache days per month by 1.9 days (95% CI -2.7 to -1.0, 2 trials, 1384 participants, high-quality evidence). The authors did not find evidence of a difference in the number of migraine attacks for both chronic and episodic migraine participants (6 trials, N = 2004, P = 0.30, low-quality evidence). For the population of both chronic and episodic migraine participants a reduction in severity of migraine rated during clinical visits, on a 10 cm visual analog scale (VAS) of 3.3 cm (95% CI -4.2 to -2.5, very low-quality evidence) in favor of botulinum toxin treatment came from four small trials (N = 209); better reporting of this outcome measure from the additional eight trials that recorded it may have improved our confidence in the pooled estimate. Global assessment and quality-of-life measures were poorly reported, and it was not possible to carry out statistical analysis of these outcome measures. Analysis of adverse events showed an increase in the risk ratio with treatment with botulinum toxin over placebo 30% (RR 1.28, 95% CI 1.12 to 1.47, moderate-quality evidence). For every 100 participants 60 experienced an adverse event in the botulinum toxin group compared with 47 in the placebo group. Three trials studied comparisons with alternative oral prophylactic medications. Meta-analyses were not possible for number of migraine days, number of headache days or number of migraine attacks due to insufficient data, but individually trials reported no differences between groups for a variety of efficacy measures in the population of both chronic and episodic migraine participants. The global impression of disease measured using Migraine Disability Assessment (MIDAS) scores were reported from two trials that showed no difference between groups. Compared with oral treatments, botulinum toxin showed no between-group difference in the risk of adverse events (2 trials, N = 114, very low-quality evidence). The relative risk reduction (RRR) for withdrawing from botulinum toxin due to adverse events compared with the alternative prophylactic agent was 72% (P = 0.02, 2 trials, N = 119). There were insufficient data available for the comparison of different doses. The quality of the evidence assessed using GRADE methods was varied but mostly very low; the quality of the evidence for the placebo and active control comparisons was low and very low, respectively for the primary outcome measure. Small trial size, high risk of bias and unexplained heterogeneity were common reasons for downgrading the quality of the evidence. The authors concluded that for chronic migraine, botulinum toxin type A may reduce the number of migraine days per month by 2 days compared with placebo treatment. Non-serious adverse events were probably experienced by 60/100 participants in the treated group compared with 47/100 in the placebo group. For people with episodic migraine, the authors remain uncertain whether or not this treatment is effective because the quality of this limited evidence is very low. Better reporting of outcome measures in published trials would provide a more complete evidence base on which to draw conclusions.

## ***Chronic Migraine Headache***

Hayes compiled a Medical Technology Directory on botulinum toxin treatment for migraine headache dated September 22, 2011.<sup>75</sup> Although a relatively large number of well-designed randomized controlled trials (RCTs) have evaluated onabotulinumtoxinA (onaBTX-A) and abobotulinumtoxinA (aboBTX-A) [BTX-A] for prevention of migraine, the clinical role of this treatment remains to be established. Many of the available placebo-controlled RCTs found that BTX-A did not provide statistically significant benefits or found that the benefits obtained were inconsistent, for instance, occurring at some time points but not at others. In contrast, the largest available RCT and one of the older RCTs found that patients who underwent treatment with onaBTX-A experienced statistically significant improvements such as reductions in migraine frequency and severity. This divergence in study results cannot be resolved based solely on differences in study size and a more likely explanation was that the benefits obtained with onaBTX-A were relatively small, perhaps too small to be clinically significant. Moreover, due to lack of long-term follow-up, the available RCTs do not provide any data concerning the durability of potential benefits from treatment with onaBTX-A. In addition, there was insufficient evidence to support conclusions regarding the efficacy of onaBTX-A relative to other types of medication for prevention of migraine. Likewise, there was very limited evidence regarding the effectiveness of aboBTX-A, and no evidence regarding other types of BTX, for the management of chronic or

recurrent headache. Therefore, Hayes has assigned a D rating (no proven benefit and/or not safe) to abobotulinumtoxinA for prevention of migraine and to rimabotulinumtoxinB as a treatment for migraine headache. Overall, onabotulinumtoxinA was safe with few serious complications reported, earning onabotulinumtoxinA a Hayes rating of C (potential but unproven benefit) for prevention of migraine headache. Further studies are needed to determine the clinical role of BTX-A relative to current treatments for prevention of migraine. An annual review of the Hayes Directory on August 21, 2019 resulted in no changes to the original findings.

### ***Chronic Tension Headache***

Hayes compiled a Medical Technology Directory on botulinum toxin treatment for chronic tension-type headache dated December 30, 2011.<sup>78</sup> A relatively large number of well-designed, randomized, placebo-controlled trials (RCTs) have evaluated the effects of botulinum toxin A (BTX-A) on patients diagnosed with chronic tension-type headache (CTTH). The majority of these studies found no benefit of BTX-A relative to placebo. The two studies that did report beneficial effects of BTX on headache frequency and intensity were very small. Overall, BTX-A was safe. None of the studies compared BTX-A with other prophylactic treatments for CTTH. An annual review of the Hayes Directory on January 13, 2015 resulted in no changes to the original findings.

### ***Detrusor Overactivity***

Hayes compiled a Medical Technology Directory on botulinum toxin treatment for detrusor instability, dated December 30, 2011.<sup>86</sup> The results of the available studies provide some evidence that onabotulinumtoxinA (onaBTX-A) improves outcomes for patients who have idiopathic or neurogenic detrusor overactivity; however, these studies do not provide sufficient evidence to establish the clinical role of botulinum toxin type A (BTX-A) for these indications. Although randomized clinical trials (RCTs) consistently found that BTX-A provided statistically significant improvements in urinary incontinence (UI) compared with placebo treatment, the largest available RCT of BTX-A for idiopathic detrusor overactivity found a placebo effect that was nearly as large as the treatment effect when expressed in terms of decrease in number of episodes of UI per week. In the largest available RCT of BTX-A for neurogenic detrusor overactivity, BTX-A treatment was associated with statistically significant increases in urinary retention and urinary tract infections. None of the studies that met the criteria for review involved long-term follow-up of patients who underwent treatment with multiple doses of BTX-A, and none of the studies compared BTX-A with augmentation cystoplasty or neuromodular implantation. At least six of the studies were sponsored by the manufacturer, creating the potential for bias. Additional controlled studies are needed to determine the long-term efficacy and safety of BTX-A relative to other current invasive treatments for idiopathic and neurogenic detrusor overactivity. An annual review of the Hayes Directory on January 9, 2015 resulted in no changes to the original findings.

### ***Strabismus***

A 2017 update to a 2012 Cochrane review was published to examine the efficacy of botulinum toxin therapy in the treatment of strabismus compared with alternative conservative or surgical treatment options.<sup>35</sup> The review also sought to determine the types of strabismus that particularly benefit from the use of botulinum toxin as a treatment option. The secondary objectives were to investigate the dose effect and complication rates associated with botulinum therapy. Six randomized controlled trials were eligible for inclusion. The authors concluded that the published literature on the use of botulinum toxin in the treatment of strabismus consists of retrospective studies, cohort studies or case reviews. These provide useful descriptive information; clarification is required as to the effective use of botulinum toxin as an independent treatment modality. Six RCTs on the therapeutic use of botulinum toxin in strabismus, graded as low and very low-certainty evidence, have shown varying responses. These include a lack of evidence for effect of botulinum toxin 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 botulinum toxin are combined. Further high quality trials using robust methodologies are required to compare the clinical and cost effectiveness of various forms of botulinum toxin (e.g. Dysport, Xeomin, etc), to compare botulinum toxin with and without adjuvant solutions and to compare botulinum toxin to alternative surgical interventions in strabismus cases with and without potential for binocular vision.

### ***Motor/Phonic Tics***

A 2018 Cochrane review was published evaluating the safety and effectiveness of botulinum toxin in treating motor and phonic tics in people with Tourette's syndrome, and to analyze the effect of botulinum toxin on premonitory urge and sensory tics.<sup>95</sup> Only one randomized placebo-controlled, double-blind cross-over study met our selection criteria. In this study, 20 participants

with motor tics were enrolled over a three-year recruitment period; 18 (14 of whom had a diagnosis of Tourette's syndrome) completed the study; in total, 21 focal motor tics were treated. Although we considered most bias domains to be at low risk of bias, the study recruited a small number of participants with relatively mild tics and provided limited data for our key outcomes. The effects of botulinum toxin injections on tic frequency, measured by videotape or rated subjectively, and on premonitory urge, are uncertain (very low-quality evidence). The quality of evidence for adverse events following botulinum toxin was very low. Nine people had muscle weakness following the injection, which could have led to unblinding of treatment group assignment. No data were available to evaluate whether botulinum injections led to immunoresistance to botulinum. The authors concluded that they are uncertain about botulinum toxin effects in the treatment of focal motor and phonic tics in select cases, as we assessed the quality of the evidence as very low. Additional randomised controlled studies are needed to demonstrate the benefits and harms of botulinum toxin therapy for the treatment of motor and phonic tics in patients with Tourette's syndrome.

## Professional Societies

### *Spasmodic Dysphonia (Laryngeal Dystonia)*

In 2018, the American Academy of Otolaryngology – Head and Neck Surgery published an update of their guideline first published in 2009.<sup>96</sup> The organization recommended that clinicians should offer or refer to a clinician who can offer botulinum toxin injections for the treatment of dysphonia caused by spasmodic dysphonia and other types of laryngeal dystonia.

A recommendation means that the benefits exceed the harms (or that the harms exceed the benefits, in the case of a negative recommendation) but that the quality of evidence is not as strong (grade B or C). In some clearly identified circumstances, recommendations may be made on the basis of lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms. Clinicians should also generally follow a recommendation but should remain alert to new information and sensitive to patient preferences.

### *Achalasia*

In 2020, the American College of Gastroenterology published an evidence-based clinical guideline for the diagnosis and management of achalasia based on a comprehensive review of the pertinent evidence and examination of relevant published data.<sup>85</sup> The recommendations for the treatment of achalasia from this guideline are as follows:

- In patients with achalasia who are candidates for definitive therapy:
  - Pneumatic dilation (PD), laparoscopic Heller myotomy (LHM), and peroral endoscopic myotomy (POEM) are comparable effective therapies for type I or type II achalasia
  - POEM would be a better treatment option in those with type III achalasia.
  - Botulinum toxin injection is reserved for those who cannot undergo the above definitive therapies
  - Recommend botulinum toxin injection as first-line therapy for patients with achalasia who are unfit for definitive therapies compared with other less effective pharmacological therapies (Grade quality: Moderate; Recommendation strength: Strong)
  - Previous treatment with botulinum toxin injection does not significantly affect performance and outcomes of myotomy (Grade quality: Low; Recommendation strength: Conditional)

### *Autonomic & Movement Disorders, Pain, and Spasticity*

In a 2013 update to the 2008 Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (AAN) published evidence-based (studies classified as Class I to IV and recommendations classified as levels A to U)<sup>69</sup> assessments on the use of botulinum neurotoxin in the treatment of autonomic disorders and pain,<sup>15</sup> movement disorders,<sup>19</sup> and spasticity.<sup>39</sup> In addition, in 2013 authors performed an assessment on the use of botulinum neurotoxin in the treatment of urologic conditions and secretory disorders<sup>88</sup> based on the AAN methodology.<sup>286</sup> The Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society also published an evidence-based review of the pharmacologic treatment of spasticity in children and adolescents with cerebral palsy in 2010.<sup>6</sup>

Recommendations from these reviews are classified as follows:

- Level A- Established as effective, ineffective, or harmful for the given condition in the specified population, requiring at least two consistent Class I studies.
- Level B- Probably effective, ineffective, or harmful for the given condition in the specified population, requiring at least one Class I study or at least two consistent Class II studies.



- Level C - Possibly effective, ineffective, or harmful for the given condition in the specified population, requiring at least one Class II study or two consistent Class III studies.
- Level U - Data inadequate or conflicting; given current knowledge, treatment is unproven.

Recommendations from these reviews are:

- BoNT should be offered as a treatment option for axillary hyperhidrosis and detrusor overactivity (detrusor hyperreflexia) (Level A). BoNT should be considered for palmar hyperhidrosis, sialorrhea, and detrusor sphincter dyssynergia after spinal cord injury (Level B).
- BoNT is probably effective for the treatment of benign prostatic hyperplasia induced lower urinary tract symptoms (Level B).
- BoNT may be considered for low back pain (Level C). BoNT is probably ineffective in episodic migraine and chronic tension-type headache (Level B).
- Evidence does not permit drawing conclusions on BoNT's efficacy in chronic daily headache (mainly transformed migraine) (Level U). Evidence does not support BoNT's efficacy for the treatment of gustatory sweating (Level U)
- BoNT should be offered as an option for the treatment of blepharospasm, cervical dystonia (Level A).
- BoNT may be offered for hemifacial spasm, focal upper extremity dystonia, and upper extremity essential tremor (Level B).
- BoNT may be considered for, adductor laryngeal dystonia, focal lower limb dystonia, oromandibular dystonia, and motor tics (Level C).
- BoNT should be offered as an option for the treatment of spasticity in adults (Level A). Spasticity in adults results from a variety of causes such as stroke, trauma, multiple sclerosis, and neoplasm involving the central nervous system.
- For localized/segmental spasticity that warrants treatment in children and adolescents with cerebral palsy, botulinum toxin type A should be offered as an effective and generally safe treatment (Level A) and there is insufficient data to support or refute the use of botulinum toxin type B (Level U).

### ***Tics in People with Tourette's Syndrome and Chronic Tic Disorder***

In 2019, the American Academy of Neurology (AAN) published evidence-based guideline recommendations regarding the use of botulinum neurotoxins in treating tics in people with Tourette's Syndrome, as well as treating chronic tic disorder (studies classified as Class I to IV and recommendations classified as levels A to C).<sup>101</sup> The recommendations for the treatment of tics in people with Tourette's Syndrome and chronic tic disorder from this guideline are as follows:

- Physicians may prescribe botulinum toxin injections for the treatment of older adolescents and adults with localized and bothersome simple motor tics when the benefits of treatment outweigh the risks (Level C).
- Physicians may prescribe botulinum toxin injections for the treatment of older adolescents and adults with severely disabling or aggressive vocal tics when the benefits of treatment outweigh the risks (Level C).
- Physicians must counsel individuals with tics that botulinum toxin injections may cause weakness and hypophonia, and that all effects are temporary (Level A).

### ***Blepharospasm, Cervical Dystonia, Adult Spasticity, and Headache***

In a 2016 update to the 2008 guidelines, the American Academy of Neurology (AAN) published evidence-based (studies classified as Class I to IV and recommendations classified as levels A to U)<sup>286</sup> assessments on the use of botulinum neurotoxins in the treatment of blepharospasm, cervical dystonia, headache, and adult spasticity.<sup>89</sup>

Recommendations from this review are classified as follows:

- Level A - Established as effective, ineffective, or harmful for the given condition in the specified population, requiring at least two consistent Class I studies.
- Level B - Probably effective, ineffective, or harmful for the given condition in the specified population, requiring at least one Class I study or at least two consistent Class II studies.
- Level C - Possibly effective, ineffective, or harmful for the given condition in the specified population, requiring at least one Class II study or two consistent Class III studies.
- Level U - Data inadequate or conflicting; given current knowledge, treatment is unproven.

Recommendations from this review for abobotulinumtoxinA (aboBoNT-A, Dysport) are as follows:

- AboBoNT-A should be offered as a treatment option for cervical dystonia, focal manifestations of upper limb spasticity, and focal manifestations of lower limb spasticity that warrant treatment (Level A).

- AboBoNT-A has been established as safe and effective for the reduction of adult upper limb spasticity and improvement of passive function (multiple Class I studies). AboBoNT-A has also been established as safe and effective for the reduction of adult lower limb spasticity (multiple Class I studies).
- Data is inadequate to determine the efficacy of aboBoNT-A for improvement of active function associated with adult upper limb spasticity (Class I studies, inconsistent results dependent on active functional outcomes). Data is also inadequate to determine the efficacy of aboBoNT-A 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).
- AboBoNT-A may be considered as a treatment option for blepharospasm (Level C).

Recommendations from this review for incobotulinumtoxinA (incoBoNT-A, Xeomin) are as follows:

- IncoBoNT-A should be offered as a treatment option for focal manifestations of upper limb spasticity (Level A).
  - IncoBoNT-A has been established as safe and effective for the reduction of adult upper limb spasticity and improvement of passive function (multiple Class I studies).
  - Data is inadequate to determine the efficacy of incoBoNT-A for improvement of active function associated with adult upper limb spasticity (Class I studies, inconsistent results dependent on active functional outcomes).
- IncoBoNT-A should be considered as a treatment option for blepharospasm and cervical dystonia (Level B).
- There is insufficient evidence to support or refute the use of incoBoNT-A for the treatment of lower limb spasticity (Level U).

Recommendations from this review for onabotulinumtoxinA (onaBoNT-A, Botox) are as follows:

- OnaBoNT-A should be offered as a treatment option for focal manifestations of upper limb spasticity, focal manifestations of lower limb spasticity that warrant treatment, and chronic migraine (Level A).
  - OnaBoNT-A has been established as safe and effective for the reduction of adult upper limb spasticity and improvement of passive function (multiple Class I studies). OnaBoNT-A has also been established as safe and effective for the reduction of adult lower limb spasticity (multiple Class I studies).
  - Data is inadequate to determine the efficacy of onaBoNT-A for improvement of active function associated with adult upper limb spasticity (Class I studies, inconsistent results dependent on active functional outcomes). Data is also inadequate to determine the efficacy of onaBoNT-A 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).
- OnaBoNT-A should be considered as a treatment option for blepharospasm and cervical dystonia (Level B).
- OnaBoNT-A should not be offered as a treatment option for episodic migraine (Level A).
- OnaBoNT-A should not be considered as a treatment option for tension-type headache (Level B).

Recommendations from this review for rimabotulinumtoxinB (rimaBoNT-B, Myobloc) are as follows:

- RimaBoNT-B should be offered as a treatment option for cervical dystonia (Level A).
- RimaBoNT-B should be considered as a treatment option for focal manifestations of upper limb spasticity (Level B).
  - RimaBoNT-B is probably safe and effective for the reduction of adult upper limb spasticity (1 Class I study).
  - Data is inadequate to determine the efficacy of rimaBoNT-B for improvement of active function associated with adult upper limb spasticity (Class I studies, inconsistent results dependent on active functional outcomes).
- There is insufficient evidence to support or refute the use of rimaBoNT-B for the treatment of blepharospasm and lower limb spasticity (Level U).

## U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

For non-cosmetic use, abobotulinumtoxinA (Dysport) is FDA approved for the treatment of adults with cervical dystonia. Dysport is also indicated for the treatment of spasticity in pediatric patients 2 years of age and older.<sup>10</sup>

IncobotulinumtoxinA (Xeomin) is FDA approved for the treatment of adults with cervical. Xeomin is also indicated for the treatment of adults with blepharospasm, upper limb spasticity in adult patients, and chronic sialorrhea. Xeomin is also indicated for the treatment of upper limb spasticity in pediatric patients 2 to 17 years of age, excluding spasticity caused by cerebral palsy.<sup>70</sup>

For non-cosmetic use, onabotulinumtoxinA (Botox) is FDA approved for the prophylaxis of headaches in adult patients with chronic migraine ( $\geq 15$  days per month with headache lasting 4 hours a day or longer). Safety and effectiveness of Botox have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month).<sup>1</sup>

Botox is also approved for treatment of spasticity in patients 2 years of age and older. Botox is also indicated for reducing the severity of abnormal head position and neck pain associated with cervical dystonia in adults; for the treatment of strabismus and blepharospasm associated with dystonia; for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency in adults who have an inadequate response or are intolerant to an anticholinergic medication; for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication; and for the treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents.<sup>1</sup> Safety and efficacy of Botox for hyperhidrosis in other body areas have not been established. Weakness of hand muscles and blepharoptosis may occur in patients who receive Botox for palmar hyperhidrosis and facial hyperhidrosis, respectively. Patients should be evaluated for potential causes of secondary hyperhidrosis (e.g., hyperthyroidism) to avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the underlying disease. Safety and effectiveness of Botox have not been established for the treatment of axillary hyperhidrosis in pediatric patients under age 18.<sup>1</sup>

RimabotulinumtoxinB (Myobloc) is FDA approved for the treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia.<sup>2</sup> It is also FDA approved for the treatment of chronic sialorrhea in adults.<sup>2</sup>

All botulinum toxin products approved by the FDA carry a black box warning regarding the possibility of the distant spread of toxin effect.<sup>1,2,10,70</sup> The warning states that post marketing reports indicate that the effects of all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity, but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and upper limb spasticity and at lower doses.

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## Policy History/Revision Information

Date	Summary of Changes
08/01/2021	<b>Application</b> <ul style="list-style-type: none"> <li>Added language to indicate this policy does not apply to the states of Indiana and North Carolina</li> </ul>
04/01/2021	<b>Supporting Information</b> <ul style="list-style-type: none"> <li>Removed <i>CMS</i> section</li> <li>Updated <i>Clinical Evidence</i>, <i>FDA</i>, and <i>References</i> sections to reflect the most current information</li> <li>Archived previous policy version CS2020D0017AB</li> </ul>

## Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.