Treating Medical Disorders with Botulinum Toxins
Comparing and Contrasting Available Agents
This educational activity is sponsored by Postgraduate Healthcare Education, LLC and supported by an educational grant from Allergan.
Faculty

Sheldon J. Rich, RPh, PhD
President, SJR Associates, LLC
Sarasota, FL
Adjunct Assistant Professor
University of Michigan
Ann Arbor, MI

Dr. Rich is President of SJR Associates, which provides consulting services to managed care organizations, physician practice groups, employers, and pharmaceutical manufacturers. He has more than 30 years of experience, having practiced in hospital, retail, and managed care pharmacies.

Dr. Rich earned his pharmacy degree from the University of Michigan and holds a Doctorate in Theocentric Business Ethics. He has served as Clinical Assistant Professor at the University of Michigan since 1982 and has held a dual appointment as Adjunct Assistant Professor with the Eugene Applebaum College of Pharmacy and Health Sciences at Wayne State University since 1994.
Jessa M. Koch, PharmD, BCPP
Assistant Professor
Department of Pharmacy Practice, Neurology
Loma Linda University School of Pharmacy and School of Medicine
Clinical Pharmacist
Loma Linda University Health
Loma Linda, CA

Dr. Koch is an assistant professor at Loma Linda University School of Pharmacy and an assistant professor in neurology with the School of Medicine. Dr. Koch is the course coordinator and lecturer for the central nervous system modules at the School of Pharmacy, and she practices in the outpatient setting within an academic medical center. She is the psychiatric pharmacist at the Social Action Community Health System (SACHS) clinic in San Bernardino, California. In this multidisciplinary setting, she helps manage behavioral health conditions. Her other practice sites are in the department of internal medicine and the department of neurology, where she collaborates with providers to assist with safe medication prescribing and deprescribing and integrated behavioral health services.
Disclosures

Drs. Rich and Koch state that they have no relevant affiliation or financial relationship or relationship to products or devices with a commercial interest related to the content of this activity to disclose.

The clinical reviewer, Sarah Dehoney, PharmD, BCPS, states she has no relevant affiliation or financial relationship or relationship to products or devices with a commercial interest related to the content of this activity to disclose.

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UAN: 0430-0000-20-084-H01-P
Credits: 1.0 hour (0.1 CEU)
Type of Activity: Application
Learning Objectives

• **Explain** the mechanism of action and role of available botulinum toxin agents in treating indicated medical disorders

• **Recognize** the differing dosing regimens for available botulinum toxins to ensure efficacy and safety

• **Discuss** the differences between the botulinum toxin agents and issues with interchangeability, and **identify** the approved indications for each agent

• **Describe** coverage considerations and formulary selection of botulinum toxin agents
Botulinum Neurotoxins: Mechanisms of Action and Clinical Uses

Jessa M. Koch, PharmD, BCPP
Botulinum Neurotoxin (BoNT)

• BoNT is produced by Clostridium botulinum, a gram-positive, anaerobic, rod-shaped bacteria

• Of 8 serotypes of BoNTs (A-G and X), only types A and B are in clinical use

• After intramuscular injection, the BoNT molecule rapidly reaches the cholinergic nerve endings via the blood stream or lymphatic system

  • At the neuromuscular junction, it blocks the release of acetylcholine from presynaptic vesicles, thereby causing decreased muscle tone and weakness

• This function is achieved through the unique molecular structure of BoNT, which is capable of carrying out sequential targeted steps at the neuromuscular junction

BoNT: Mechanism of Action (Five Steps)

1. Binding to the synaptic membrane
2. Passage through the membrane into the cytosol
3. Synaptic vesicle membrane translocation
4. Reduction of disulfide interchain bond
5. SNARE protein cleavage
   • Deactivation of SNARE occurs via different mechanisms for BoNT serotypes A & B
     • BoNT-A: catalytically cleaves SNAP-25 (synaptosomal-associated membrane protein)
     • BoNT-B: cleaves VAMP (vesicle-associated membrane protein)

## Current U.S. Marketed Botulinum Toxin Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botox®</td>
<td>OnabotulinumtoxinA</td>
</tr>
<tr>
<td>Dysport®</td>
<td>AbobotulinumtoxinA</td>
</tr>
<tr>
<td>Xeomin®</td>
<td>IncobotulinumtoxinA</td>
</tr>
<tr>
<td>Myobloc®</td>
<td>RimabotulinumtoxinB</td>
</tr>
<tr>
<td></td>
<td>Botox® (OnabotulinumtoxinA)</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Allergan (USA)</td>
</tr>
<tr>
<td>Toxin type</td>
<td>A1</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>900-KDa complex</td>
</tr>
<tr>
<td>Progenitor toxin</td>
<td>Yes</td>
</tr>
<tr>
<td>Pharmaceutical form</td>
<td>Vacuum-dried powder for reconstitution</td>
</tr>
<tr>
<td>pH (reconst)</td>
<td>7.4</td>
</tr>
<tr>
<td>Unit/vial</td>
<td>100 U and 200 U</td>
</tr>
<tr>
<td>Protein load</td>
<td>5 ng/100 unit</td>
</tr>
<tr>
<td>Number of FDA-approved indications</td>
<td>11</td>
</tr>
</tbody>
</table>

*For Xeomin, concentration is measured by Elisa method.


FDA, United States Food and Drug Administration.
Lethality tests utilized to determine units vary greatly among products

Each manufacturer has its own assay method for testing potency units

Non-interchangeability of units has been demonstrated
• A study compared incobotulinumtoxinA and onabotulinumtoxinA
• IncobotulinumtoxinA was found to be less than 100 Allergan units (i.e., 69-78 units for 3 different lots)

Clinical Use of BoNTs

There are 5 major areas of clinical use for BoNTs:

1. Hyperkinetic movement disorders (dystonias and hemifacial spasm)
2. Spasticity, conditions associated with increased muscle tone (post-stroke/post-traumatic spasticity, cerebral palsy, multiple sclerosis)
3. Bladder dysfunction and autonomic disorders (sialorrhea, hyperhidrosis)
4. Pain disorders (chronic migraine & other pain syndromes)
5. Aesthetic indications
BoNT General Adverse Effects

• Typically, adverse effects occur within the first week of treatment

• In general, the most common adverse effects regardless of BoNT used/indication include:
  • Localized pain
  • Tenderness
  • Erythema
  • Bleeding/bruising
  • Muscle weakness
  • Flu-like symptoms

BoNT Immunogenicity

• BoNT are proteins, so there is the potential for antibody formation and subsequent development of immunogenicity
  • Primary immunogenicity: lack of response to the first BoNT injection
  • Secondary immunogenicity: in patients who have previously responded to BoNT, the development of neutralizing antibodies has decreased effectiveness of BoNT

• Possible risks that may increase immunogenicity
  • More inactive protein
  • Higher toxin doses
  • More frequent administration intervals

• If immunogenicity were to develop to 1 serotype, then a change to another serotype is indicated

• “Old Botox” refers to the original formulation prior to the development of the newer/current formulation
  • Older formulation had higher amounts of inactive proteins compared to current product
  • Antibody formation was 6 times more likely with the original formulation
• Clinical rates of immunogenicity
  • Varies by product and indication
  • Non-responsiveness rates tend to be even less than immunogenicity rates

<table>
<thead>
<tr>
<th>Product</th>
<th>Botox® (OnabotulinumtoxinA)</th>
<th>Dysport® (AbobotulinumtoxinA)</th>
<th>Xeomin® (IncobotulinumtoxinA)</th>
<th>Myobloc® (RimabotulinumtoxinB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunogenicity rates</td>
<td>0%-3.6%</td>
<td>0.2%-3.6%</td>
<td>0.2%-1.8%</td>
<td>18%-42.4%</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>BoNT FDA-Approved Indications</th>
<th>Botox®&lt;sup&gt;®&lt;/sup&gt; (OnabotulinumtoxinA)</th>
<th>Dysport®&lt;sup&gt;®&lt;/sup&gt; (AbobotulinumtoxinA)</th>
<th>Xeomin®&lt;sup&gt;®&lt;/sup&gt; (IncobotulinumtoxinA)</th>
<th>Myobloc®&lt;sup&gt;®&lt;/sup&gt; (RimabotulinumtoxinB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult lower limb spasticity</td>
<td>Adult lower limb spasticity</td>
<td>Adult upper limb spasticity</td>
<td>Cervical dystonia</td>
<td></td>
</tr>
<tr>
<td>Adult upper limb spasticity</td>
<td>Adult upper limb spasticity</td>
<td>Blepharospasm</td>
<td>Chronic sialorrhea</td>
<td></td>
</tr>
<tr>
<td>Blepharospasm</td>
<td>Cervical dystonia</td>
<td>Cervical dystonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical dystonia</td>
<td>Pediatric upper limb spasticity</td>
<td>Chronic sialorrhea</td>
<td></td>
<td></td>
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<tr>
<td>Chronic migraine</td>
<td>Pediatric lower limb spasticity</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Detrusor overactivity</td>
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<td></td>
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</tr>
<tr>
<td>Overactive bladder</td>
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<tr>
<td>Pediatric lower limb spasticity</td>
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<td></td>
</tr>
<tr>
<td>Pediatric upper limb spasticity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary axillary hyperhidrosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Strabismus</td>
<td></td>
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</tbody>
</table>
## AAN 2016 Guideline Update: BoNT for Blepharospasm, Cervical Dystonia, Adult Spasticity, & Headache

<table>
<thead>
<tr>
<th>Indication</th>
<th>Level A Effective</th>
<th>Level B Probably effective</th>
<th>Level C Possibly effective</th>
<th>Level U Insufficient evidence</th>
<th>Level A Ineffective</th>
<th>Level B Ineffective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blepharospasm</td>
<td>onaBoNT-A</td>
<td>aboBoNT-A</td>
<td>rimaBoNT-B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical dystonia</td>
<td>aboBoNT-A rimaBoNT-B</td>
<td>onaBoNT-A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper limb spasticity</td>
<td>aboBoNT-A onaBoNT-A rimaBoNT-A</td>
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<td></td>
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<td></td>
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<tr>
<td>Lower limb spasticity</td>
<td>onaBoNT-A aboBoNT-A</td>
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<td></td>
<td></td>
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<tr>
<td>Chronic migraine</td>
<td>onaBoNT-A</td>
<td></td>
<td></td>
<td>onaBoNT-A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episodic migraine</td>
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<td></td>
<td>onaBoNT-A</td>
<td></td>
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<tr>
<td>Tension-type headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>onaBoNT-A</td>
</tr>
</tbody>
</table>

• **Dystonia**: sustained or intermittent muscle contraction causing abnormal movement and/or posture

• Cervical dystonia is the most common type of focal dystonia, with a prevalence of 5/100,000 and a female predominance of 74%

• Neck postures can be rotational (torticollis), neck tilt (laterocollis), neck retraction (retrocollis), or neck bending (anterocollis)

• A satisfactory response to BoNT treatment is seen in two-thirds of patients with cervical dystonia after the first injection

• All 3 type A toxins (ona, abo, and onco) and the B toxin (rima) are approved by the FDA for treatment of cervical dystonia


BoNTs FDA Approved for Dystonia

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication</th>
<th>Dose</th>
<th>Dosing interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botox® (OnabotulinumtoxinA)</td>
<td>Cervical dystonia</td>
<td>500 – 1000 units</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Dysport® (AbobotulinumtoxinA)</td>
<td>Cervical dystonia</td>
<td>120 – 240 units</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Xeomin® (IncobotulinumtoxinA)</td>
<td>Cervical dystonia</td>
<td>2500 – 5000 units</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Myobloc® (RimabotulinumtoxinB)</td>
<td>Cervical dystonia</td>
<td></td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

Indication-specific side effects: dysphagia, neck pain, headache, dry mouth, upper respiratory infection

Blepharospasm

• **Blepharospasm**: dystonia involving the orbicularis oculi, the muscle that opens and closes the eyelids

• Less common than cervical dystonia: 16-133 cases/million

• Frequent blinking and forced eye closure can significantly impair quality of life

• BoNT injection is the treatment of choice for blepharospasm

• More than 90% improve with BoNT injection

BoNTs FDA Approved for Blepharospasm

<table>
<thead>
<tr>
<th>Product</th>
<th>Botox® (OnabotulinumtoxinA)</th>
<th>Xeomin® (IncobotulinumtoxinA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Blepharospasm</td>
<td>Blepharospasm</td>
</tr>
<tr>
<td>Dose</td>
<td>1.25 – 5 units/site</td>
<td>50 – 100 units</td>
</tr>
<tr>
<td>Dosing interval</td>
<td>12 weeks</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

Indication-specific side effects: dry eye, drooping of the eyelid, vision problems
BoNT Therapy: Other Dystonia Indications

- Task-specific dystonia (writers, typists, musicians, golfers)
- Laryngeal dystonia
- Oromandibular
- Focal limb dystonia

Spasticity

- **Spasticity**: an abnormal muscle condition characterized by increased muscle tone, associated with increased tendon reflexes
- It is a sign of damage to the central nervous system at brain or spinal cord level
- Common causes of spasticity are traumatic brain or spinal cord injury, stroke, cerebral palsy (in children), and multiple sclerosis
- The spastic muscles gradually become very stiff and lose function
- Early and aggressive treatment prevents disability

Physical therapy should be started early and combined with other modes of treatment

Pharmacological therapy

- Baclofen 10-80 mg/day, diazepam 10-40 mg/day, tizanidine 4-36 mg/day, and dantrolene 25-200 mg/day

- Baclofen pump is used in advanced spasticity

- Side effects: sedation, confusion, nausea, hypotension, and hepatotoxicity

BoNT injection of affected muscles is a powerful tool for treatment of spasticity

- Side effects are less common than with spasticity medications

- Early BoNT therapy combined with physical therapy prevents fixed deformity and irreversible muscle damage
BoNTs FDA Approved for **Adult Lower Limb Spasticity**

<table>
<thead>
<tr>
<th>Product</th>
<th>Botox® (OnabotulinumtoxinA)</th>
<th>Dysport® (AbobotulinumtoxinA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Adult lower limb spasticity</td>
<td>Adult lower limb spasticity</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>300 – 400 units</td>
<td>1000 – 1500 units</td>
</tr>
<tr>
<td><strong>Dosing interval</strong></td>
<td>12 weeks</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

*Indication-specific side effects: muscle weakness, pain in extremity, arthralgia, falls*

BoNTs FDA Approved for **Adult Upper Limb Spasticity**

<table>
<thead>
<tr>
<th>Product</th>
<th>Botox® (OnabotulinumtoxinA)</th>
<th>Dysport® (AbobotulinumtoxinA)</th>
<th>Xeomin® (IncobotulinumtoxinA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Adult upper limb spasticity</td>
<td>Adult upper limb spasticity</td>
<td>Adult upper limb spasticity</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>75 – 400 units</td>
<td>500 – 1000 units</td>
<td>Varies by muscle</td>
</tr>
<tr>
<td><strong>Dosing interval</strong></td>
<td>12 weeks</td>
<td>12 weeks</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

*Indication-specific side effects: muscle weakness, arthralgia, myalgia*

BoNTs FDA Approved for Pediatric Lower Limb Spasticity

<table>
<thead>
<tr>
<th>Product</th>
<th>Botox® (OnabotulinumtoxinA)</th>
<th>Dysport® (AbobotulinumtoxinA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Pediatric lower limb spasticity</td>
<td>Pediatric lower limb spasticity</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>4 – 8 units/kg</td>
<td>10 – 15 units/kg</td>
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<td><strong>Dosing interval</strong></td>
<td>12 weeks</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

*Indication-specific side effects: upper respiratory tract infection*

BoNTs FDA Approved for **Pediatric Upper Limb Spasticity**

<table>
<thead>
<tr>
<th>Product</th>
<th>Botox® (OnabotulinumtoxinA)</th>
<th>Dysport® (AbobotulinumtoxinA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Pediatric upper limb spasticity</td>
<td>Pediatric upper limb spasticity</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>3 – 6 units/kg</td>
<td>8 – 16 units/kg</td>
</tr>
<tr>
<td><strong>Dosing interval</strong></td>
<td>12 weeks</td>
<td>16 weeks</td>
</tr>
</tbody>
</table>

*Indication-specific side effects: upper respiratory tract infections*

BoNT Treatment in Pain Disorders – Effect on Pain Transmitters

• Evidence from animal studies indicates that BoNTs block or diminish the effect of pain transmitters, such as substance-P, CGRP, and glutamate, and reduce activity of sodium channels

• This effect occurs at different levels of the sensory system: skin pain receptors, peripheral nerve endings, sensory ganglions, and spinal cord

Figure from: C. Steede, MD.
**BoNT Therapy for Chronic Migraine**

- **Chronic migraine**: a pain disorder with a frequency of at least 15 headaches/month of which at least 8 meet the criteria for migraine

- Chronic migraine affects 1%-2% of the world’s population
  
  - Affects 40 million Americans

- Migraine ranks second to low back pain as the most disabling condition worldwide

- Preventative migraine treatments include divalproex, topiramate, propranolol, amitriptyline, venlafaxine, CGRP monoclonal antibodies, and onabotulinumtoxinA

- Advantages of onabotulinumtoxinA use include long duration of action, efficacy, and relatively good tolerability compared to oral therapies

BoNT Therapy for Chronic Migraine

- OnabotulinumtoxinA is approved in North America and Europe for treatment of chronic migraine on the basis of 2 large, randomized, double-blind, placebo-controlled trials that studied nearly 1400 patients (PREEMPT I & II)

- Follow-up studies of the PREEMPT cohort for several years have shown improvement of efficacy with subsequent injections and improvement of quality of life

- Further pooled analyses from PREEMPT have even found that headache-day frequency non-responders demonstrate benefit with a reduction in severity of headaches with onabotulinumtoxinA injection

- 31 injection sites

BoNT FDA Approved for **Chronic Migraine**

<table>
<thead>
<tr>
<th>Product</th>
<th>Botox® (OnabotulinumtoxinA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Chronic migraine</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>155 units</td>
</tr>
<tr>
<td><strong>Dosing interval</strong></td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

*Indication-specific side effects: neck pain, headache*

Note: there is a lack of research on use in individuals who are pregnant

High-quality studies in small cohorts indicate that intradermal, subcutaneous, or intramuscular injection of BoNTs can improve several pain disorders:

1. Painful diabetic neuropathy
2. Post-traumatic painful neuropathy
3. Post-herpetic neuralgia
4. Trigeminal neuralgia
5. Plantar fasciitis
6. Non-surgical low back pain
OnabotulinumtoxinA is approved by the FDA for treatment of neurogenic (2011) and overactive bladder (2013).

- In June of 2020, the indication was expanded to include pediatric patients with neurogenic detrusor overactivity.

- Injections into the bladder wall through a cystoscope improves urge incontinence.
  - The effect can last 6-12 months.

- The number of injection sites varies from 15 to 40 and injections may or may not involve bladder trigone.

BoNT FDA Approved for Overactive Bladder

<table>
<thead>
<tr>
<th>Product</th>
<th>Botox® (OnabotulinumtoxinA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Overactive bladder</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>100 units</td>
</tr>
<tr>
<td><strong>Dosing interval</strong></td>
<td>12 – 24 weeks</td>
</tr>
</tbody>
</table>

*Indication-specific side effects: urinary tract infection, dysuria, urinary retention*

BoNT FDA Approved for **Neurogenic Detrusor Overactivity**

<table>
<thead>
<tr>
<th>Product</th>
<th>Botox® <em>(OnabotulinumtoxinA)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Detrusor overactivity</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>200 units</td>
</tr>
<tr>
<td><strong>Dosing interval</strong></td>
<td>12 – 48 weeks</td>
</tr>
</tbody>
</table>

*Indication-specific side effects: urinary tract infection, urinary retention*

Sialorrhea is a major issue in adults with neurodegenerative disorders and children with cerebral palsy.

Accumulation of saliva in the mouth can cause choking; drooling is a social embarrassment.

Topical treatment with scopolamine or tropicamide and oral treatment with glycopyrrolate are partially effective but have disturbing side effects.

Both types A and B BoNTs effectively reduce saliva after local injection into the salivary glands.

- Xeomin® and Myobloc® are FDA approved for this indication.

Parotid glands are usually injected in 4 sites and submaxillary glands in 2 sites.

Ultrasound-guided injection is the gold standard.

BoNTs FDA Approved for Sialorrhea

<table>
<thead>
<tr>
<th>Product</th>
<th>Xeomin® (IncobotulinumtoxinA)</th>
<th>Myobloc® (RimabotulinumtoxinB)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Chronic sialorrhea</td>
<td>Chronic sialorrhea</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>100 units</td>
<td>1500 – 3500 units</td>
</tr>
<tr>
<td><strong>Dosing interval</strong></td>
<td>16 weeks</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

*Common side effects: dry mouth, tooth extraction*

BoNT Treatment of Autonomic Disorders - Hyperhidrosis

- **Primary hyperhidrosis (excessive sweating): a genetic disorder that causes social embarrassment and work discord**
  - Hyperhidrosis can also occur secondary to drugs
- BoNTs are FDA approved for axillary hyperhidrosis but are also quite effective in palmar and plantar hyperhidrosis
- Injections are subcutaneous and superficial
- First numb the skin with Emla® cream (applied 1 hour before injections), then use an anesthetic spray during injections for further skin anesthesia
- Reinjection is required every 3-5 months

BoNT FDA Approved for Hyperhidrosis

<table>
<thead>
<tr>
<th>Product</th>
<th>Botox® (OnabotulinumtoxinA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Primary axillary hyperhidrosis</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>50 units/axilla</td>
</tr>
<tr>
<td><strong>Dosing interval</strong></td>
<td>12 – 24 weeks</td>
</tr>
</tbody>
</table>

*Common side effects: non-axillary sweating*

Pharmacist Considerations in Managing Use of Botulinum Toxins

Sheldon J. Rich, RPh, PhD
• **Dosage form**: 100 or 200 units vacuum-dried powder in a single-dose vial
  • Reconstitution required with sterile, preservative-free 0.9% sodium chloride
  • Use within 24 hours after reconstitution
    • Refrigeration of unused product recommended
    • Some institutions may have a requirement to use within 1 hour of reconstitution if prepared at bedside
  • Botox® and Botox Cosmetic® are different dilutions and uses and should not be interchanged

**Dosing: Botox® (OnabotulinumtoxinA)**

Dosing: Botox® (OnabotulinumtoxinA)

- Dosing is indication specific
- Initiation of treatment should be done using the lowest recommended dose per indication

- Adult maximum cumulative dose in a 3-month interval:
  - \( \leq 400 \text{ units} \)
- Pediatric maximum cumulative dose in a 3-month interval:
  - \( \leq 340 \text{ units} \) OR 10 units/kg total body weight
Dosing: Dysport® (AbobotulinumtoxinA)

• **Dosage form**: 300 or 500 units lyophilized powder in a single-dose vial
  • Reconstitution required with sterile, preservative-free 0.9% sodium chloride
  • Use within 24 hours after reconstitution
    • Refrigeration of unused product recommended
Dosing is indication specific
Initiation of treatment should be done using the lowest recommended dose per indication
Maximum dose varies per indication
Dosing: Xeomin® (IncobotulinumtoxinA)

• **Dosage form:** 50, 100, or 200 units lyophilized powder in a single-dose vial
  - Reconstitution required with sterile, preservative-free 0.9% sodium chloride
    - Use within 24 hours after reconstitution
    - Refrigeration of unused product recommended
  - Refrigeration of unopened vials NOT required
Dosing: Xeomin® (IncobotulinumtoxinA)

- Dosing is indication specific
- Initiation of treatment should be done using the lowest recommended dose per indication
- Maximum cumulative dose per treatment session:
  - \( \leq 400 \text{ units} \)

Dosing: Myobloc®
(RimabotulinumtoxinB)

• **Dosage form**: 2500 units/0.5 mL, 5000 units/mL, and 10,000 units/2 mL
  • NO reconstitution required
  • Single-use vials, so discard after use for 1 patient
Dosing: Myobloc® (RimabotulinumtoxinB)

• Dosing is indication specific
• Initiation of treatment should be done using the lowest recommended dose per indication

• This medicine is injected into a muscle by a healthcare provider
• BoNT injections should be spaced at least 3 months apart
• BoNT injections may be given into more than 1 area at a time, depending on the condition being treated
• While receiving injections for eye muscle conditions, patients may need to use eye drops, ointment, a special contact lens, or other device to protect the surface of the eye
  • Advise patients to follow their doctor’s instructions
• It may take only 1 to 3 days after injection before eye muscle spasm symptoms begin to improve. Greatest improvement may be noticed after 2 to 6 weeks.

• If patients are being treated for excessive sweating, advise them to shave underarms about 24 hours before injection. Do not apply antiperspirant or deodorant for 24 hours before or after receiving the injection. Avoid exercise and hot foods or beverages within 30 minutes before the injection.

• It may take up to 2 weeks after injection before neck muscle spasm symptoms begin to improve. Greatest improvement noticed after 6 weeks.

• The effects of a BoNT injection are temporary. Symptoms may return completely within 3 months. After repeat injections, it may take less and less time before symptoms return, especially if a patient’s body develops antibodies to the BoNT.

• Advise patients not to seek BoNT injections from more than 1 medical professional at a time. If a patient switches healthcare providers, they should tell the new provider how long it has been since the last BoNT injection.

• Using this medication more often than prescribed will not make it more effective and may result in serious side effects.

Advise patients to call their doctor at once if they have any of these side effects (up to several hours or several weeks after an injection):

- General
  - Unusual or severe muscle weakness (especially in a body area that was not injected with the medication)
  - Trouble breathing, talking, or swallowing
  - Chest pain or pressure, pain spreading to the jaw or shoulder, or irregular heartbeats
  - Sore throat, cough, chest tightness, or shortness of breath
- Urinary
  - Loss of bladder control
  - Pain or burning when urinating, trouble emptying bladder
- Facial
  - Hoarse voice, drooping eyelids
  - Vision changes, eye pain, severely dry or irritated eyes (eyes may also be more sensitive to light)
  - Eyelid swelling, crusting or drainage from eyes, problems with vision

Patient Education

Common BoNT side effects may include:
- Muscle weakness near where the medicine was injected
- Trouble swallowing for several months after treatment
- Muscle stiffness, neck pain, pain in arms or legs
- Blurred vision, puffy eyelids, dry eyes, drooping eyebrows
- Dry mouth
- Headache, tiredness
- Increased sweating in areas other than the underarms
- Bruising, bleeding, pain, redness, or swelling where the injection was given

• Train on proper use and proper injection technique
• Prior to treatment with BoNT, verify the patient’s benefits:
  • Prior authorization requirements
  • Drug acquisition
    • Buy and bill
    • Specialty pharmacy
    • Other
  • Treatment limits
  • Patient financial responsibility
    • Deductible
    • Co-payment
    • Co-insurance

Provider Education

Boxed Warning for all BoNTs

- **WARNING**: Distant spread of toxin effect
  All botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. 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.
Coverage Considerations
Potential Factors in Formulary Decision-Making

- Efficacy
- Politics & public image
- Willingness to pay
- Acquisition costs
- HEDIS, JCAHO, and NCQA
- Safety
- Productivity, satisfaction, and QOL
- Physician support
- Budget impact
- PBM, physician, and pharmacist contracts
- Discounts and rebates
- Cost-effectiveness
- Disease management programs

HEDIS, Healthcare Effectiveness Data and Information Set; JCAHO, Joint Commission on Accreditation of Healthcare Organizations; NCQA, National Committee for Quality Assurance; PBM, pharmacy benefit manager; QOL, quality of life.

Factors Considered by P&T Committee

- Clinical efficacy
- Safety
- Therapeutic need
- Clinical guidelines
- Standards of medical practice
- Pharmacoeconomics
- Cost
- Potential for wasted product
- Who supplies product: patient or provider?
• Medical benefit vs. pharmacy benefit: each MCO can design and deliver its own product and services
• Causes a lot of confusion for products that may be medical or pharmacy
• Has led to additional formulary tiers (i.e., Tier 4, Tier 5, and Tier 6)
• Traditionally associated with higher co-pays or co-insurances (e.g., 33% of the total drug cost monthly)
• Many plans are moving towards new benefit designs for specialty drugs and therapies, including a “specialty formulary”
• Formularies may add extra tiers to drive higher member contributions for targeted drug classes/categories
  • Examples:
    • Specialty injectables
    • Lifestyle medications

MCO, managed care organization.
Choosing A Botulinum Toxin Agent

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Cost</th>
<th># of FDA approved indications</th>
<th>Clinical pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botox®</td>
<td>$721.20/100 units</td>
<td>11</td>
<td>First toxin approved by FDA</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Most studied</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tends to be toxin of choice</td>
</tr>
<tr>
<td>Dysport®</td>
<td>$618.60/300 units</td>
<td>5</td>
<td>Used in Europe prior to FDA approval</td>
</tr>
<tr>
<td>Xeomin®</td>
<td>$578.40/100 units</td>
<td>4</td>
<td>Manufactured free of potentially immunogenic proteins</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unopened vials do not require refrigeration</td>
</tr>
<tr>
<td>Myobloc®</td>
<td>$697.20/5000 units</td>
<td>2</td>
<td>Only approved botulinum toxin type B in the U.S.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No reconstitution needed</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>More stinging upon injection</td>
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</table>

The Academy of Managed Care Pharmacy (AMCP) Professional Practice Committee has developed the following 9 specific concepts for effective prior authorization practices by MCOs:

1. Patient safety and appropriate medication use
2. Clinical decision-making
3. Evidence-based review criteria
4. Automated decision support
5. Transparency and advanced notice
6. Emergency access
7. Provider collaboration
8. Need for timeliness and avoiding disruptions in therapy
9. Cost-effectiveness and value

Prior Authorization Management

AMCP Professional Practice Committee conclusions:

MCOs should focus on ensuring access to appropriate, evidence-based, and cost-effective medications for their members. These concepts provide a framework to ensure that prior authorization and utilization management are timely, transparent, and collaborative, which is ultimately synonymous with patient-centered care. MCOs have the responsibility and opportunity to incorporate clinical and technology advancements into these processes with a constant goal of improving health outcomes and cost-effectiveness.
### TABLE 2

<table>
<thead>
<tr>
<th>Theme</th>
<th>AMA Consensus Statement</th>
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<th>NPF</th>
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<td>–</td>
<td>✓</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Note: ✓ = stakeholder discusses theme; – = stakeholder silent on theme.

*Signifying organizations included American Hospital Association, America’s Health Insurance Plans, American Medical Association, American Pharmacists Association, BlueCross BlueShield Association, and Medical Group Management Association.


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Prior Authorization Management

AMCP Partnership Forum: Optimizing Prior Authorization for Appropriate Medication Selection

AMCP Partnership Forum: Optimizing Prior Authorization for Appropriate Medication Selection

**FIGURE 1** Description of Pharmacist-Initiated PA in a Centralized Refill Clinic

When a new medication is prescribed for a patient, the clinic pharmacist would:

- Check the patient’s insurance plan to determine if a PA is required.
- The pharmacist, working under a collaborative practice agreement, would either perform a therapeutic interchange or initiate a PA request. When a PA is needed, the pharmacist accesses the patient’s medical record to gather required information.
- Appropriate forms are completed (either electronically or manually) and a letter of medical necessity, written by the pharmacist, accompanies each form. The letter of medical necessity covers patient-specific reasons why the prescribed medication is preferred over alternative formulary options.
- After the determination by the insurance company is made, this information is communicated to the pharmacist who informs the prescriber and patient.
- In the event of a denial, the pharmacist recommends alternative options to the prescriber and/or patient, including another medication, patient-assistance programs, coupons, or vouchers.

PA = prior authorization.
Prior Authorization Management

AMCP Partnership Forum: Optimizing Prior Authorization for Appropriate Medication Selection

**Figure 2** Description of PA Sunset Programs

A PA sunset program includes the regular review of the list of medical services and prescription drugs that are subject to PA requirements to help identify therapies that no longer warrant PA due to, for example, low variation in utilization or low PA denial rates. Regular review can also help identify services, particularly new and emerging therapies, where PA may be warranted due to a lack of evidence on effectiveness or safety concerns.

Plans considering implementing a PA sunset program should consider using multiple evaluation criteria and data points and ensure that the metrics are powered appropriately to assess utilization, especially for medications used in small populations or for rare diseases.

**Criteria for review could include:**
- Review of medical services and prescription drugs requiring PA on at least a consistent ___[time; at least annually]____ basis, with the input of ___[list key internal and external stakeholders]__________
- Revision of PA requirements should be based on data and up-to-date clinical criteria, including:
  - PA denial rates less than ___[%]____
  - PA approval rates more than ___[%]____
  - PA appeal rates
  - PA request rates less than ___[%]____
  - Financial impact____[savings over time period]__________
  - Treatment options in therapeutic class____[FDA approvals, new generics]____
  - Safety____[boxed warnings, REMS]_________
  - Updated clinical information, such as____[guidelines]_____[NCQA, state regulations]_____
- Plans should communicate changes to the lists of medical services and prescription drugs requiring PA via (a) provider-accessible ______[platform, websites]_________, (b) at least ___[time frequency]_____ and (c) ______[other]_________

**FDA** = U.S. Food and Drug Administration; **NCQA** = National Committee for Quality Assurance; **PA** = prior authorization; **REMS** = Risk Evaluation and Mitigation Strategy.
Prior Authorization Management

• Prior authorization differs from health plan to health plan
• Examples of botulinum toxin prior authorization policies can be found at:

Conclusions

• Currently, there are 4 botulinum toxins available for clinical use in the U.S.: Botox®, Dysport®, Xeomin®, and Myobloc®

• Each of the 4 commercially available toxins differs in a variety of ways, a key being differences in current FDA-approved uses

• The toxins are NOT interchangeable

• Approved uses for the toxins is an expanding field

• Patients need to understand side effects and precautions

• Prior authorization is very common for botulinum toxins and pharmacists can be extremely helpful in working through this process
Wrap-Up

- Thank you for your participation!
Questions and Answers
Thank You!