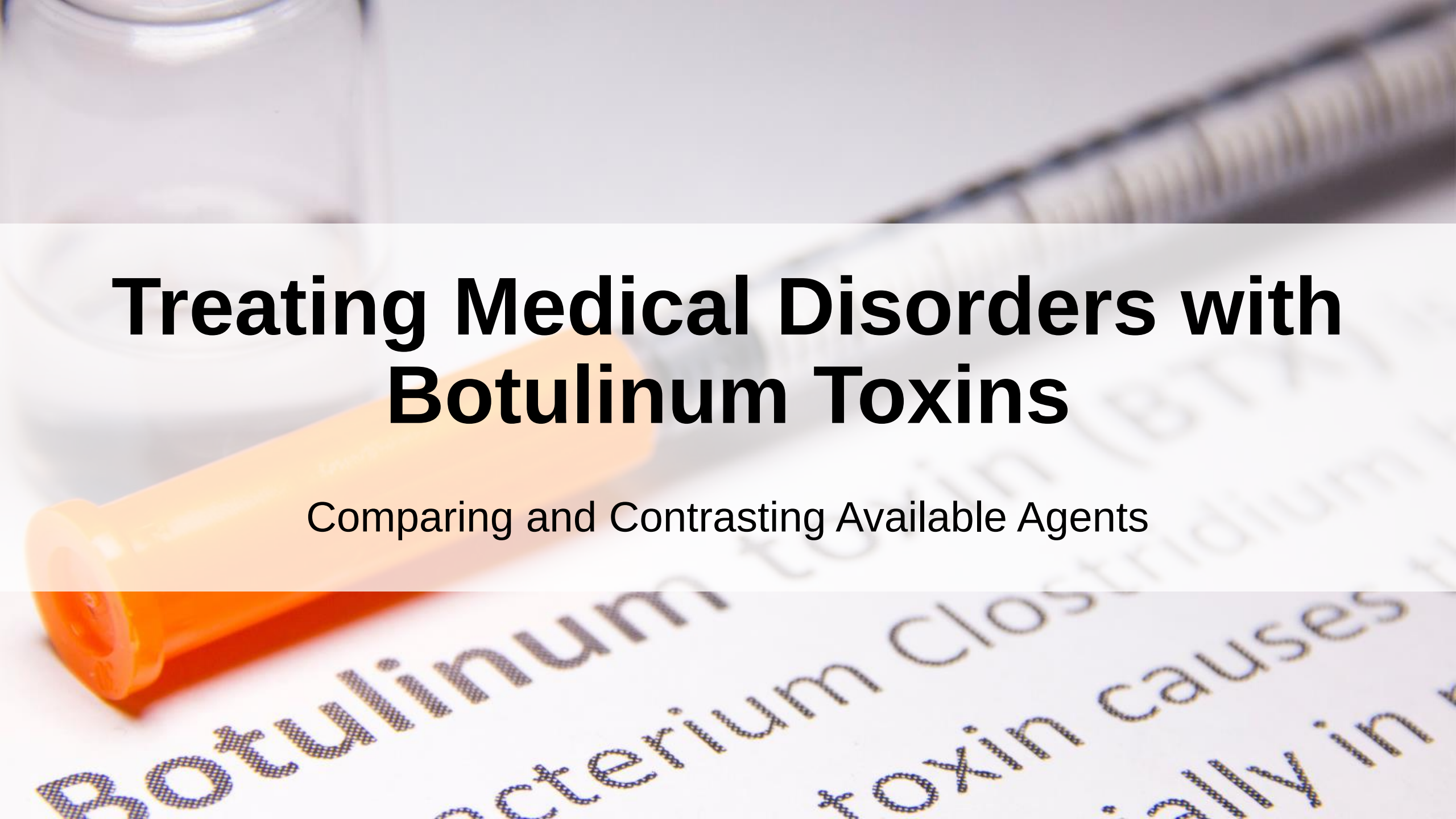

Treating Medical Disorders with Botulinum Toxins

Comparing and Contrasting Available Agents

This educational activity is sponsored by Postgraduate Healthcare Education, LLC and supported by an educational grant from Allergan.

Faculty

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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.

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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

Rosetto O, et al. *Handbook of Experimental Pharmacology*. Springer Nature; 2020.

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)

Rosetto O, et al. *Handbook of Experimental Pharmacology*. Springer Nature; 2020.

Current U.S. Marketed Botulinum Toxin Products

- Botox®
  (OnabotulinumtoxinA)
- Dysport®
  (AbobotulinumtoxinA)
- Xeomin®
  (IncobotulinumtoxinA)
- Myobloc®
  (RimabotulinumtoxinB)

Comparison of Marketed Botulinum Toxin Products
(Units are Manufacturer Specific and Not Interchangeable)

	Botox® (OnabotulinumtoxinA)	Dysport® (AbobotulinumtoxinA)	Xeomin®* (IncobotulinumtoxinA)	Myobloc® (RimabotulinumtoxinB)
Manufacturer	Allergan (USA)	Ipsen Pharma (France)	Merz Pharma (Germany)	US WorldMeds (USA)
Toxin type	A1	A1	A1	B1
Molecular weight	900-KDa complex	750 KDa	150 KDa	700 KDa
Progenitor toxin	Yes	Yes	No	Yes
Pharmaceutical form	Vacuum-dried powder for reconstitution	Vacuum-dried powder for reconstitution	Vacuum-dried powder for reconstitution	Ready-to-use solution
pH (reconst)	7.4	7.4	7.4	5.6
Unit/vial	100 U and 200 U	300 U and 500 U	100 U and 200 U	5000 U and 10,000 U
Protein load	5 ng/100 unit	4.35 ng/500 unit	0.44 ng/100 unit	55 ng/2500 unit
Number of FDA-approved indications	11	5	4	2

Pirazzini M, et al. *Pharmacol Rev*. 2017;69(2):200-35.
*For Xeomin, concentration is measured by Elisa method.

FDA, United States Food and Drug Administration.

Toxin Non-Interchangeability

- 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)

Brin MF, et al. *Biologics*. 2014;8:227-41.; Field M, et al. *Toxins (Basel)*. 2018;10(12):535.; Hunt T, Clarke K. *Clin Neuropharmacol.* 2009;32(1):28-31.

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

BOTOX (onabotulinumtoxinA) [package insert]. Irvine, CA: Allergan, Inc; 2019.; DYSPORT (abobotulinumtoxinA) [package insert]. Basking Ridge, NJ: Ipsen Biopharmaceuticals, Inc; 2019.; MYOBLOC [package insert]. South San Francisco, CA: Solstice Neurosciences, Inc; 2019.; XEOMIN [package insert]. Raleigh, NC: Merz North America, Inc; 2015.

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

Chen JJ, Dashtipour K. *Pharmacotherapy.* 2013;33(3):304-18.;
Dashtipour K, Pedouim F. *Semin Neurol.* 2016;36(1):29-33.

BoNT Immunogenicity

- "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

Product	Botox® (OnabotulinumtoxinA)	Dysport® (AbobotulinumtoxinA)	Xeomin® (IncobotulinumtoxinA)	Myobloc® (RimabotulinumtoxinB)
Immunogenicity rates	0%-3.6%	0.2%-3.6%	0.2%-1.8%	18%-42.4%

Bellows S, Jankovic J. *Toxins.* 2019;11(9):491. BOTOX (onabotulinumtoxinA) [package insert]. Irvine, CA: Allergan, Inc; 2019.; DYSPORT (abobotulinumtoxinA) [package insert]. Basking Ridge, NJ: Ipsen Biopharmaceuticals, Inc; 2019.; MYOBLOC [package insert]. South San Francisco, CA: Solstice Neurosciences, Inc; 2019.; XEOMIN [package insert]. Raleigh, NC: Merz North America, Inc; 2015. Lacroix-Desmazes S, Mouly S, et al. *Basal Ganglia.* 2017; 9: 12-17. Fabbri M, et al. *Neurotox Res.* 29, 105-117 (2016).

BoNT FDA-Approved Indications

Botox® (OnabotulinumtoxinA)	Dysport® (AbobotulinumtoxinA)	Xeomin® (IncobotulinumtoxinA)	Myobloc® (RimabotulinumtoxinB)
Adult lower limb spasticity	Adult lower limb spasticity	Adult upper limb spasticity	Cervical dystonia
Adult upper limb spasticity	Adult upper limb spasticity	Blepharospasm	Chronic sialorrhea
Blepharospasm	Cervical dystonia	Cervical dystonia	
Cervical dystonia	Pediatric upper limb spasticity	Chronic sialorrhea	
Chronic migraine	Pediatric lower limb spasticity		
Detrusor overactivity			
Overactive bladder			
Pediatric lower limb spasticity			
Pediatric upper limb spasticity			
Primary axillary hyperhidrosis			
Strabismus			

AAN 2016 Guideline Update: BoNT for Blepharospasm, Cervical Dystonia, Adult Spasticity, & Headache

Indication	Level A *Effective*	Level B *Probably effective*	Level C *Possibly effective*	Level U *Insufficient evidence*	Level A *Ineffective*	Level B *Ineffective*
Blepharospasm		onaBoNT-A incoBoNT-A	aboBoNT-A	rimaBoNT-B		
Cervical dystonia	aboBoNT-A rimaBoNT-B	onaBoNT-A incoBoNT-A				
Upper limb spasticity	aboBoNT-A onaBoNT-A incoBoNT-A	rimaBoNT-B				
Lower limb spasticity	onaBoNT-A aboBoNT-A			incoBoNT-A rimaBoNT-B		
Chronic migraine	onaBoNT-A					
Episodic migraine					onaBoNT-A	
Tension-type headache						onaBoNT-A

Simpson DM, et al. *Neurology.* 2016;86(19):1818-26.

AAN, American Academy of Neurology.

Dystonia

- *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

Forward
Antercollis

To the side
Laterocollis

Backward
Retrocollis

Rotated
Torticollis

Bledsoe IO, Comella CL. *Semin Neurol*. 2016;36(1):47-53.
Illustrations from: http://www.botoxcervicaldystonia.com/about. Accessed May 27, 2020.

BoNTs FDA Approved for Dystonia

Product	Botox® (OnabotulinumtoxinA)	Dysport® (AbobotulinumtoxinA)	Xeomin® (IncobotulinumtoxinA)	Myobloc® (RimabotulinumtoxinB)
Indication	Cervical dystonia	Cervical dystonia	Cervical dystonia	Cervical dystonia
Dose	Varies	500 – 1000 units	120 – 240 units	2500 – 5000 units
Dosing interval	12 weeks	12 weeks	12 weeks	12 weeks

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

BOTOX (onabotulinumtoxinA) [package insert]. Irvine, CA: Allergan, Inc; 2019.; DYSPORT (abobotulinumtoxinA) [package insert]. Basking Ridge, NJ: Ipsen Biopharmaceuticals, Inc; 2019.; MYOBLOC [package insert]. South San Francisco, CA: Solstice Neurosciences, Inc; 2019.; XEOMIN [package insert]. Raleigh, NC: Merz North America, Inc; 2015.

Blepharospasm

- *Blepharospasm: dystonia involving the orbicularis occuli, 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

Karp B, Alter K. *Semin Neurol.* 2016;36(1):84-91.
Drawing courtesy of: T. Mousavi, MD.

BoNTs FDA Approved for Blepharospasm

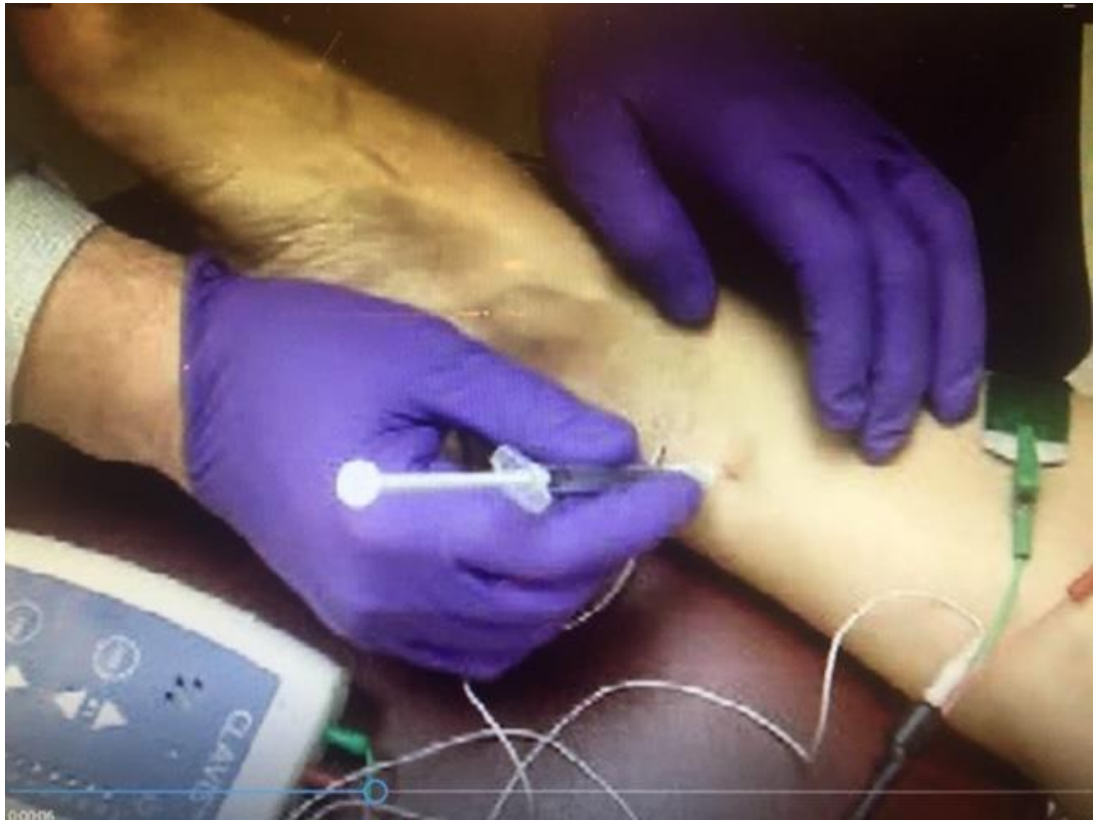
Product	Botox® (OnabotulinumtoxinA)	Xeomin® (IncobotulinumtoxinA)
Indication	Blepharospasm	Blepharospasm
Dose	1.25 – 5 units/site	50 – 100 units
Dosing interval	12 weeks	12 weeks

Indication-specific side effects: dry eye, drooping of the eyelid, vision problems

BOTOX (onabotulinumtoxinA) [package insert]. Irvine, CA: Allergan, Inc; 2019.; XEOMIN [package insert]. Raleigh, NC: Merz North America, Inc; 2015.

BoNT Therapy: Other Dystonia Indications

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



BoNT injection using EMG guidance for focal dystonia presenting as foot inversion; From: B. Jabbari, Yale University.

Lungu C, Ahmad OF. *Semin Neurol.* 2016;36(1):41-6.

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

Moeini-Naghani I, et al. *Semin Neurol*. 2016;36(1):64-72.

Treatment of Spasticity

- 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

Moeini-Naghani I, et al. *Semin Neurol*. 2016;36(1):64-72.

BoNTs FDA Approved for Adult Lower Limb Spasticity

Product	Botox® (OnabotulinumtoxinA)	Dysport® (AbobotulinumtoxinA)
Indication	Adult lower limb spasticity	Adult lower limb spasticity
Dose	300 – 400 units	1000 – 1500 units
Dosing interval	12 weeks	12 weeks

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

BOTOX (onabotulinumtoxinA) [package insert]. Irvine, CA: Allergan, Inc; 2019.; DYSPORT (abobotulinumtoxinA) [package insert]. Basking Ridge, NJ: Ipsen Biopharmaceuticals, Inc; 2019.

BoNTs FDA Approved for Adult Upper Limb Spasticity

Product	Botox® (OnabotulinumtoxinA)	Dysport® (AbobotulinumtoxinA)	Xeomin® (IncobotulinumtoxinA)
Indication	Adult upper limb spasticity	Adult upper limb spasticity	Adult upper limb spasticity
Dose	75 – 400 units	500 – 1000 units	Varies by muscle
Dosing interval	12 weeks	12 weeks	12 weeks

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

BOTOX (onabotulinumtoxinA) [package insert]. Irvine, CA: Allergan, Inc; 2019.; DYSPORT (abobotulinumtoxinA) [package insert]. Basking Ridge, NJ: Ipsen Biopharmaceuticals, Inc; 2019.; XEOMIN [package insert]. Raleigh, NC: Merz North America, Inc; 2015.

BoNTs FDA Approved for Pediatric Lower Limb Spasticity

Product	Botox® (OnabotulinumtoxinA)	Dysport® (AbobotulinumtoxinA)
Indication	Pediatric lower limb spasticity	Pediatric lower limb spasticity
Dose	4 – 8 units/kg	10 – 15 units/kg
Dosing interval	12 weeks	12 weeks

Indication-specific side effects: upper respiratory tract infection

BOTOX (onabotulinumtoxinA) [package insert]. Irvine, CA: Allergan, Inc; 2019.; DYSPORT (abobotulinumtoxinA) [package insert]. Basking Ridge, NJ: Ipsen Biopharmaceuticals, Inc; 2019.

BoNTs FDA Approved for Pediatric Upper Limb Spasticity

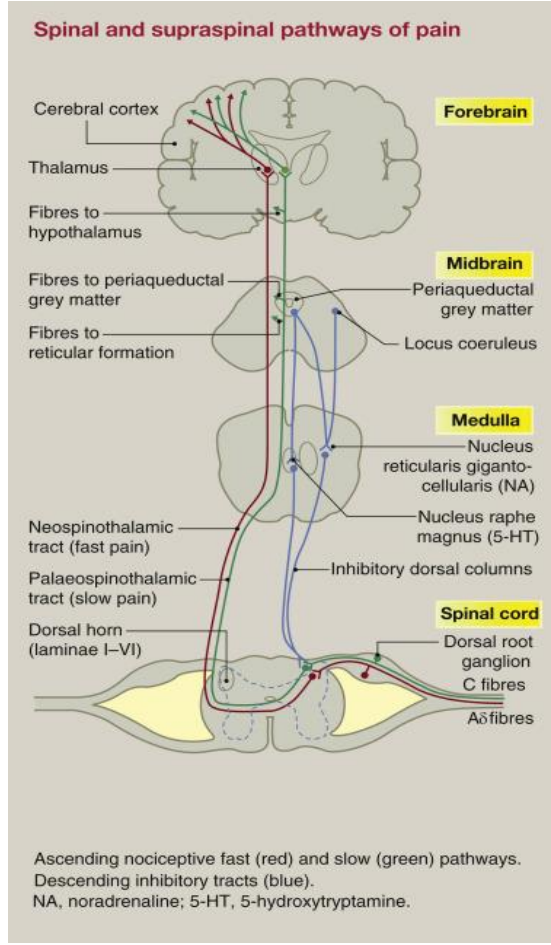
Product	Botox® (OnabotulinumtoxinA)	Dysport® (AbobotulinumtoxinA)
Indication	Pediatric upper limb spasticity	Pediatric upper limb spasticity
Dose	3 – 6 units/kg	8 – 16 units/kg
Dosing interval	12 weeks	16 weeks

Indication-specific side effects: upper respiratory tract infections

BOTOX (onabotulinumtoxinA) [package insert]. Irvine, CA: Allergan, Inc; 2019.; DYSPORT (abobotulinumtoxinA) [package insert]. Basking Ridge, NJ: Ipsen Biopharmaceuticals, Inc; 2019.

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



Matak I, et al. *Toxins (Basel).* 2019;11(8):459.
Figure from: C. Steede, MD.

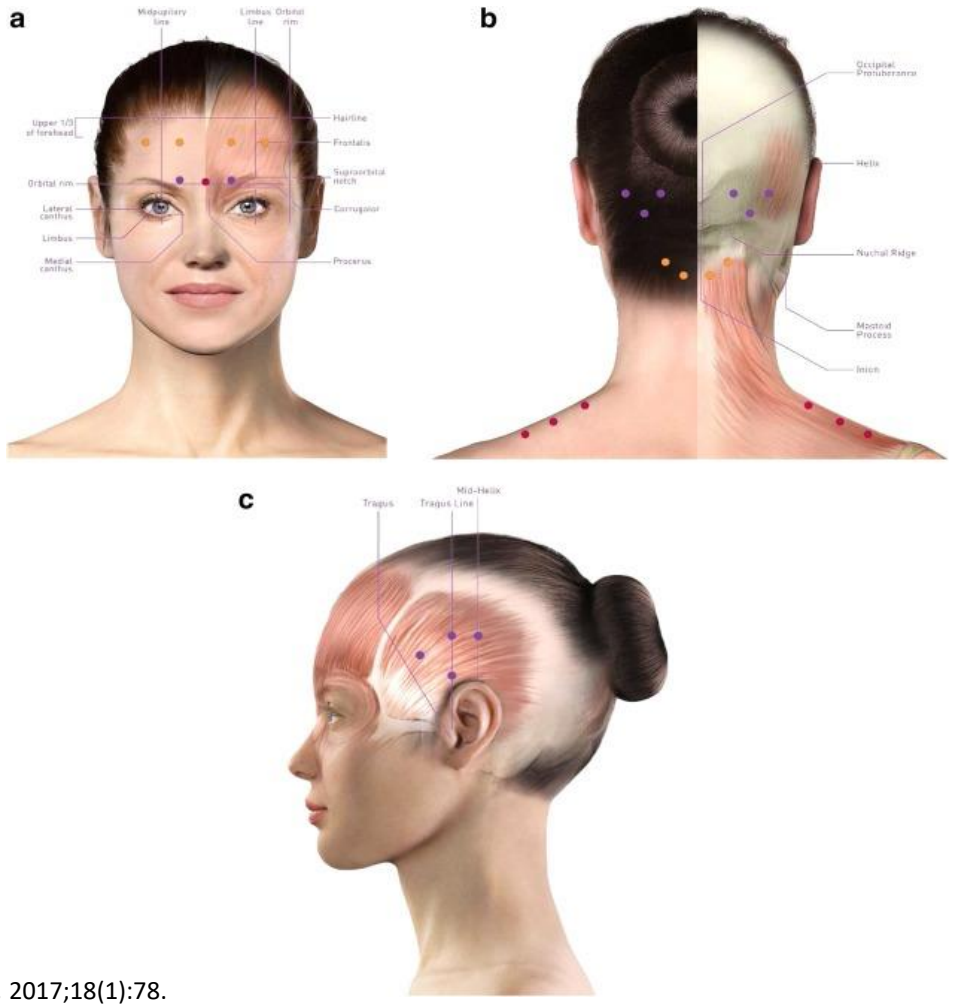
BoNT Therapy for Chronic Migraine

- *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

Burch RC, et al. *Neurol Clin.* 2019;37(4):631-49.; Natoli JL, et al. *Cephalalgia.* 2009;30(5)599-609.; Silberstein SD, et al. *Neurology.* 2012;78(17):1337-45.

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



Blumenfeld AM, et al. *Headache.* 2017;57(5):766-77.; Dodick DW, et al. *Headache.* 2020;5(6):921-36.; Matharu M, et al. *J Headache Pain.* 2017;18(1):78.

BoNT FDA Approved for Chronic Migraine

Product	Botox® (OnabotulinumtoxinA)
Indication	Chronic migraine
Dose	155 units
Dosing interval	12 weeks

Indication-specific side effects: neck pain, headache

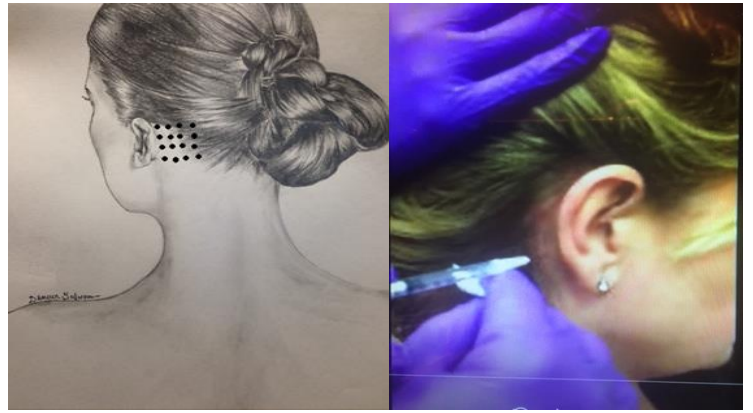
Note: there is a lack of research on use in individuals who are pregnant

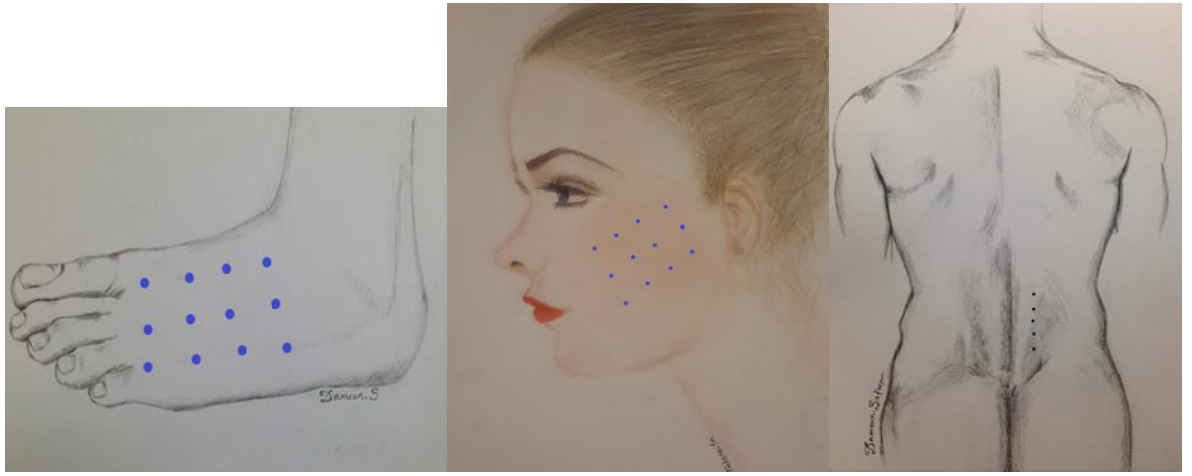
BOTOX (onabotulinumtoxinA) [package insert]. Irvine, CA: Allergan, Inc; 2019.

BoNT Treatment in Pain Disorders

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





Jabbari B. *Botulinum Toxin Treatment of Pain Disorders*. Springer; 2015.

Figures courtesy of: T. Mousavi, MD and D. Safarpour, MD.

Botulinum Toxin Treatment of Bladder and Autonomic Disorders

- 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

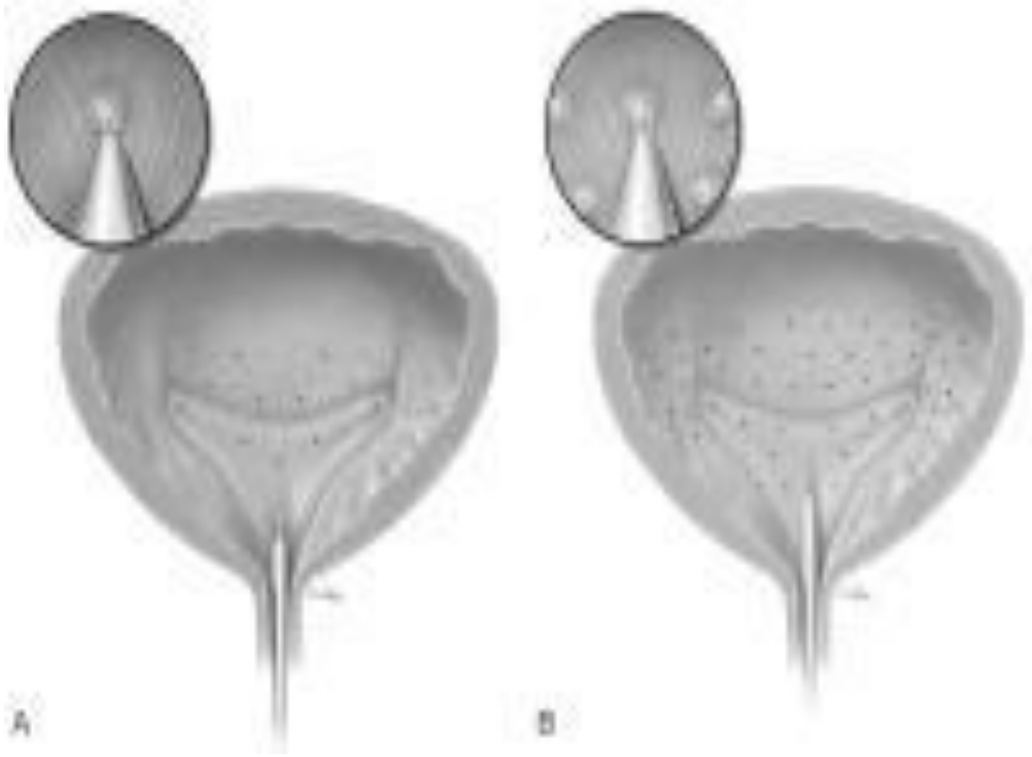


Figure courtesy of: Smith C, et al. *Semin Neurol.* 2016;36(1):5-9.

BoNT FDA Approved for Overactive Bladder

Product	Botox® (OnabotulinumtoxinA)
Indication	Overactive bladder
Dose	100 units
Dosing interval	12 – 24 weeks

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

BOTOX (onabotulinumtoxinA) [package insert]. Irvine, CA: Allergan, Inc; 2019.

BoNT FDA Approved for Neurogenic Detrusor Overactivity

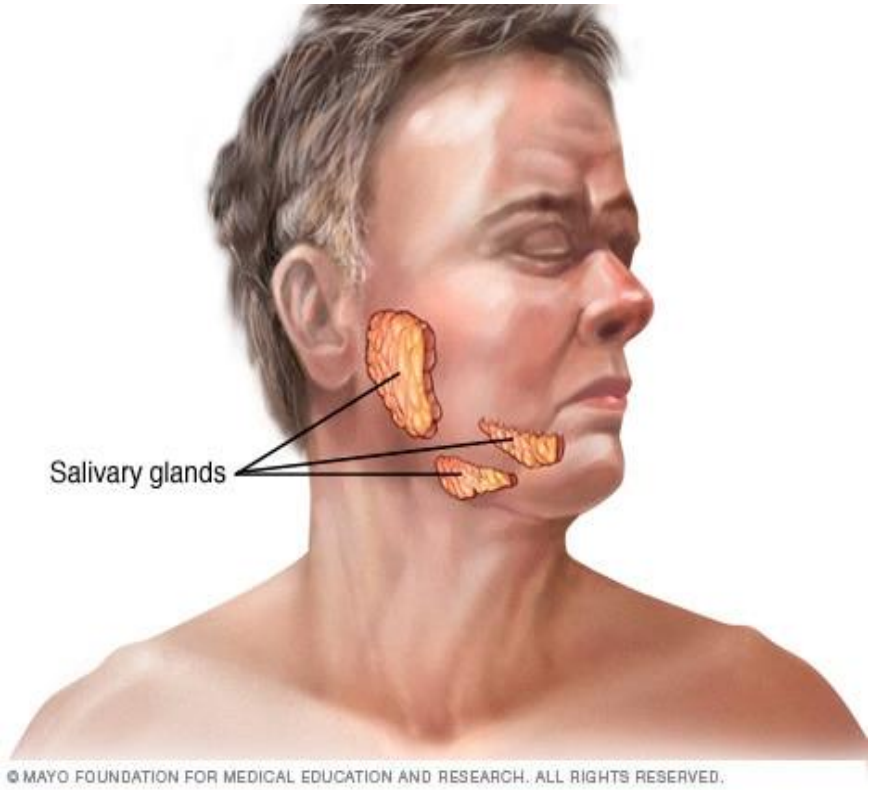
Product	Botox® (OnabotulinumtoxinA)
Indication	Detrusor overactivity
Dose	200 units
Dosing interval	12 – 48 weeks

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

BOTOX (onabotulinumtoxinA) [package insert]. Irvine, CA: Allergan, Inc; 2019.

BoNT Treatment of Autonomic Disorders – Sialorrhea (Drooling)

- 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



Lakraj AA, et al. *Toxins (Basel).* 2013,5(5):1010-35.

BoNTs FDA Approved for Sialorrhea

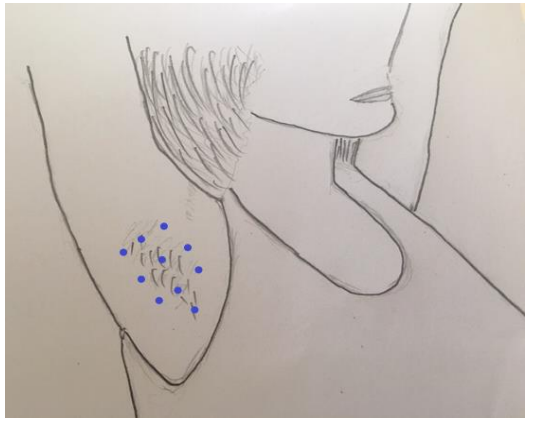
Product	Xeomin® (IncobotulinumtoxinA)	Myobloc® (RimabotulinumtoxinB)
Indication	Chronic sialorrhea	Chronic sialorrhea
Dose	100 units	1500 – 3500 units
Dosing interval	16 weeks	12 weeks

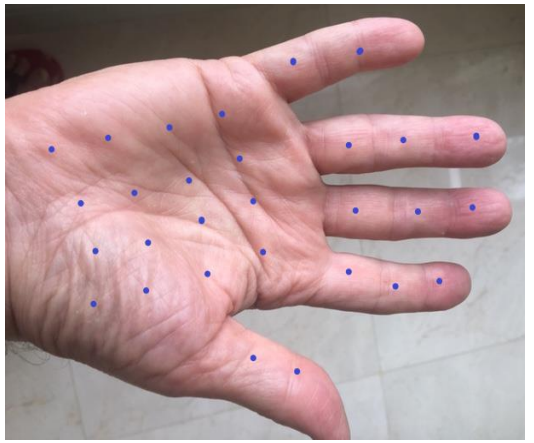
Common side effects: dry mouth, tooth extraction

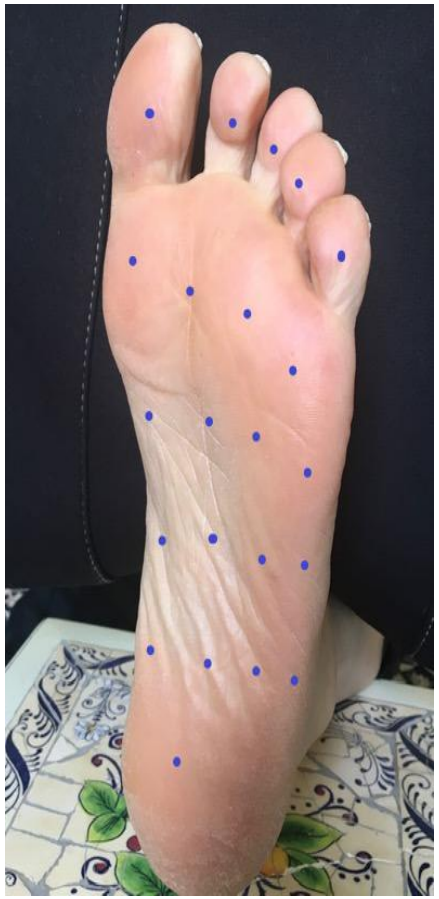
MYOBLOC [package insert]. South San Francisco, CA: Solstice Neurosciences, Inc; 2019.; XEOMIN [package insert]. Raleigh, NC: Merz North America, Inc; 2015.

BoNT Treatment of Autonomic Disorders - Hyperhidrosis

- *<u>Primary hyperhidrosis (excessive sweating)</u>: 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







Lakraj AA, et al. *Toxins (Basel).* 2013;5(4):821-40.

BoNT FDA Approved for Hyperhidrosis

Product	Botox® (OnabotulinumtoxinA)
Indication	Primary axillary hyperhidrosis
Dose	50 units/axilla
Dosing interval	12 – 24 weeks

Common side effects: non-axillary sweating

BOTOX (onabotulinumtoxinA) [package insert]. Irvine, CA: Allergan, Inc; 2019.

Pharmacist Considerations in Managing Use of Botulinum Toxins

Sheldon J. Rich, RPh, PhD

Dosing: Botox® (OnabotulinumtoxinA)

- **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

BOTOX (onabotulinumtoxinA) [package insert]. Irvine, CA: Allergan, Inc; 2019.

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:
  - ≤ 400 *units*
- Pediatric maximum cumulative dose in a 3-month interval:
  - ≤ 340 *units* OR 10 units/kg total body weight

BOTOX (onabotulinumtoxinA) [package insert]. Irvine, CA: Allergan, Inc; 2019.

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

DYSPORT (abobotulinumtoxinA) [package insert]. Basking Ridge, NJ: Ipsen Biopharmaceuticals, Inc; 2019.

Dosing: Dysport® (AbobotulinumtoxinA)

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

DYSPORT (abobotulinumtoxinA) [package insert]. Basking Ridge, NJ: Ipsen Biopharmaceuticals, Inc; 2019.

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

XEOMIN [package insert]. Raleigh, NC: Merz North America, Inc; 2015.

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:
  - ≤ 400 *units*

XEOMIN [package insert]. Raleigh, NC: Merz North America, Inc; 2015.

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

MYOBLOC [package insert]. South San Francisco, CA: Solstice Neurosciences, Inc; 2019.

Dosing: Myobloc® (RimabotulinumtoxinB)

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

MYOBLOC [package insert]. South San Francisco, CA: Solstice Neurosciences, Inc; 2019.

Appropriate Use

- 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.

Botox. https://www.drugs.com/botox.html. Accessed May 2, 2020.

Appropriate Use

- 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.

Botox. https://www.drugs.com/botox.html. Accessed May 2, 2020.

Adverse Event Management

- 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

Botox. https://www.drugs.com/botox.html. Accessed May 2, 2020.

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

Botox. https://www.drugs.com/botox.html. Accessed May 2, 2020.

Provider Education

- 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

Botox Patient Navigator Program. https://www.botoxmedical.com/Common/Assets/APC43LW16_BPNP_NavigatingTheBOTOXReimbursementLandscapeModule.pdf. Accessed May 2, 2020.

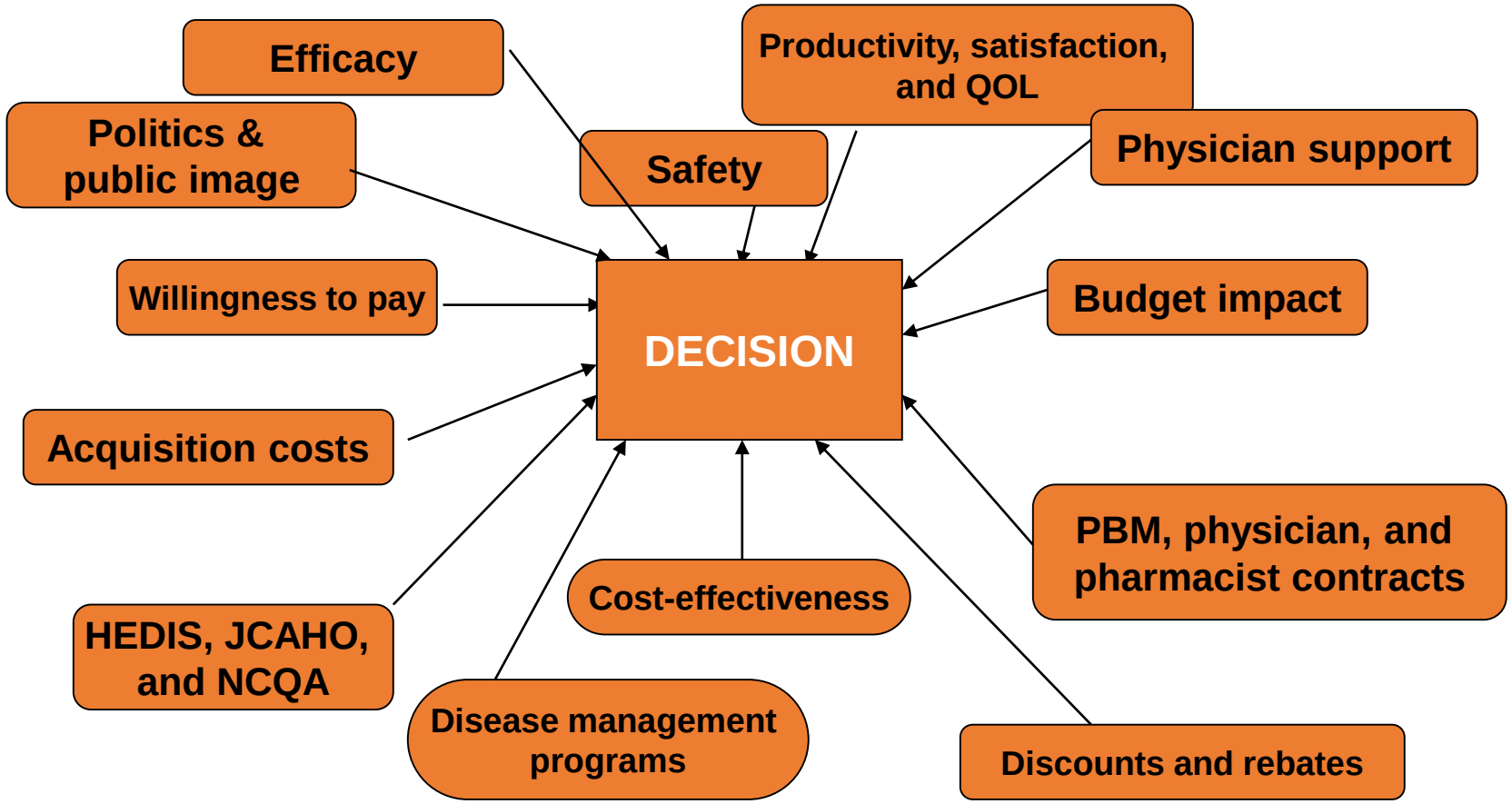
Boxed Warning for all BoNTs

- **<u>WARNING</u>**: 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



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.

Adapted from Gibson JL, et al. In: Format for Formulary Submission, Version 2.0. Academy of Managed Care Pharmacy, October 2002.

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?

Benefit Designs

- 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

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

Lexicomp®; Chen JJ, Dastipour K. *Pharmacotherapy*. 2013;33(3):304-18.

Prior Authorization Management

- 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

J Manag Care Spec Pharm. 2019;25(6):641-4.

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.

J Manag Care Spec Pharm. 2019;25(6):641-4.

Prior Authorization Management

AMCP Partnership Forum: Optimizing Prior Authorization for Appropriate Medication Selection

TABLE 2 Key Themes in Guiding Principles for Utilization Management Reform[12-18]

Theme	Organization					
	AMA Consensus Statement[a]	ASCO	NPF	SAIM	NAF	AMCP
Clinical criteria for protocol development	✓	✓	✓	✓	✓	✓
Transparency of protocol	✓	✓	✓	✓	✓	✓
Continuity of care	✓	✓	✓	✓	✓	✓
Opportunity to appeal	✓	✓	✓	✓	✓	✓
Flexibility for provider input	✓	✓	✓	✓	✓	✓
Financial considerations	✓	–	–	–	–	✓
Evaluation of program impact	✓	✓	–	✓	–	–
Protocol updates	–	✓	–	✓	–	✓

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

[a]*Signing organizations included American Hospital Association, America's Health Insurance Plans, American Medical Association, American Pharmacists Association, BlueCross BlueShield Association, and Medical Group Management Association.*

AMA = American Medical Association, ASCO = American Society of Clinical Oncologists, NPF = National Psoriasis Foundation, SAIM = State Access to Innovative Medicines Coalition, NAF = National Arthritis Foundation.

J Manag Care Spec Pharm. 2020;26(1):55-62.

Prior Authorization Management

AMCP Partnership Forum: Optimizing Prior Authorization for Appropriate Medication Selection

FIGURE 1 Description of Pharmacist-Initiated PA in a Centralized Refill Clinic[20]

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.

J Manag Care Spec Pharm. 2020;26(1):55-62.

Prior Authorization Management

AMCP Partnership Forum: Optimizing Prior Authorization for Appropriate Medication Selection

FIGURE 2 Description of PA Sunset Programs[22]

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.

J Manag Care Spec Pharm. 2020;26(1):55-62.

Prior Authorization Management

- Prior authorization differs from health plan to health plan
- Examples of botulinum toxin prior authorization policies can be found at:
  - https://www.bluecrossma.com/common/en_US/medical_policies/006%20Botulinum%20Toxin%20Injections%20SP%20prn.pdf
  - http://www.aetna.com/pharmacy-insurance/healthcare - professional/documents/botox-precert-form.pdf
  - https://cignaforhcp.cigna.com/public/content/pdf/resourceLibrary/prescription/Botox.pdf

Accessed on July 14, 2020.

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!