Botulinum Toxins Review

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Lecture Objectives

• Review the history of botulinum toxins (BoNT)
• Describe the mechanism of action of BoNT at the motor neuron
• Discuss pharmacologic differences observed with the currently available BoNT preparations
• Introduce the clinical utility of botulinum toxin
Botulinum Toxin Timeline

*Manufactured by Solstice Neurosciences, Inc. since 2004.

C. botulinum 1700’s-1800’s

900 kD Complex

E. Schantz 1944

1968

A. Scott

1944

1970’s -80’s

Strabismus
Blepharospasm

1970’s -80’s

Allergan
BOTOX® Cosmetic 2002

2009-2011:
Dysport, Xeomin: CD
Botox: Spasticity

Allergan
BOTOX® 1989

Solstice*
Myobloc® / NeuroBloc® 2000

1° Axillary HH 2004

2004

Ipsen
Dysport® 1991

2009

Dysport, Xeomin: CD
Botox: Spasticity

*Manufactured by Solstice Neurosciences, Inc. since 2004.
BoNT

• A biological product of the bacterium *Clostridium botulinum*\(^1\)

• Treatment for focal and multifocal muscle overactivity in the UMN syndrome \(^2\) and other conditions

• Seven botulinum toxin serotypes (A-G)\(^1\)

• Only types A and B are available for clinical use\(^3\)

Botulinum Toxin: Worldwide Available Preparations

• Botulinum toxin type A Preparations: World Wide
  – BOTOX®; Allergan, Inc.
  – Dysport®; Ipsen Pharmaceuticals¹
  – Xeomin®; Merz
  – Puretox, Mentor
  – Reloxin, Europe
  – BTXA, China

• Botulinum toxin type B (Serotypes)
  – Myobloc®/NeuroBloc®*; Solstice Neurosciences)¹
  – Licensed for distribution in the US, Europe, and Japan

• Preparations are different and units are not interchangeable¹,²:
  – Different strains of C. botulinum used in manufacturing process
  – Purification and formulation methods differ

*Brand name in Europe.
In 2009 the FDA revised prescribing information for all FDA licensed BoNT preparations

- **A Boxed Warning was added to all BoNTs**
  - Highlighting the possibility potentially life-threatening distant spread of toxin effect after local injection.
  - A Risk Evaluation and Mitigation Strategy (REMS) was added to include a *Medication Guide* for patients understand detailing risks/benefits of BoNT

- To reinforce the differences in toxin potency and reduce potential for dosing errors the FDA established unique generic drug names for each toxin

- The new established names reinforce these differences and the lack of interchangeability among products.

- Units/dosing are specific to each BoNT product
  - The practice of using conversion tables between toxins is not recommended
  - Dose or units of biological activity cannot be compared or converted between products.
BoNTs: U.S. Preparations: FDA Unique Generic Names & Indications (2011)

- **OnaBotulinumtoxinA (BOTOX®; Allergan, Inc.)**\(^1\)
  - Licensed for distribution worldwide
  - Indications: Cervical dystonia, strabismus, blepharospasm, hemifacial spasm, hyperhidrosis; post stroke spasticity, overactive bladder, improved appearance of glabellar lines

- **AboBotulinumtoxinA (Dysport®; Ipsen Pharmaceuticals)**\(^1\)
  - Licensed for distribution in the USA, UK and Europe
  - Indication: Cervical dystonia. In clinical trials in USA for other conditions

- **IncoBotulinumtoxinA (Xeomin®; Merz)**
  - Licensed for distribution in Europe, US
  - Indication: Cervical dystonia, blepharospasm, glabellar Lines

- **RimaBotulinumB (Myobloc®/NeuroBloc®*; Solstice Neurosciences)**\(^1\)
  - Licensed for distribution in the US, Europe, and Japan
  - Indication: Cervical dystonia

*Brand name in Europe.
Reported Uses Clinical Applications of BoNTs

- **Abnormal Muscular Contractions**
  - Strabismus\(^1\)
  - Cerebral palsy
  - Multiple sclerosis
  - Spasticity (Post-CVA or TBI)
  - Spastic bladder (OAB, detrusor)
  - Achalasia (esophageal)
  - Chronic anal fissures,

- **Other Applications**
  - Hyperhidrosis\(^1\)
  - Migraine & tension-type HA
  - Myofascial pain
  - Sialorrhea
  - Obesity
  - GU: OAB, BPH, sphincter dyssnergia

- **Focal Dystonias**
  - Blepharospasm\(^1\)
  - Cervical dystonia\(^1,2\)
  - Oromandibular facial-lingual
  - Spasmodic dysphonia
  - Task-specific (Writer’s Cramp)

- **Other Involuntary Movements**
  - Voice, head, and limb tremor
  - VII nerve facial spasm disorder\(^1\)
  - Hemifacial spasm
  - Palatal myoclonus
  - Tics


1. FDA-approved use for BOTOX®
2. FDA-approved for Myobloc®
Mechanism of Action

• All botulinum toxins
  – Work presynaptically
  – Block the release of acetylcholine
  – Cause graded amount of weakness depending on dose of toxin used

• Different serotypes have different
  – Intracellular targets
  – Duration of effect
  – “Potency”
Structure of Botulinum Toxin

- Light Chain (50kDa)
- Heavy Chain (100kDa)

Total complex size: 500-900kD
Neurotoxin Component: 150kD

Associated (Accessory) Proteins:
- HA
- NTNH
Mechanism of Action

*Types A and B bind to distinct acceptors*

- Botulinum Type A cleaves SNAP-25
- Botulinum Type B cleaves synaptobrevin (VAMP)

Hallett NEJM 1999;341 (2): 118
Normal Innervation
BoNT: Binding/Endocytosis
Light Chain Cleavage/Translocation
BoNT: SNARE Protein Cleavage
Denervation/Reinnervation
# Botulinum Neurotoxins: Clinical Differentiation

<table>
<thead>
<tr>
<th>Complex Size</th>
<th>Target Protein</th>
<th>Amount of Protein</th>
<th>Reconstituted pH</th>
<th>Final Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>900 kD</td>
<td>SNAP-25</td>
<td>5 ng/100U</td>
<td>Neutral</td>
<td>Vacuum Extraction</td>
</tr>
<tr>
<td>~900 kD</td>
<td>SNAP-25</td>
<td>12.5 ng/500U</td>
<td>Neutral</td>
<td>Lyophilization</td>
</tr>
<tr>
<td>~150 kD</td>
<td>SNAP-25</td>
<td>0.6 ng/100U</td>
<td>Neutral</td>
<td>Lypholization</td>
</tr>
<tr>
<td>500-700 kD</td>
<td>VAMP</td>
<td>50 ng/5000U</td>
<td>5.6</td>
<td>Solution</td>
</tr>
</tbody>
</table>

*Allergan, Inc-Botox® Package Insert. †Solstice Neurosciences-Myobloc™ Package Insert. ‡Ipsen Ltd-Dysport® Package Insert.
BoNT Storage and Dilution

• Onabotulinumtoxin A/Botox® is available in 100 unit vials. 1 vial is diluted with 1, 2, 4, or 8 mL of preservative-free 0.9% saline, yielding preparations of 10.0, 5.0, 2.5, or 1.25 units / 0.1 mL, respectively. Reconstituted Botox® should be used within 24 hours and stored at 2º - 8º C (200 unit vials available).

• AbobotulinumtoxinA/Dysport™ is available in 300 or 500 unit vials. For CD, one 500-unit vial is diluted with 1 mL preservative-free 0.9% saline, yielding a preparation of 500 units/mL. Reconstituted Dysport™ should be used within 4 hours and should be stored at 2º to 8º C

• IncobotulinumtoxinA/Xeomin BoNT-A® is available in 50 and 100 unit vials and reconstituted with 0.9% saline. Reconstituted Xeomin™ should be used within 24 hours and should be stored at 2º to 8º C. Unopened vials can be stored at room temperature, refrigerated or frozen.

• BoNT-B formulated as Myobloc® is supplied as a sterile injectable solution at a concentration of 5,000 units/mL. Vials contain 0.5 mL (2500 units), 1.0 mL (5000 units), or 2.0 mL (10,000 units)
Differences in Serotype Pharmacology: Clinical Considerations

- Toxin Subtype
- Differences
- Complex size
- Protein load
- Diffusion characteristics
- Intracellular target
- Activation level

Different Therapeutic Profile
- Dose
- Duration
- Migration
- Safety
- Antigenicity
BoNT: Clinical Effects on Muscle Overactivity

- Onset usually within 3 to 5 days; maximum effect at approximately 4 weeks

- Clinical benefit usually >12 weeks; may be extended with adjunctive therapy

- Can be used in conjunction with phenol, surgery, oral medications, intrathecal baclofen, and other rehabilitation modalities

The Basis for Botulinum Toxin Use in Pain

• Pain improvement was noted in initial dystonia and spasticity studies

• Brin 1986 series: cervical dystonia:
  – 64% motor improvement
  – 74% pain improvement

Facial expression of pain drawn by Sir Charles Bell  (From: The Anatomy and Philosophy of Expression: as Connected with the Fine Arts. 5th ed. London: Henry G. Bohn, 1865)

http://www.library.ucla.edu/libraries/biomed/his/PainExhibit/panel3.htm
Regulated Exocytosis Multiple Neurotransmitters/Neuropeptides Released From Vesicle

Adapted from *Trends in Cell Biology*, July 1997.
Goals/Clinical Benefits of BoNT Treatment of UMNS

- Improved passive and active function: better mobility, activity, daily function, and independence
- Increased patient comfort: less pain, better limb positioning for sitting and sleeping
- Reduced disfigurement
- Prevention or delay of musculoskeletal complications
- Improved quality of life and increased well-being
- Reduced burden of care
Summary Guidelines for BoNT Injection

- Determine which muscles need to be injected
- Determine the appropriate dosage and the number and volume of injections per session
- Use the smallest effective total dose and volume
- Use appropriate techniques to achieve precise injection and reduce the risk of complications
  - For limb muscles, use of electromyography (EMG) guidance or electrical stimulation may be helpful in identifying specific muscles (eg, smaller muscles such as flexor digitorum sublimis)
BoNT Technical Considerations

• Dose calculation: It may be more relevant to consider muscle mass, degree of spasticity, and patient body weight than the disease for dose calculation.

• Administration: BoNT is administered by intramuscular injection with relatively contained diffusion and avid binding to endplates of the motor neuron and muscle spindle.

• Injection technique: Methods of target muscle localization include the anatomical method, electromyographic guidance, electrical stimulation, and ultrasound.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomic approach</td>
<td>• No equipment needed&lt;br&gt;• Some muscles are accurately, quickly, and easily isolated</td>
<td>• Accuracy may be a problem&lt;br&gt;  – Examiner inexperience&lt;br&gt;  – Anatomic variation&lt;br&gt;  – Anatomic rearrangement&lt;br&gt;  • Due to spasticity, contractures, deformity, surgery&lt;br&gt;  – Difficulty isolating deep or overlapping muscles&lt;br&gt;  – Requires patient cooperation&lt;br&gt;  • Impaired motor control may cause difficulties</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• EMG signal falsely attributed to target muscle&lt;br&gt;  – Co-contraction, mass synergy&lt;br&gt;  – Impaired selective motor control may cause difficulties&lt;br&gt;  – Anatomic variations/rearrangements due to spasticity, surgery, deformities&lt;br&gt;  • Requires patient cooperation&lt;br&gt;  • Impaired motor control&lt;br&gt;  • May require sedation in children&lt;br&gt;  • Uses larger needle/more painful</td>
</tr>
<tr>
<td>EMG</td>
<td>• EMG is widely available&lt;br&gt;• Amplifier boxes are inexpensive&lt;br&gt;• Clinician familiarity with EMG&lt;br&gt;• Provides auditory feedback for needle localization and muscle activity</td>
<td></td>
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</table>
## Techniques for BoNT Injections

<table>
<thead>
<tr>
<th>Technique</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Electrical stimulation | • Equipment is inexpensive, widely accessible  
• May be more accurate than EMG  
• Some muscles are quickly and easily isolated | • Requires stimulator or EMG machine  
• Time-consuming/cost  
• Pain  
• Requires patient cooperation  
• Anatomic variations/ rearrangement due to spasticity, contracture, surgery may cause problems with accuracy  
• Difficult to isolate deep or overlapping muscles |
| Ultrasound         | • Improved accuracy  
• Involuntary muscle activity limits muscle localization with recruitment  
  – Visualize target muscle with/without AROM* | • Equipment availability  
• Cost  
• Steep learning curve for clinicians |

Some Side Effects of BoNTs

- Weakness
  - Local: most important is dysphagia
  - Systemic: minimal weakness, malaise

- Autonomic effects
  - Dry mouth, constipation

- Local effects
  - Pain, hematoma, infection, rash

- Antibodies (subsequent resistance)
Some Examples of Equipment for Specific Muscles

<table>
<thead>
<tr>
<th>Target Muscle</th>
<th>Needle Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craniofacial muscles</td>
<td>30-gauge, 0.5 inch</td>
</tr>
<tr>
<td>Superficial muscles, upper back</td>
<td>25- to 27-gauge, 1- to 1.5-inch</td>
</tr>
<tr>
<td>Scalenes</td>
<td>1.5-inch, 26- or 27-gauge, injectable, monopolar electrode</td>
</tr>
<tr>
<td>Deep compartment muscles of the lumbosacral region</td>
<td>Longer injectable monopolar electrode needles, 100 to 120 mm or longer spinal needles</td>
</tr>
</tbody>
</table>
BoNT Injection

- Administered by intramuscular injection\(^1\)
- Smaller muscles require only 1 injection site within the belly of the muscle\(^2\)
- For larger, longer, or wider muscles it is best to inject at 2 to 4 injection sites\(^2\)

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Nonresponse to BoNT Therapy

- Primary nonresponder: no response to initial injection
- Secondary nonresponder: relative or complete loss of efficacy at subsequent injections
- Reasons for nonresponse
  - Inadequate muscle injection technique
  - Inappropriate muscle selection
  - Dose may be too low
  - Change in pattern of muscle involvement
  - Soft tissue contracture
  - Neutralizing antibodies may be present (but in spasticity, rare)
- Tests for nonresponse: frontalis test, antibody assays (limited sensitivity, specificity)

BoNT: Resistance/Antibody Formation

- **Avoiding resistance**
  - Extend treatment interval as long as possible with at least 3 months between treatments
  - Avoid “booster” or “touch up” injections

- **Factors that influence antibody formation**
  - Toxin dose
  - Duration of treatment and frequency of injections
  - A prior immunoreistance to another BoNT serotype
  - Amount of protein load
  - Antigen quality and amount

Why Are Neutralizing Antibodies Important?

- Loss of therapeutic effect
  - Patients must seek alternatives that are less effective or are associated with more adverse events

- Therefore, it is important to minimize risk of antibody formation

- Use lowest dose in units
  - Less neurotoxin protein load (ng)$^{1,2}$

- Use longest interval between injections$^{1,2}$
  - This will be determined by the duration of effect

Post BoNT Injection Instructions

• Explain that effect of BoNT will be evident in 3 to 7 days

• Initiate aggressive stretching of injected muscles, may include splinting and bracing

• Initiate strengthening of opposing muscles

• Functional retraining with therapist

• No re-injection of any BoNT for at least 90 days
BoNT may be useful for treating a wide variety of conditions by toxin mediated reduction in neurotransmitter release. This includes blocking of acetylcholine at the
- NMJ of muscles
- Muscle spindles
- Neur glandular junction

Antinociceptive effects of BoNTs may be due to
- Direct effects of the toxin i.e. reduced release of pain neurotransmitters
- Indirect effects of reduced muscle contraction/spasm

Commercially available BoNTs are non-interchangeable