Overview of Botulinum toxins

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“Sausage Poisoning”

Justinius Kerner
1786-1862

Kerner’s 2nd monograph on “fatty poison” (1822)
The pioneers of botulinum toxin therapeutics

Edward Schantz, PhD
Allan Scott, MD

Botulinum toxin: First clinical preparation

- 1979: Original batch BoNTA (Oculinum)
  - 150 mg was used for more than 250,000 injections in humans.
  - Approximately 20% developed resistance
Objectives

- Describe the structure and mechanism of botulinum toxins
- Distinguish between the brands and serotype
- Outline efficacy and safety data
- Describe basic treatment principles

Botulinum Toxin

- Most potent neurotoxin known
- Nanogram amounts sufficient to be lethal
- Listed among 6 highest risk threat agents of bioterrorism by the Centers for Disease Control and Prevention (CDC)
Botulinum Toxin

- Produced by clostridium botulinum
- 7 distinct serotypes of toxin
  - A, B, C, D, E, F, G
    - Subtypes distinguished through genetic sequencing
  - Serotypes A and B available for human use
  - Serotype X recently identified
    - Cleaves VAMP 1,2,3 as others, but also VAMP 4,5,Ykt6

- Botulinum toxin complex
  - Hemagglutinin and non-hemagglutinin proteins
  - Neurotoxin

Zhang S et al. Nat Comm 2017

Botulinum Neurotoxin: A Marvel of Protein Design

A

B

Chen et al. Toxins 2012, 1196-1222
## Botulinum Toxin Serotypes: Cleavage of SNARE Proteins

<table>
<thead>
<tr>
<th>Toxin Type</th>
<th>Substrate</th>
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<tbody>
<tr>
<td>BTX A</td>
<td>SNAP-25</td>
</tr>
<tr>
<td>BTX B</td>
<td>VAMP/Synaptobrevin</td>
</tr>
<tr>
<td>BTX C</td>
<td>Syntaxin SNAP-25</td>
</tr>
<tr>
<td>BTX D</td>
<td>VAMP/Synaptobrevin</td>
</tr>
<tr>
<td>BTX E</td>
<td>SNAP-25</td>
</tr>
<tr>
<td>BTX F</td>
<td>VAMP/Synaptobrevin</td>
</tr>
<tr>
<td>BTX G</td>
<td>VAMP/Synaptobrevin</td>
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</tbody>
</table>

### BoNT

- **Interrupts neuromuscular transmission**
  - Muscle weakness
- **Local effect: predominant in the injected muscle**
- **Reversible**
  - Recovery of NMJ in approximately 3-6 months
Recovery of NMJ following BoNT

Newer concepts of BoNT mechanism

• May not be only a peripheral effect

• Central effects important (muscle afferents)
  - Normalization of altered brain network activity
  - Normalization of left/right asymmetries of white matter microstructure (fractional anisotropy)

Brodoehl et al. Neuroimage Clin 2019
Blood A et al. Fron Neruol 2019
Practice Guideline Summary

Table 2: Evidence-based conclusions and recommendations for the efficacy of various botulinum neurotoxin formulations by indication

<table>
<thead>
<tr>
<th>Indication</th>
<th>Level A effective</th>
<th>Level B possibly effective</th>
<th>Level C possibly effective</th>
<th>Level D insufficient evidence</th>
<th>Level E ineffectiv</th>
<th>Level F ineffectiv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blepharospasm</td>
<td>OnabotulinumtoxinA, IncobotulinumtoxinA</td>
<td></td>
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<tr>
<td>Cervical dystonia</td>
<td>OnabotulinumtoxinA, IncobotulinumtoxinA, RimabotulinumtoxinB</td>
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</tr>
<tr>
<td>Upper limb spasticity</td>
<td>OnabotulinumtoxinA, IncobotulinumtoxinA</td>
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<td></td>
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<td></td>
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<tr>
<td>Lower limb spasticity</td>
<td>OnabotulinumtoxinA, IncobotulinumtoxinA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic migraine</td>
<td>OnabotulinumtoxinA</td>
<td></td>
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<tr>
<td>Episodic migraine</td>
<td>OnabotulinumtoxinA</td>
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<tr>
<td>Tension-type headache</td>
<td>OnabotulinumtoxinA</td>
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</tr>
</tbody>
</table>

Abbreviations: aboBoNT-A = abobotulinumtoxinA, incBoNT-A = incobotulinumtoxinA, onaBoNT-A = onabotulinumtoxinA, rimBoNT-B = rimabotulinumtoxinB.
Clinical applications for BoNT

<table>
<thead>
<tr>
<th>Dystonia</th>
<th>Pain</th>
<th>Gastrointestinal disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Blepharospasm*</td>
<td>• Chronic migraine*</td>
<td>• Gastroesophageal reflux</td>
</tr>
<tr>
<td>• Hemifacial spasm*</td>
<td>• Osteoarthritis</td>
<td>• Delayed gastric emptying</td>
</tr>
<tr>
<td>• Spasmodic dysphonia</td>
<td>• Plantar fasciitis</td>
<td>• Achalasia</td>
</tr>
<tr>
<td>• Trismus</td>
<td>• Temporomandibular joint disorders</td>
<td>• Anal fissures</td>
</tr>
<tr>
<td>• Limb dystonia</td>
<td>• Neurotic pain</td>
<td>• Chronic sialorrhea in PD</td>
</tr>
<tr>
<td>• Oromandibular dystonia</td>
<td>• Lower back pain</td>
<td>• Upper and lower limb spasticity</td>
</tr>
<tr>
<td>Strabismus*</td>
<td></td>
<td>• Detrusor overactivity</td>
</tr>
<tr>
<td>Spasticity</td>
<td></td>
<td>• Hyperhydrosis</td>
</tr>
<tr>
<td>• Upper limb</td>
<td></td>
<td>• Vaginism</td>
</tr>
<tr>
<td>• Lower limb</td>
<td></td>
<td>• Pelvic pain</td>
</tr>
<tr>
<td>Other neurological disorders</td>
<td></td>
<td>• Erectile dysfunction</td>
</tr>
<tr>
<td>• Tic disorders</td>
<td></td>
<td>• Vaginitis</td>
</tr>
<tr>
<td>• Tics</td>
<td></td>
<td>• Vulvodynia</td>
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<tr>
<td>• Cerebellar syndrome</td>
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<td>• Vaginism</td>
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<tr>
<td>• Parkinson disease</td>
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<td>• Analgesic action</td>
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<td>• Restless Leg syndrome</td>
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<td>• Vaginal hyperplasia</td>
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<tr>
<td>• Syringomyelia</td>
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<td>• Vaginism</td>
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<tr>
<td>• Dyssynergia</td>
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<td>• Analgesic action</td>
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<tr>
<td>• Bruxism</td>
<td></td>
<td>• Vaginism</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td>• Vaginism</td>
</tr>
</tbody>
</table>

FDA approvals for Botulinum toxins

- Blepharospasm
- Cervical dystonia
- Strabismus
- Chronic sialorrhea in PD
- Upper and lower limb spasticity
- Chronic migraine
- Hyperhydrosis
- Detrusor overactivity
- Cosmetic indications
  - Glabellar lines, canthal lines
Newer versions of BoNT with pilot clinical data

• BoNT Type E
  - Rapid onset (days)
  - Short duration of effect (4 weeks)

• DaxibotulinumtoxinA with novel excipient
  - Long duration of effect

Mechanism proposed for BoNT-E

• Similarities to BoNT-A
  - Binds to SV2 on presynaptic terminal
  - Internalized via synaptic vesicles
  - Translocates active protease subunit into cytosol
  - Cleaves SNAP-25 (different location than BoNT-A)

• Differences from BoNT-A
  - BoNT-E light chain translocates more rapidly into the neuron cytosol
  - BoNT-E light chain protease activity cleared rapidly in intoxicated neurons

Keller et al. Bioche 2004
Potential benefits of rapid onset, short duration BoNT

- Rapid onset treatment of muscle related pain (spasms/contractions)
- Potential to be a longer-acting, non-opioid without the side effects and addictive potential of opioids
- Short duration treatment effect allowing “test” of pattern of injection before injection of longer duration BoNT
- Short term “booster” improvement for suboptimal results from longer duration BoNT without the overlap at next injection visit
  - ? Immunoresistance
- Contribute to healing after injury, reduce scar formation by reducing muscle activity

Possible longer duration BoNTA

DaxibotulinumtoxinA

- Purified 150 kDa BoNTA without accessory proteins
  - TransMTS® carrier peptide (RTP004)
    - Novel excipient
    - May reduce spread of toxin, extend the half life of effect
- Safety and tolerability study completed
  - 34 CD patients enrolled, 25 followed to week 24
  - Low dose (100-240U), High dose (300-450U)

Jankovic et al. Move Disord Clin Prac 2018
DaxibotulinumtoxinA for cervical dystonia
Results of open label tolerability study

• Side effects:
  - Dysphagia 14% all mild
  - Muscle weakness 5% (1 mild, 1 moderate)
  - Neck pain 3%

Potential benefits of longer duration toxin

• Less waning of effect between injections
  - Improved patient satisfaction
  - Longer optimal benefit

• Fewer injections over time
  - Less inconvenience for patients
  - Less expense?
  - Less likelihood of development of neutralizing antibodies?
Other BoNT A

- PrabotulinumtoxinA (FDA approved for cosmetic only)
- Evosyal
- Linurase
- Chinese BTX-A
  - Chintox
  - Prosigne
  - Lantox
  - Redux
- Neuronox/Meditoxin/Botulift

Can BoNT Brands and Serotypes Be Used Interchangeably?

**No!**

- Botulinum brands are unique drugs. There is no interchangeable dosing.
- When starting a new brand, base dosing on the package insert, clinical studies, and the patient
- Consider changing from one brand to another:
  - if there is resistance to one serotype
  - based on patient need or insurance
  - co-pay programs
- Avoid “rotating” brands and serotypes
Treatment Principles

- Know functional neuroanatomy
- Select appropriate muscles
- Dosing for each muscle
- Target injection into intended muscles
- Follow up for benefit and side effects

Treatment goals

- Establish clear treatment goals
  - Reduction of pain
  - Improvement in posture/movement
  - Increase in function
  - Enhancement of QOL

- Discuss with patient!
Safety: Black Box Warning

- The effects of all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects.
- Swallowing and breathing difficulties can be life threatening, and there have been reports of death.
- Risk probably greatest in children treated for spasticity, but also occur in adults.
  - particularly patients with underlying conditions predisposing them to these side effects.

Basic treatment principles

- Muscle selection
- Muscle localization for injection
  - Clinical, Electromyography, Ultrasound
- Dose into each muscle
- Number of injection sites per muscle
- Outcomes
  - Benefit/side effects
  - Use of scales, global impressions.
Know functional anatomy
Is Electromyography Useful?

- Increases the magnitude of improvement at the same dose of BoNT in single blind study
  - Comella 1992
- Targeting muscle is not accurate without EMG guidance
  - Van Gerpen 2000
- Sternocleidomastoid “missed” in 20%; splenius capitis and deeper muscles missed up to 60% of the time without EMG guidance
  - Brans 1996
- Accuracy in forearm approximately 37% without EMG
  - Molloy 2002

Ultrasound Guidance

- Direct visualization of muscles for injection
  - Used complementary to clinical examination
  - Offers comparable benefit as EMG when injected for spasticity (both EMG and USG better than surface landmarks)
  - Picelli 2013
- May better limit spread, decrease side effects (such as dysphagia)

Caveats
- Ultrasound equipment is expensive
- Requires specific training
Failure to Benefit

• Common reasons for lack of efficacy
  - Injection into the wrong muscles
  - Inadequate dosing
  - Unrealistic patient expectations
  - Stress-induced exacerbation

• Uncommon reasons for lack of efficacy
  - Change in dystonia
  - Immunoresistance (? <2% patients)

Manage patient expectations

• Symptom treatment, not a cure
  - Will not improve 100%
  - May take an injection or two to find right muscle pattern and dose

• Profile of Clinical Response
  - Onset: 3-10 days
  - Peak effect: 2-4 weeks
  - Duration of benefit:
    • 10-16 weeks
Online Survey through international dystonia foundations

- 1071 self-identified as CD
- 907 receiving BoNT
  - 56% fairly/very satisfied
  - 25% fairly/very dissatisfied
    - 46% no benefit
    - 33% adverse events

BoNT in a real world setting

- Why do patients discontinue?
  - Lack of efficacy
    - Dose/muscle selection; complex CD
  - Adverse effects
  - Expense
  - Unrealistic expectations
  - Inconvenience

Comella, Bhatia et al, J Neurol 2014
Comella and Bhatia, J Neurol 2015
Brashear et al. Mov Disord 2000
Jinnah et al J Neurol 2016
Botulinum toxin: health care coverage

- Preauthorization from health care coverage often required prior to treatment
- Diagnosis code, procedure code, drug code
- Consider drug company reimbursement programs for support of patient expenses (deductible, co-pay) if not Medicare in the US

Overview
Botulinum toxins

- Treatment of choice for focal dystonia, spasticity and other disorders
- Can improve posture, pain, quality of life, activities of daily living if injected appropriately
Future directions for botulinum toxins

- New formulations of botulinum toxin
  - Shorter duration toxins
  - Longer duration toxins
  - Fewer adverse effects
  - "Designer" toxins
- Improved muscle targeting
  - Muscle imaging
  - Ultrasound
- New indications