Botulinum Toxins as Neuromodulators in Chronic Pain Management

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Learning Objectives

- Review the proven and proposed mechanisms of action of botulinum toxins (BTX)
- Contrast the different botulinum toxin products commercially available in the US
- Describe the emerging role and novel indications for the use of botulinum toxins in pain management
Disclosures

- Consultant/Speakers Bureau: Allergan
- Speakers Bureau: Ipsen, Merz

Neurotoxins as Neuromodulators

- Emerging role of botulinum neurotoxins in the management of complex/intractable chronic pain syndromes, including neuropathic pain more so than those believed to be of muscle overactivity etiology
- Chemical neuromodulation in neurogenic inflammation
- More players: wider and more promising horizon and greater availability but greater potential for errors and problems...
The Current Playing Field....

<table>
<thead>
<tr>
<th>Name</th>
<th>Type</th>
<th>Forms</th>
<th>Process</th>
<th>Indications</th>
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</thead>
<tbody>
<tr>
<td>ULS (Xeomin)</td>
<td>A</td>
<td>100U, 200U,</td>
<td>Vacuum-drying (NSS/albumin)</td>
<td>Strab, CD, BS, CN7 d/o, AH,</td>
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<td></td>
<td></td>
<td>50U</td>
<td></td>
<td>Cosm, U&amp;LLS, CMH, HB</td>
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<tr>
<td>OnabotulinumtoxinA (Botox® - Allergan, Inc.)</td>
<td>A</td>
<td>300U, 500U</td>
<td>Lyophilized (ferment/precipit/dialysis/chromatography)</td>
<td>CD, Cosm, ULS, LLS (child)</td>
</tr>
<tr>
<td>AbobotulinumtoxinA (Dysport™ - Ipsen, Ltd)</td>
<td>A</td>
<td>50U, 100U</td>
<td>Lyophilized Albumin, sucrose</td>
<td>CD, BS, Cosm</td>
</tr>
<tr>
<td>IncobotulinumtoxinA (Xeomin® - Merz)</td>
<td>B</td>
<td>2.5k U, 5k U, 10k U</td>
<td>Ferm/precipitation/chromatography</td>
<td>CD</td>
</tr>
<tr>
<td>RimabotulinumtoxinB (Myobloc® - Solstice)</td>
<td>B</td>
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Botulinum Toxins in the US
**Botulinum Toxins**

- **BOXED WARNING**
  - May spread to areas distant to site of injection producing symptoms consistent with botulinum toxin effects
  - Risk probably greatest in children treated for spasticity

- *** Units not interchangeable; No conversion factors recommended
- *** None approved for use in children

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**BTX Uses**

- Dystonias
- Spasticity
- Tremors
- Cosmetic/wound healing
- Blapharospasm/CN VII disorders
- GI: achalasia, anismus, obesity
- GU: neurogenic bladder, vaginismus, BPH
- Pain management...
**BTX in Pain Management**

- Myofascial pain syndromes
  - Upper back/neck
  - TOS
  - Piriformis syndrome
- CLBP
- Facial and head pain (migraines, occipital neuralgia, TN, atypical facial pain, TMJ pain)
- Intractable joint pain
- Lateral epicondylitis/plantar fasciitis
- Focal neuropathies
- Vascular pain (Raynaud’s)
- Postradiation fibrosis pain

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**Analgesia With Botulinum Toxins**

*Initial thinking on BTX-A pain relief came from CD literature*

- 1980s: Clinical observations after BTX-A injections for cervical dystonia (CD)
  - Benefits on pain occurred sooner and outlasted posture, suggesting a dual effect (Brin, et al. 1986; Jankovic, et al. 1987)
Antinociception Observations Using Botox®

▪ Inhibition of release of AcH and sP (not NE) in rabbits (iris)¹
▪ Inhibition of release of AcH and sP (vesicle-dependent exocytosis) in cultured DRG neurons induced by capsaicin²
▪ sP inhibition (vesicle fusion inhibition) in the embryonic rat DRG model³


Antinociception Observations Using Botox (cont’d)

▪ Dose dependent inhibition of CGRP in TG nerve of rats¹
▪ Block release of glutamate induced by formalin and decreased activity at the WDR neuron upon stimulation (second pain)²
▪ Fos, a product of c-fos gene that is expressed with neuronal stimuli, was prevented³

¹ Durham P. Cephalgia 2003; 23(7): 690
² Aoki KR. Headache 2003; 43(1): S9-15
³ Cui ML. Pain 2004; 107(1-2): 125-33
Peripheral Sensitization Leads to Central Sensitization

Peripheral Stimulation → Release of Glutamate and Peptides → Antidromic Activation

Peripheral Sensitization
Release of glutamate, substance P, CGRP
Increased afferent signals

Central Sensitization

Antidromic Activation → Additional Activation

Prevents:
• Release of Glutamate, CGRP, SP
• Peripheral Sensitization
• Formalin Phase II pain
• TRPV1 expression

Botulinum Toxin Prevents Peripheral Sensitization (Direct) and Central Sensitization (Indirect)

Botulinum Stimulation

Prevents:
• Release of Glutamate, CGRP, SP
• Peripheral Sensitization
• Formalin Phase II pain
• TRPV1 expression

Indirectly Prevents:
• Central Sensitization
• c-Fos expression
• Receptive field expansion
• Allodynia

Clinical relevance of these preclinical results remain to be established
Current Theory: Regulated Exocytosis

The common link between both effects

BTX-A cleaves SNAP-25, inhibiting exocytosis of co-located substances

- BTX-A inhibits ACh release
- BTX-A inhibits vesicular release of neuropeptides

Clinical Applications
Headaches

- FDA-approved for chronic migraine prophylaxis
- Not tension-type HAs
- Mechanism—proposed to be related to action at the TG nucleus
- Still difficult to predict responders
  - Concept of “exploding” vs “imploding”
  - Ocular migraine/menstrual migraine

IHS Classification

- A1: Migraine
  - A1.1. Migraine w/o Aura
    - Pure menstrual
    - Menstrually-related
    - Nonmenstrual
  - A1.2. Migraine w/ Aura
  - A1.5. Chronic Migraine
Chronic Migraine Headache

BTX in MPS: Theories

- Reduction of intrafusal muscle spindle discharges
- Changes in sympathetic transmission
- Reduction of the inhibitory effect of Renshaw cells on the Ia inhibitory interneurons
- Reduction in muscle spasm
- Analgesic effects of BTX
**Myofascial Pain Syndromes**

- Most consistent and better studied responses in clinical practice have been in the cervicothoracic region¹
- Compartment techniques vs trigger point approach—midbelly of muscle, not tender areas (TPIs); may be targeting motor points²
- Follow the pain but beware of pain referral patterns³


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**Forward-Head Syndrome**

- Cervical protraction, capital extension with shortened cervical paraspinals, elevated and shortened upper trapezius and levator scapula, scalene and pectoral shortening
- Eccentric lengthening of the rhomboids and middle trapezius
- Scapular protraction/internal rotation of the shoulder girdles
Forward-Head Syndrome (cont’d)

Thoracic Outlet Syndrome

- Not a common condition
- High index of suspicion needed and special techniques\(^1\)
- Target scalenes, particularly, anterior/middle\(^2,3\)
- Technically difficult injection: risk of dysphagia and neurovascular injury

\(^1\) Cuevas-Trisan R, Cruz-Jimenez M. Am J Phys Med Rehabil. 2003; 82(9) 712-715
\(^3\) Odderson I. Arch Phys Med Rehabil 2008
Scalene Contribution

Part of df/dx of “sciatica”
- Seen often postspinal surgery, or prompting it
- Commonly postural; less common compressive
- 100 units of Botox® IM¹,²
- Must use targeting techniques (EMG/fluoro)
- A more effective than B with less S/Es³


Piriformis Syndrome
Piriformis Syndrome (cont’d)

Low Back Pain

- RCT – double blind
- \( N = 31 \) CLBP (> 6 months; lateralized)
- 15 received 200 U of Botox®
  (40 units/site – 0.4 cc); 16 received NSS
- Unilateral paraspinals
  (5 levels – L1-L5 or L2-S1)

Foster L, et al Neurology 2001; 56:1290-1293
Postlaminectomy Syndrome

- 26 consecutive patients with persistent somatic and radicular pain, who had failed multiple other treatments
- Treated with repeated BTX-A injections every 3 months for over 3 years
- Significant pain reduction and functional improvement sustained
- Subgroup of 10 patients most benefited: postlaminectomy patients with cutaneous allodynia as a complication

Intractable Joint Pain

- Degenerative joint disease
- Limited/emerging evidence¹
- Working theory: inhibition of low-grade inflammatory mediators
- Role of IL-1
  - Blocking of IL-1 receptor signaling complex²


BTX-A in Joint Pain

- What has been reported to date?
  - 1 paper: review of long term use, retrospective
    (open label; 3 knees, 3 ankles, 9 shoulders; bupivacaine as diluent)¹
  - 6 abstracts: hip, knee, ankle, shoulder, zygapophyseal, sternoclavicular, sacroiliac

- Mahowald et al., 2006 (American Rheumatological Society Annual Meeting)
  - Moderate and severe knee pain secondary to OA
  - N = 37; randomized to 100U Botox w/ lidocaine vs lidocaine/NSS IA

¹Mahowald M, Singh J, Dykstra D. Neurotox Res 2006
BTX-A in Joint Pain (cont’d)

- Severe OA: sig decrease in WOMAC-pain and WOMAC physical function, walking pain, day pain, night pain
- Moderate OA: sig decrease in day pain only

Postarthroplasty Intractable Pain

- Of particular interest given lack of options
- Must r/o correctable causes: low grade infection, loosening, hardware failure
- 100 units intraarticular - strict sterile technique
- Main goal: opioid-sparing effect
- Personal experience: n = 8

Kamen ICoN 2006 Meeting Abstract, Hollywood, FL
Other Painful Syndromes

Lateral Epicondylitis

Wong¹: 60 U Dysport®

- RCT; N = 60 (30 placebo-saline/ 30 active), significant differences in pain reduction
  (66% in BTX group) at 4 & 12 weeks; no statistically significant difference in grip strength but mild paresis of finger extensors reported
  in 13% of BTX group

Lateral Epicondylitis (cont’d)

Hayton² - 50 U Botox®

- RCT; N = 40 (20 - placebo / 20 - active – IM 5cm distal to max point of tenderness at the lat epicondyle in line with mid-wrist), results at 3 months:
  - no significant difference in grip strength, pain, and QOL


Plantar Fasciitis

- Babcock¹: N = 43 feet (27 subjects); RCT (70U Botox vs NSS)
  - 40 U over medial tender aspect of heel
  - 30 U arch of foot at most tender area, between an inch anterior to the heel and middle of the foot
  - Statistically-significant improvement at 3 and 8 weeks:
    - Maryland Foot Score
    - Pain
    - Pressure algometry

Plantar Fasciitis (cont’d)

- Placzek: N = 9; open label
  - 1 injection of 200U of Dysport subfascially into painful area
  - Improvements in rest and weight-bearing pain (up to 14 weeks)


Facial Pain

- Atypical, TN, TMJ (including bruxism\(^1\)), etc
- Various studies
- Dose: highly variable; 20-150 U
- Injection site: variable; depends on painful area; SQ/intradermal\(^2\)
- Maintain cosmetic symmetry

\(^2\) Cuevas-Trisan R. AAPM Meeting 10/07, LV, NV
Occipital Neuralgia

- Retrospective series (N=6) severe occipital neuralgia
  - Failed conservative and interventional therapies
  - GON blocks using BTX-A 50U/side (100U if bilateral)
  - Significant decreases in pain / improvement in Pain Disability Index (PDI) @ 4 wks in 5 patients
  - Duration of the pain relief averaged 16.3 ±3.2 weeks (median 16 weeks)
- Others

1 Kapural et al. AAPM meeting 2/07 New Orleans

Raynaud’s Syndrome

- Retrospective series (N=33) severe Raynauds
  - Failed conservative and interventional therapies; some amputations
  - Technique using BTX-A 100U
  - 85%: significant decreases in pain/ improvement in perfusion
  - Duration of relief averaged
    - 16.3 ±3.2 wks (median 16 wks)

Raynaud’s Syndrome

Postradiation Fibrosis Pain

- Two publications on the use of toxins for management of symptoms associated with postradiation fibrosis have reported a possible role yielding modest results\textsuperscript{1,2}
- Patient selection and dosing paradigms are yet to be determined
- Recent case report with remarkable results\textsuperscript{3}

\textsuperscript{1} Stubblefield Arch Phys Med Rehabil 2008
\textsuperscript{2} Bach et al. Eur Ann Otorhinolaringology 2012
\textsuperscript{3} Cuevas-Trisan R. (Abst) PainWeek 9/13, LV, NV
OTHER USES

- Stump/neuroma pain
- Intractable pes anserinus bursitis
- Other focal peripheral nerve injuries

Focal Neuropathies

- Focal neuropathy case – painful paresthesias/dysesthesias in distal leg
- Excellent relief with SQ injections to affected area
Other Toxins

- Chinese type A botulinum toxin (CBTX-A)—Lanzhou Biological Products Institute, China; commercially available since approximately 2001
- Dysport RU (Ready Use)—20U, 50 U, 75 U already reconstituted syringe currently on phase 3 trials
- Neuronox®—type A manufactured by Medy Tox, Inc., a Biotech Company in Korea; commercially available since 2006
- Many others and lots of counterfeits; check alibaba.com for tons of Chinese products
Current Clinical Trials

- Raynaud’s—Southern Illinois Univ, Emory, Johns Hopkins
- Skin injections for SCI-related pain—Mt. Sinai, NY
- Chronic neck and back pain—VA Connecticut
- Pelvic pain in endometriosis—NINDS (NIH)
- Shoulder & knee OA pain—Minneapolis VAMC
- Peripheral neuropathic pain—France (completed)

Current Clinical Trials (cont’d)

- Cervicobrachial MPS—UCLA (completed)
- TOS—University of British Columbia (completed)
- Neuroma pain—Southern Illinois Univ/Stanford
- LE CPRS—Stanford (completed)
- TKR pain—University of Minneapolis—completed
- Painful diabetic neuropathy—Taipei Medical Center
Current Clinical Trials (cont’d)

- Ganglion impar injections for proctalgia—Nantes University
- Psoriasis—University of Minnesota
- Peyronie’s disease, vaginismus, restless legs, alopecia areata

Source: NIHclinicaltrials.gov as of 8/1/16

Thanks!