Botulinum Toxin and Pain

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Disclosures

• Speakers Bureau for Allergan and Pfizer
Botulinum Toxin for Pain
Learning Objectives

• Review the mechanism of action for botulinum toxin
• Review FDA approved uses
• Recognize that pain is non FDA approved use
• Review efficacy studies for non FDA approved uses

Painful Conditions that have been treated with Botulinum Toxin (I am not recommending all these treatments)

• Cervical Pain Associated with Cervical Dystonia
• Headache
• Myofascial Pain
• Plantar Fasciitis
• Piriformis Syndrome
• Chronic Low Back Pain
• Joint Pain (Knee, shoulder, wrist)
• Lateral epicondylitis and other tendonitis
• Chronic pain and pelvic floor spasm
• Complex Regional Pain Syndrome
• Chronic Interstitial Cystitis
• Painful bladder syndrome
• Radiation fibrosis syndrome
• Hallux valgus
• Post whiplash neck pain
• Phantom- and stump pain
• Chronic facial pain associated with masticatory hyperactivity
• Temporomandibular pain
• Spastic shoulder pain
• Spinal cord pathology
• Post-herpetic neuralgia
Types of BoNT Currently Available

• BoNT Type A:
  – Botox® (Allergan, Inc., USA)
  – Dysport® (Ipsen, Ltd., UK) [coming soon to US]
  – Xeomin® (Merz Pharmaceuticals, Germany)
  – Chinese version (Lanzhou Biological Prod., ROC)

• BoNT Type B:
  – Myobloc® (Solstice Neurosciences, Inc., USA)

Botulinum Toxin B
Current FDA-Approved Uses

• Blepharospasm
• Glabellar rhytides
• Cervical dystonia
• Hemifacial spasm
• Strabismus
• Severe primary axillary hyperhidrosis
• Spasticity (in Canada only)
Botulinum Toxin B
FDA approval

- FDA approval for cervical dystonia

Botulinum toxin timeline

- 1981: “Oculinum” (BoNT-A) used to treat strabismus in humans
- 1989: US FDA approves BoNT-A for the Tx of strabismus, blepharospasm & hemifacial spasm
- 2000: BoNT-A & B approved for the Tx of cervical dystonia
- 2002: BoNT-A approved for temporary improvement of mod-to-severe glabellar lines
- 2004: FDA approves BoNT-A to treat severe primary axillary hyperhidrosis
Types of Botulinum Toxin

- Botulinum toxin exists in eight distinct subtypes designated as A, B, C₁, C₂, D, E, F, and G
- All subtypes, except C₂, are capable of inhibiting acetylcholine release;
  - C₂ appears to be a lethal vasodilating toxin
  - C and D affect animals only
- Only toxins A and B have been approved by the U.S. Food and Drug Administration (FDA) for use in human beings  
  Cooper 2007

Basic Mechanism

- At the neuromuscular junction (NMJ), BoNT:
  - Binds pre-synaptically
  - Is internalized into the presynaptic neuron
  - The light chain from the BoTN is released into the cytosol
  - SNAP-25 (A, E) or Synaptobrevin/VAMP (B, D, F, G) are cleaved, preventing acetylcholine release
Botulinum does not only inhibit at the Neuromuscular junction

- Acetylcholine in the intrafusal muscle fibers (muscle spindle)
- Acetylcholine in sweat glands
- Decrease in other neuropeptides that happen to be related to pain modulation.
  - Glutamate
  - Substance P
  - Calcitonin Gene Related Peptide (CGRP)
  - Norepinephrine
**Botulinum Toxin and Pain**

- Inhibition of acetylcholine release at the NMJ is unlikely to fully explain the effects of BoNT-A in pain disorders
- The exact mechanism of action of BoNT in causing analgesic effect is not known
- BoNT-A may exert its anti-nociceptive effects through modification of perception-of-pain signals, or direct inhibition of peripheral nociceptive fiber sensitization, which in turn, indirectly reduces central sensitization

**How Can BoTN Decrease Pain?**

- Reduction of Muscle contractions in alpha motor neuron
- Reduction of 1A afferent activity from the muscle spindle (gamma motor neuron)
  - This may decrease muscle spasm and contraction that will decrease pain
- Decrease in neuropeptides.
  - *Glutamate, Substance P, Calcitonin Gene Related Peptide (CGRP)*
- Alteration in CNS processing
Effect on central pain

Possible areas of BTX Affect in Pain

From Headache, 2003; 43[suppl 1]: S9-15

BoNT in the CNS

• Despite reports of the systemic distribution of injected BoNT, direct effects on the central nervous system have not been clearly demonstrated
  – With its size of 150 kDa, BoNT cannot penetrate the blood-brain barrier

BoNT in the CNS

• Possibility of retrograde neuronal transport of radioactively labeled BoNT from the muscle into the dorsal root and the spinal cord was first suggested by Wiegand et al. in 1976
  • No trans-synaptic transport was observed
  • Time lag associated with the retrograde transport was so long that BoNT was apparently inactivated before it reached the central nervous system
BoNT in the CNS

- 1 review suggests that BoNT-A has a complex mechanism of action, and while acting directly at the NMJ, the toxin most probably alters sensory inputs to the CNS
  - Indirectly inducing 2° central changes
  - Limited evidence for direct central changes
    Currà, et al., Movement Disorders, 2004

Botulinum Toxin and Pain

- BoNT-A has shown efficacy at the autonomic pre- and post-ganglionic synapses and the synapse-rich areas of the hippocampus and cerebellum, as well as Renshaw cells (ventral horn) *in vitro* but not *in vivo*
- When injected into cat gastrocnemius. muscle, the neurotoxin left these central mechanisms unchanged
  Currà, et al., Movement Disorders, 2004
Analgesic effects of botulinum toxin A in Humans (I)

• Assessed for a possible direct analgesic effect of BTX-A on C and A-delta fibers in skin
• A randomized, double-blind, placebo trial
• 16 healthy volunteers received 30 U BTX-A intradermally into one forearm and pure saline into the other.
• Thermal sensory testing of heat pain (threshold and tolerance) and neuroselective current sensory testing of current pain threshold/tolerance were performed at baseline and 3, 14, and 28 days after treatment.

Voller Neurology 2003 Austria

Analgesic effects of botulinum toxin A in Humans (II)

• On day 28 capsaicin was administered simultaneously into both forearms to evaluate a possible peripheral effect and central effect on pain processing and on the axon reflex flare.
• RESULTS: no significant difference in any of the perception outcome measures between BTX-A and placebo pretreated areas.
• Flare areas occur as a result of the release of neuropeptides after capsaicin application showed no differences.
• The results suggest that pain reduction after BTX-A treatment is mediated through its effect on muscle tone rather than a direct analgesic effect.

Voller Neurology 2003 Austria
Cervical Pain Associated with Cervical Dystonia

*Cochrane Database Syst Rev. 2005*

- Cervical dystonia is involuntary posturing of the head and frequently associated with neck pain.
- 680 patients treated in 13 high quality RCT with BoTN-A
- Statistically and clinically significant improvements on objective rating scales and subjective rating scales (pain relief)
- Side effects include: neck weakness, dysphagia, dry mouth/sore throat and voice changes hoarseness
- Repeat injections continue to work for most patients

*Cochrane Database Syst Rev. 2005*

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Cervical Pain Associated with Cervical Dystonia

*Cochrane Database Syst Rev. 2005*

- Botulinum toxin type B for cervical dystonia
- Meta-analysis of three RCT 308 participants
- Clear improvement in:
  - Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) (includes pain and disability)
  - Subjective rating scales
    - Patient Analog Pain Assessment
    - Patient Global Assessment of Change,
    - Investigator Global Assessment of Change
- Adverse events included dysphagia and dry mouth

*Cochrane Database Syst Rev. 2005*
Pain and Cervical Dystonia

- Multiple studies using evidence based criteria show efficacy of BoTN – A and BoTN – B
- There is no solid evidence to say which is better BoTN–A or BoTN – B  
  
Cochrane 2005
- Making the diagnosis of CD is frequently difficult and subjective.
- These studies showed improvement in motion and function in addition to pain.
- This is basically the end of the FDA approved indications for pain

Botulinum Toxin and Pain Treatment in Specific Conditions

- These are off label non FDA approved
Expensive Placebos Work Better than Cheap Placebos (I)

• 82 healthy paid volunteers in Boston,
• Told this was a new opioid analgesic
• After randomization, half of the participants were informed that the drug had a regular price of $2.50 per pill and the other half that the price had been discounted to $0.10 per pill
  – (no reason for the discount was mentioned).
• All participants received identical placebo pills and were paid $30 to participate

Ariely et al. JAMA 2008

Expensive Placebos Work Better than Cheap Placebos (II)

• Electrical shocks to the wrist were calibrated to each participant's pain tolerance.
• After calibration, participants received the test shocks, rating the pain
• Participants received all possible shocks in 2.5V increments (before and after taking the pill)
• In the regular-price group, 85.4% reported pain reduction vs 61.0% in the low-price (discounted) group ($P = .02$).

Ariely et al. JAMA 2008
**Botulinum Toxin and Pain**

**Is it Better than Placebo?**

- Is expensive
- Has a lot of mystique and ritual with the injection process
- Will be a potent placebo whether we know it or not
- It should be better than placebo, or we should use something else
- To determine if this really works assess for: function, drug use (opioids), work attendance and other behaviors not just “I think I am better”
- No way am I advocating the use of botulinum toxin for all the problems I am reviewing!
**Chronic Daily Headache with a Migrainous Component (Chronic Migraine) (I)**

- RCT double blind for 11 months at 13 NA headache centers
- Subgroup analysis of 228/355 patients not taking prophylactic medications
- Initial 355 was chosen as non placebo responders from a single-blind, placebo injection
- This group was injected with BoNT-A or placebo and assessed every 30 days for 9 months
- The initial study did not show clear efficacy for migraine headache patients

*Aurora Expert Opin Pharmacother 2006 Seattle*

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**Chronic Daily Headache with a Migrainous Component (Chronic Migraine) (II)**

- After two injection sessions the frequency of headaches per 30 days was decreased by 3.3 (P=.032)
- This continued after the third injection with a decrease of 4.2 headaches per 30 days (P=.023) for 180 through 270 days
- “BoNT-A is an effective and well-tolerated prophylactic treatment in migraine patients with CDH who are not using other prophylactic medications.”

*Aurora Expert Opin Pharmacother 2006 Seattle*
Predictors of response to BoTN-A in chronic daily headache (I)

• 71 patients with Chronic Migraine (CM) and 11 patients with chronic tension-type headache (CTTH) were treated with 100 units BoNT-A
  – Every patient received at least 2 sets of injections at intervals of 12-15 weeks;
  – fixed sites, fixed dose, and "follow-the-pain" approaches were used for the injections.
• Patients were divided into responders and non-responders (50% reduction in both headache frequency and MIDAS scores compared with baseline)

Mathew et al  Headache 2008

Predictors of response to BoTN-A in chronic daily headache (II)

• A greater percentage of patients with CM (76.1% 54/71) responded to BoNT-A than patients with CTTH (36.4% 4/11).
• In Chronic Migraine predictors of response to BoNT-A were:
  – Predominantly unilateral in location,
  – Associated with scalp allodynia and
  – Pericranial muscle tenderness
• In Chronic Tension Type Headache
  – pericranial muscle tenderness may be a predictor of response

Mathew et al  Headache 2008
Imploding Migraine Responds Better than Exploding Headache (I)

- 63 patients were compared prospectively (n=27) and retrospectively (n=36) for neurological symptoms associated with their migraine.
- 100 units of BTX-A divided into 21 injections sites across pericranial and neck muscles
- 39 responders had improvement in their number of migraine days per month from 16.0 before BTX-A to 0.8 after BTX-A (down 95.3%) and
- 24 non-responders remained unchanged (11.3 days vs. 11.7 days)

Jakubowski Pain 2006 Harvard

Imploding Migraine Responds Better than Exploding Headache (II)

- The prevalence of aura, photophobia, phonophobia, osmophobia, nausea, and throbbing was similar between responders and non-responders
- Among non-responders, 92% described a buildup of pressure inside their head “exploding headache”
- Among responders, 74% perceived their head to be crushed, clamped or stubbed by external forces “imploding headache”
  - 13% attested to an eye-popping pain (ocular headache).

Jakubowski Pain 2006 Harvard
Chronic Facial Pain Associated with Masticatory Hyperactivity

- Randomized blinded placebo-controlled study, 90 patients (60 BoTN A 30 placebo) with chronic facial pain
- Injections into masticatory muscles
  - Average 35 units of BoTN-A
  - Most injections were intra-oral
  - Medial Ptergoid, Masseter, Temporalis,
- Decrease of 3.2 on a visual analog pain scale which was better than placebo

J Oral Maxillofac Surg. 2003 von Lindern Germany

Temporomandibular pain

- No real data but anecdotal experiences.

- Schwartz, Freund Clin J Pain. 2002 Toronto
Post-whiplash Neck Pain

- RCT of 20 patients with cervical myofascial pain, 2 to 48 weeks after Whiplash
- 200 U of BTX-A or placebo at 4 tender points
- Follow-ups 3, 6, 9, 12, and 24 weeks
- A time-dependent improvement in all the parameters was found in both groups, which was consistently larger in the BTX-A treated group, but mostly not at a significant level
- Some outcomes reached significance at 42 weeks
- More study needed

Braker C Clin J Pain 2008 Israel

Myofascial Pain (I)

- Prospective, randomized double-blind placebo-controlled 12-week multi-centre
- moderate-to-severe myofascial pain syndrome
  – cervical and/or shoulder muscles (10 trigger points)
  – disease duration 6-24 months
- Injections were made into the 10 most tender trigger points (40 units per site)
- BoTN–A or saline

Göbel Pain 2006 Germany
Myofascial Pain (II)

- At week 5, significantly more patients in the BoTN-A group reported mild or no pain (51%),
- Compared with the patients in the placebo group (26%; p=0.002)
- Significantly greater change from baseline in pain intensity during weeks 5-8 (p<0.05)
- Significantly fewer days per week without pain between weeks 5 and 12 (p=0.036)
- Injections were well tolerated

Pain 2006 Göbel Germany

Botulinum toxin A for myofascial trigger point injection: a qualitative systematic review

- Five clinical trials met the inclusion criteria.
- One trial concluded that BTA was effective
- Four concluded that it was not effective for reducing pain arising from trigger points
- “The current evidence does not support the use of BTA injection in trigger points for myofascial pain. The data is limited and clinically heterogeneous.”

Ho, Tan Eur J Pain 2007
Botulinum toxin A and chronic low back pain (I)

- randomized, double-blind study
- Thirty-one patients with chronic LBP:
  - 15 received 200 units of botulinum toxin type A
  - 40 units/site at five lumbar paravertebral levels on the side of maximum discomfort
  - 16 received subjects received normal saline
- Outcomes: (VAS) and the Oswestry Low Back Pain Questionnaire (OLBPQ). The authors reevaluated the patients at 3 and 8 weeks (visual analogue scale) and at 8 weeks (OLBPQ)

  Foster L, Neurology 2001

Botulinum toxin A and chronic low back pain (II)

- At 3 weeks improvement in:
  - >50% pain relief (73.3% vs 25%) (p=0.012)
- At 8 weeks improvement in:
  - > 50% Pain relief (60% vs 12.5%) (p=0.009)
  - Oswestry Low Back Pain Questionnaire (66.7% vs. 18.8%) (p=0.011)

  Foster L, Neurology 2001
**Piriformis Muscle Syndrome (I)**

- Double-blind, single group, crossover study
- Nine women with chronic buttock, hip, and lower limb pain without evidence of lumbar disk herniation or nerve root impingement on imaging studies participated in the study.
- The analgesic efficacy of a fluoroscopic/EMG guided unilateral intramuscular piriformis injection with 100 units botulinum toxin type A was compared with a similar injection of vehicle alone.


**Piriformis Muscle Syndrome (II)**

- After injection with BoTN -A improvement was observed under all 4 VAS categories (pain intensity, distress, spasm, and interference with activities)
- Vehicle (placebo) group showed improvement in 1 of 4 (distress).

Complex Regional Pain Syndrome

- Nine cases of post-traumatic cervical dystonia
- Treated with Botulinum toxin
- “complex regional pain syndrome (CRPS) could represent a variant of posttraumatic cervical dystonia that may develop over time after the initiation of dystonia.”

Frei et al Mov Disord 2004 California

Post-herpetic Neuralgia

- One case of an 80-year-old man who suffered from severe pain of post-herpetic neuralgia which was refractory to the usual therapies.
- Neuropathic pain was dramatically relieved by multiple BTX-A injection and the pain relief lasted 52 days.

Liu, et al Pain Med. 2006 Taiwan
Chronic lateral epicondylitis

- RCT of 40 patients with chronic tennis elbow
  – all treatments including steroid injection had failed
- 50 units BTX A vs saline solution (triple blinded?)
- The intramuscular injections were performed 5 cm distal to the maximum point of tenderness at the lateral epicondyle
- With the numbers studied there was no significant difference between the two groups

*Hayton J Bone Joint Surg 2005 United Kingdom*

Chronic Arthritis

- Case series of 11 patients (15 joints) with chronic arthritis (5 DJD, 5 RA, 1 psoriatic) 12 month F/U
- 6 lower extremity joints (3 knees, 3 ankles) with 25-50 units
- 9 shoulders with 50-100 units
- Leg: Pain decrease was 55% (p =0.02) and 36% improvement in Timed Stands Test was noted at four to ten weeks after injection. (p =0.044)
- Shoulder: Pain dropped 71% in the shoulder (p <0.001) Active ROM increased 67% in flexion and 42% in abduction (p =0.01).

*Mahowald, Singh, Dykstra Neurotox Res. 2006 Minneapolis*
**Chronic Anterior Knee Pain (I)**

- Open label pilot study case study of 8 females with chronic (>6 months) anterior knee pain,
- Intramuscular [300 - 500 units] to the distal third of Vastus Lateralis
  - followed by a 12-week customized home exercise program to improve recruitment of Vastus Medialis muscle and functional knee control.

  *Singer Disabil Rehabil. 2006 Australia*

**Chronic Anterior Knee Pain (II)**

- Results: reduced knee pain and brace dependency and increased participation in sporting and daily living activities.
- Isometric quadriceps muscle strength was maintained or improved despite significant atrophy, (evident on CT) of the distal component of Vastus Lateralis in the treated limb.
- Time taken to ascend and descend a flight of stairs improved in all subjects. Subjective and objective improvements were maintained at 24-week follow-up.

  *Singer Disabil Rehabil. 2006 Australia*
**Spastic Shoulder Pain After Stroke**

- Double-blind randomized clinical trial.
- Fourteen treated with 500 units of BoTN-A in the pectoralis major muscle of the paretic side, and 15 with placebo.
  - After infiltration, both groups received TENS for 6 weeks.
- RESULTS: The patients treated with botulinum toxin type A showed a significantly greater pain improvement from the first week post-infiltration for 6 months between 2.43- and 3.11-fold higher likelihood of pain relief.

  *Marco et al J Rehabil Med. 2007 Spain*

**Plantar Fasciitis (I)**

- RCT double-blind botulinum toxin A
- 27 patients (43 feet) with plantar fasciitis.
  - In patients with bilateral symptoms one foot was a control
- Tx group got 70 units divided into two sites.
  - Tender area in the medial aspect of the heel close to the calcaneal tuberosity (40 units),
  - arch of the foot between an inch anterior to the heel and middle of the foot (30 units)
- Assessed at 3 and 8 wks

  *Babcock MS, Foster L, Pasquina P, Jabbari B Am J Phys Med Rehabil. 2005 Walter Reed Army Medical Center, Washington, DC*
Plantar Fasciitis (II)

• RESULTS: Improvements in all outcome measures
  • Pain Visual Analog Scale (P < 0.005)
  • Maryland Foot Score (P = 0.001)
  • Pain Relief Visual Analog Scale (P < 0.0005)
  • pressure algometry response (P = 0.003)
  • No side effects were noted


Hallux Valgus

• One case in which botulinum toxin A injection reduced not only the hallux valgus deformity clinically and radiographically but also its associated pain.

Radovic J Am Podiatr Med Assoc 2008 USA
Spinal Cord Pathology

- Two patients with spinal cord lesions at the cervical level (tumor and stroke)
- Allodynia and pain in dermatomes corresponding to the cord lesions
- BoTN A was injected subcutaneously at multiple points (16 to 20 sites, 5 units/site) in the area of burning pain and allodynia
- The analgesic effect of botulinum toxin A lasted at least 3 months and was sustained over follow-up periods of 2 and 3 years with repeated administration at 4-month intervals.

Jabbari Pain Med 2003 Bethesda, Maryland

Painful Bladder Syndrome

- Prospective case study of 15 patients with painful bladder symptoms associated with increased urinary frequency
- Botulinum A toxin (200 u) intravesically in the bladder trigone and lateral walls through cystoscope.
- Overall 13 patients (86.6%) reported subjective improvement at 1 and 3-months
- At 12 months after treatment pain recurred in all patients

J Urol. 2008 Giannantoni A Italy
Radiation Fibrosis Syndrome

- Retrospective case series of 23 patients
  - radiation-induced cervical dystonia in 18 (78%),
  - trigeminal neuralgia (60 injections in the skin) or cervical plexus neuralgia in 10 (43%),
  - trismus in 7 (30%),
  - migraine in 3 (13%), and
  - thoracic pain in 1 (4%)

Stubblefield  Arch Phys Med Rehabil. 2008
and in Cooper 2007

Phantom- and Stump Pain After Amputation

- Single case report over a 1-year period
- Injected 4 x 25 IU of botulinum toxin A (Botox) into trigger points of the stump muscles
- four injections every 3 months
- “patient became almost completely pain-free”
- intrathecal morphine therapy “could be” reduced to 40% of the initial dose.
- Intrathecal clonidine and oral analgesics were eliminated completely

Kern Nervenarzt. 2004 Wiesbaden Germany
Chronic Pain and Pelvic Floor Spasm

• Double-blinded RCT LEVEL OF EVIDENCE: I
• 60 women with chronic pelvic pain and pelvic floor muscle spasm
• 80 units of BoTN A injected into the pelvic floor muscles vs saline (30 in each group)
• RESULTS: More improvement in the treatment group for:
  – dyspareunia (P < 0.001) both groups improved
  – nonmenstrual pelvic pain (P = 0.009).
  – pelvic floor pressure reduction (cm of H2O)

Abbott Obstet Gynecol. 2006 Australia

Conclusions: Botulinum and Pain

• BoTN works on several neurotransmitters related to pain
• There may be affects in the periphery that may alter the CNS pain perception
• There are many painful conditions that are being studied and used for pain treatments
• We should try to show botulinum toxin is better than an expensive placebo and should be aggressively studied before these treatments are widely used.
• End of talk