



## **Botulinum Toxins as Neuromodulators in Chronic Pain Management**

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### **Learning Objectives**

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- 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

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- Consultant/Speakers Bureau: Allergan, Ipsen

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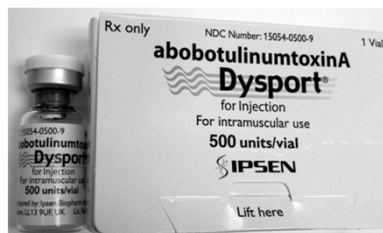
## Neurotoxins as Neuromodulators

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- 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.....

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## The Current Playing Field....



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## Botulinum Toxins in the US

Name	Type	Forms	Process	Indications
OnabotulinumtoxinA (Botox® —Allergan, Inc.)	A	100U, 200U, 50U	Vacuum-drying (NSS/albumin)	Strab, CD, BS, CN7 d/o, AH, Cosm, U&LLS, CM, OAB/DH
AbobotulinumtoxinA (Dysport™—Ipsen, Ltd)	A	300U, 500U	Lyophilized (fermentat/precipit/ dialysis/chromatography)	CD, Cosm, U&LLS; LLS (child)
IncobotulinumtoxinA (Xeomin®—Merz)	A	50U, 100U	Lyophilized Albumin, sucrose	CD, BS, Cosm, ULS
RimabotulinumtoxinB (Myobloc®—Solstice)	B	2.5k U, 5k U, 10k U	Ferm/precipitation/ chromatography	CD

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## Botulinum Toxins

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- **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

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

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## BTX in Pain Management

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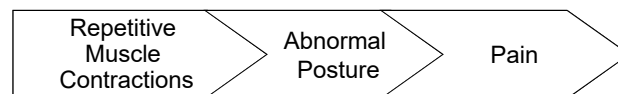
- Myofascial pain syndromes
  - Upper back/neck
  - TOS
  - Piriformis syndrome
- CLBP
- Facial and head pain  
(migraines, occipital neuralgia, TN, atypical facial pain, TMJ pain)
- Intractable joint pain
- Lateral epicondylitis/plantar fasciitis
- Focal/generalized neuropathies
- Vascular pain (Raynaud's)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

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## Analgesia With Botulinum Toxins

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*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)

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## Antinociception Observations Using Botox®

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- Inhibition of release of ACh and sP (not NE) in rabbits (iris)<sup>1</sup>
- Inhibition of release of ACh and sP (vesicle-dependent exocytosis) in cultured DRG neurons induced by capsaicin<sup>2</sup>
- sP inhibition (vesicle fusion inhibition) in the embryonic rat DRG model<sup>3</sup>

<sup>1</sup> Ishikawa H, et al. Jpn J Ophthalmol 2000

<sup>2</sup> Purkiss J, et al. Biochem Pharmacol 2000

<sup>3</sup> Welch MJ, et al. Toxicol. 2000

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## Antinociception Observations Using Botox (cont'd)

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- Dose dependent inhibition of CGRP in TG nerve of rats<sup>1</sup>
- Block release of glutamate induced by formalin and decreased activity at the WDR neuron upon stimulation (second pain)<sup>2</sup>
- Fos, a product of c-fos gene that is expressed with neuronal stimuli, was prevented<sup>3</sup>

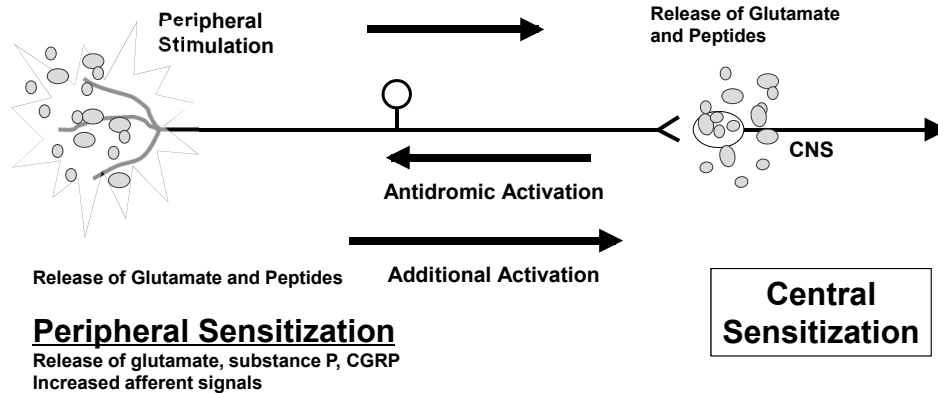
<sup>1</sup> Durham P. Cephalgia 2003; 23(7): 690

<sup>2</sup> Aoki KR. Headache 2003; 43(1): S9-15

<sup>3</sup> Cui ML. Pain 2004; 107(1-2): 125-33

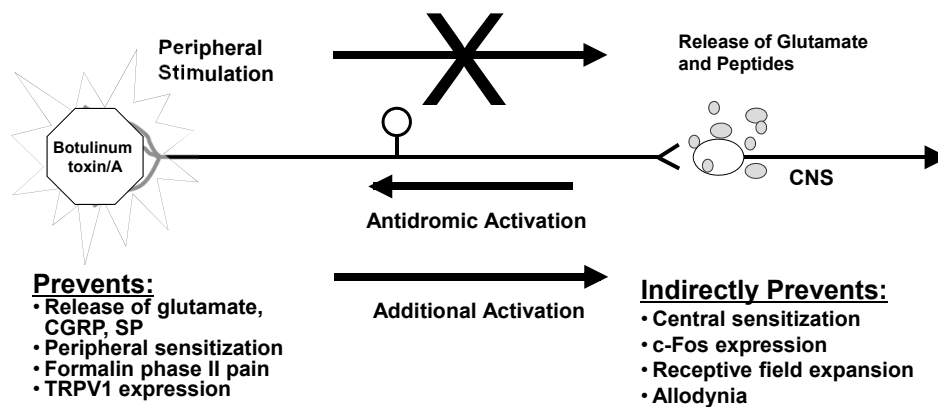
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## Peripheral Sensitization Leads to Central Sensitization



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



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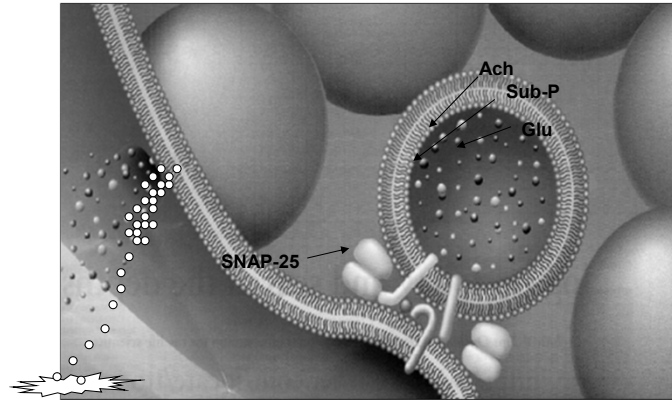
*Clinical relevance of these preclinical results remain to be established*

## 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



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## Clinical Applications



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## Headaches

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- 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

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## IHS Classification

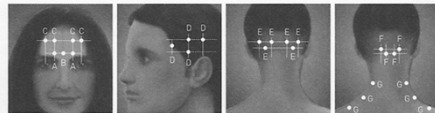
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- A1: Migraine
  - A1.1. Migraine w/o Aura
    - Pure menstrual
    - Menstrually-related
    - Nonmenstrual
  - A1.2. Migraine w/ Aura
  - A1.5. Chronic Migraine

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## Chronic Migraine Headache

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## BTX in MPS: Theories

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- 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

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## Myofascial Pain Syndromes

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- Most consistent and better studied responses in clinical practice have been in the cervicothoracic region<sup>1</sup>
- Compartment techniques vs trigger point approach—midbelly of muscle, not tender areas (TPIs); may be targeting motor points<sup>2</sup>
- Follow the pain but beware of pain referral patterns<sup>3</sup>

<sup>1</sup> De Andres et al J Pain. 2003 Jul-Aug;19(4):269-75.

<sup>2</sup> Lang A. Am J Pain Medicine 2000; 10:105-109

<sup>3</sup> Reilich J Neurol 2004; 251(Suppl 1): I36-I38

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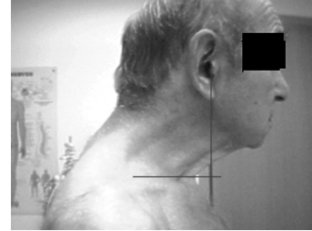
## Forward-Head Syndrome

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- 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

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## Forward-Head Syndrome (cont'd)



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## Thoracic Outlet Syndrome

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

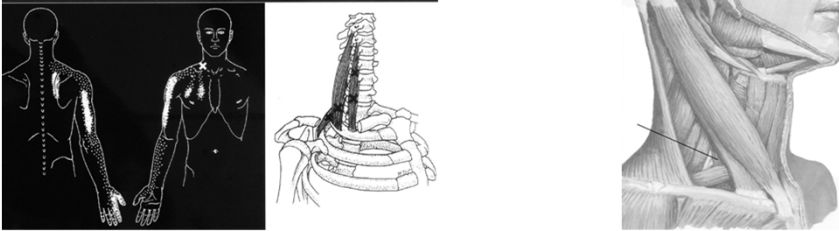
<sup>1</sup> Cuevas-Trisan R, Cruz-Jimenez M. Am J Phys Med Rehabil. 2003; 82(9) 712-715

<sup>2</sup> Jordan SE, et al Ann Vasc Surg. 2000 Jul;14(4):365-9

<sup>3</sup> Odderson I. Arch Phys Med Rehabil 2008

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## Scalene Contribution



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## Piriformis Syndrome

- Part of dx of “sciatica”
- Seen often postspinal surgery, or prompting it
- Commonly postural; less common compressive
- 100 units of Botox<sup>®</sup> IM<sup>1,2</sup>
- Must use targeting techniques (EMG/fluoro)
- A more effective than B with less S/Es<sup>3</sup>

<sup>1</sup> Lang Am J Pain Manage 2000; 10:108-112.

<sup>2</sup> Childers et al. Am J Phys Med Rehabil 2002; 81: 1-9.

<sup>3</sup> Lang Am J Phys Med Rehabil 2004; 83: 198-202.

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## Piriformis Syndrome (cont'd)

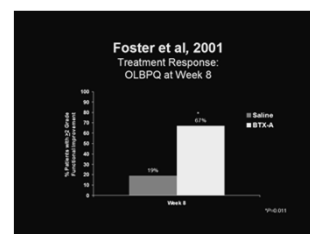
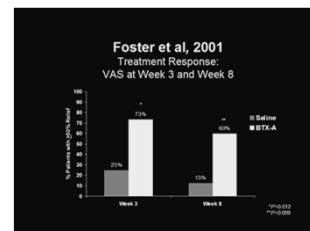


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## Low Back Pain

- 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



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## Postlaminectomy Syndrome

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- 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

Edwards K, et al. Poster APS Annual Meeting Washington, DC 5/07

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## Novel Uses

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## Intractable Joint Pain

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- Degenerative joint disease
- Limited/emerging evidence<sup>1</sup>
- Working theory: inhibition of low-grade inflammatory mediators
- Role of IL-1
  - Blocking of IL-1 receptor signaling complex<sup>2</sup>

<sup>1</sup> DePuy T, et al. Am J Phys Med Rehabil 2007; 86 (10): 777-783.

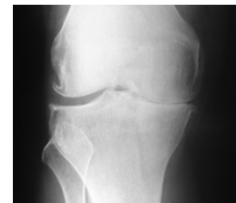
<sup>2</sup> Namazi H, Majd Z. Am J Immunol. 2005. 1(2):94-95

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## BTX-A in Joint Pain

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- Multiple retrospective / open label / small case series<sup>1</sup>
- Various joints:
  - hip, knee, ankle, shoulder, zygapophyseal, sternoclavicular, sacroiliac
- Prospective RCT in Mod-Sev knee pain 2<sup>ary</sup> to OA<sup>2</sup>
- N = 23 per group; 100U IA Botox vs education
- Botox: superior providing pain relief and improved function short- (1 week) and long-term (6 months)



<sup>1</sup> Mahowald M, Singh J, Dykstra D. *Neurotox Res* 2006

<sup>2</sup> Lin-Fen H, et al. *PM&R* 2016

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## BTX-A in Joint Pain (cont'd)

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- Evidence remains inconsistent and controversial for the use of IA therapies for knee OA<sup>1</sup>

1. Nguyen C et al. *Ann Phys Med Rehabil* 2016

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## Postarthroplasty Intractable Pain

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- 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

Singh, Mahowald, et al ICoN 2006 Meeting Abstract, Hollywood, FL  
Kamen ICoN 2006 Meeting Abstract, Hollywood, FL

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## Other Painful Syndromes

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### Lateral Epicondylitis

Wong<sup>1</sup>: 60 U Dysport<sup>®</sup>

- 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 in 13% of BTX group

Hayton<sup>2</sup> - 50 U Botox<sup>®</sup>

- RCT; N = 40 (20 - placebo / 20 - active)
  - IM 5cm distal to max point of tenderness
- At 3 months: no significant difference in grip strength, pain, and QOL

1. Wong SM et al. *Ann Intern Med.* 2005 Dec 6;143(11):793-7.

2. Hayton MJ, et al.. *J Bone Joint Surg Am* 2005; 87(3): 503-7

Fig 1  
The injection (black arrow) was administered 5 cm distal to the area of maximal tenderness at the lateral epicondyle (white circle), in the middle of the wrist, and the 20-gauge needle was inserted into the vein (red arrow).



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## Plantar Fasciitis

- Babcock<sup>1</sup>: 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
  - Statistically-significant improvement at 3 and 8 weeks:
    - Maryland Foot Score / pain / pressure algometry
- Placzek<sup>2</sup>: 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)

1. Babcock MS et al *Am J Phys Med Rehabil.* 2005  
 2. Placzek R et al *Clin J Pain.* 2006

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## Facial Pain

- Atypical, TN, TMJ  
(including bruxism<sup>1</sup>), etc
- Various studies
- Dose: highly variable; 20-150 U
- Injection site: variable; depends on painful area; SQ/intradermal<sup>2,3</sup>
- Maintain cosmetic symmetry

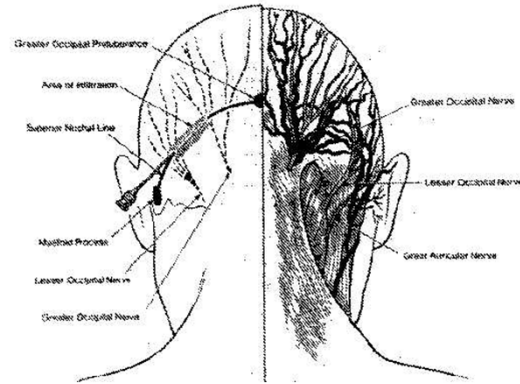


<sup>1</sup> Guarda-Landini, et al. *J CranioMand Prac* 2008  
<sup>2</sup> Cuevas-Trisan R. AAPM Meeting 10/07, LV, NV  
<sup>3</sup> Singh. *F1000 Research* 2013.

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## Occipital Neuralgia

- Retrospective series (N=6) severe occipital neuralgia<sup>1</sup>
- 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  $16.3 \pm 3.2$  weeks (median 16 weeks)
- Others<sup>2</sup>



1 Kapural et al. AAPM meeting 2/07 New Orleans  
 2 Volcy et al. *Cephalgia*. 2005;25:990.

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## Raynaud's Syndrome

- Retrospective series (N=33) severe Raynaud's<sup>1</sup>
- Failed conservative and interventional therapies; some amputations
- Technique using BTX-A 100U
- 85%: significant decreases in pain / improvement in perfusion
- Duration of relief averaged  $16.3 \pm 3.2$  wks (median 16 wks)



<sup>1</sup> Neumeister MW *J Hand Surg* 2010; 35A: 2085-92.

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## Raynaud's Syndrome

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## Postradiation Fibrosis Pain

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- Two publications on the use of toxins for management of symptoms associated with post-radiation fibrosis have reported a possible role yielding modest results<sup>1,2</sup>
- Patient selection and dosing paradigms are yet to be determined
- Recent case report with remarkable results<sup>3</sup>

<sup>1</sup> Stubblefield *Arch Phys Med Rehabil* 2008

<sup>2</sup> Bach et al. *Eur Ann Otorhinolaryngology* 2012

<sup>3</sup> Cuevas-Trisan R. (Abst) *PainWeek* 9/13, LV, NV



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## Other Uses

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

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## Peripheral Neuropathies

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- DPN<sup>1,2</sup>
- Dysport 100 U intradermal vs saline; n=20/group
- Statistically significant decrease in neuropathic symptoms in Dysport group
- Botox 50 U intradermal vs saline; n = 18/group
- Statistically significant decrease in neuropathic symptoms in Botox group
- PN3
- Dysport up to 300 U vs Saline; n=34 vs 32/group x 2 (12 wks apart)
- Statistically significant decrease in neuropathic pain in Dysport group

1. Ghasemi et al. J Res Med Sci 2014
2. Yuan, et al. Neurology 2009
3. Attal, et al. Lancet Neurology 2016

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## Focal Neuropathies

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



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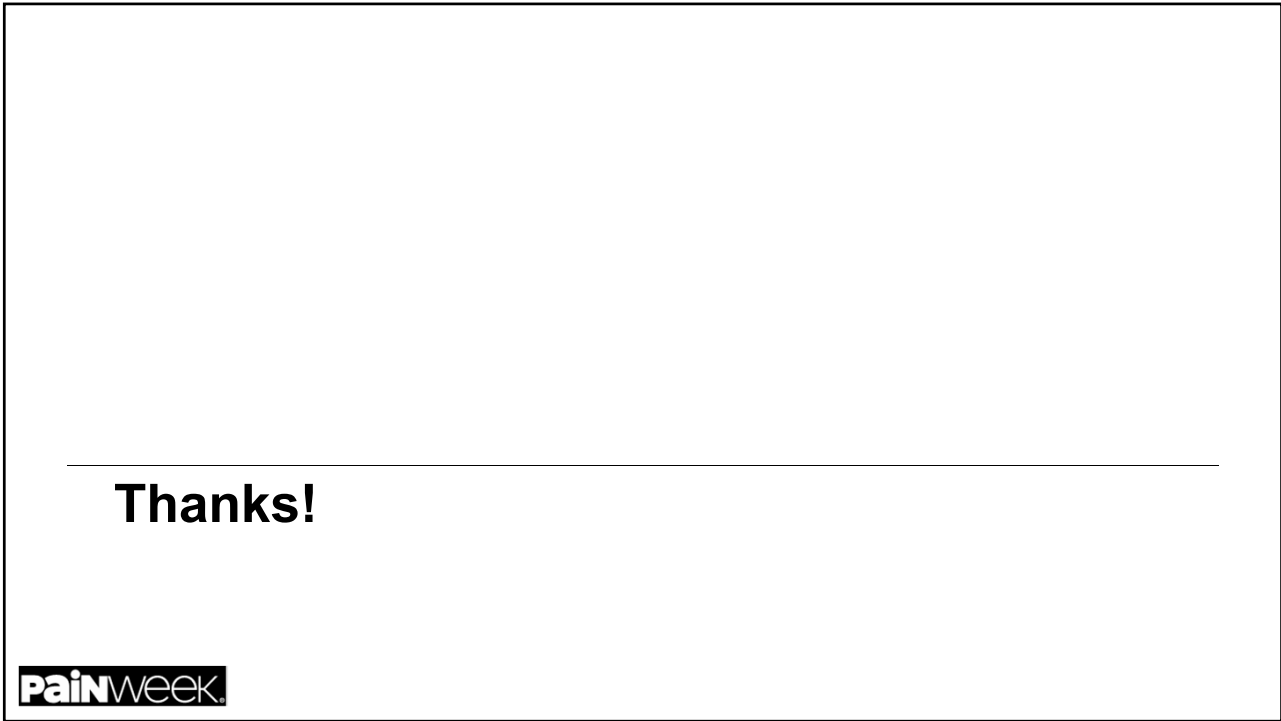
## Current Clinical Trials

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- 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 / Painful diabetic neuropathy—Taipei Medical Center
- Cervicobrachial MPS—UCLA / TOS—University of British Columbia
- Neuroma pain—Southern Illinois Univ/Stanford
- LE CRPS—Stanford
- TKR pain—University of Minneapolis-completed
- Ganglion impar injections for proctalgia—Nantes University
- Psoriasis—University of Minnesota
- Peyronie's disease, vaginismus, restless legs, alopecia areata

Source: [NIHclinicaltrials.gov](http://NIHclinicaltrials.gov)

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**Thanks!**

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