



# Indications for BoNT Therapy

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## Disclosures

- Conflict of interest
  - I am a co-inventor of an immunotoxin, patented by NIH, that is being developed (very slowly) for similar purposes as BoNT, but this will not be discussed
- Off-label and experimental therapies will be discussed extensively

## Commercial Products

- Type A preparations
  - BOTOX® (Allergan Inc., Irvine, California)
  - Dysport® (Ipsen Ltd., Slough, Berkshire, UK)
  - Xeomin® (Merz Pharma, Frankfurt, Germany)
- Type B preparation
  - Myobloc® (Solstice Neurosciences, Malvern, Pennsylvania)

## FDA Approved Uses

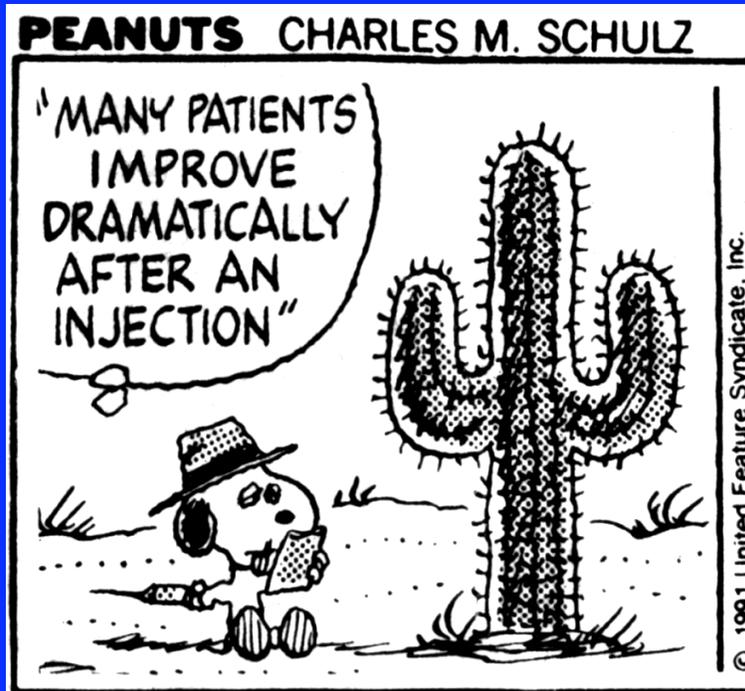
- Botox
  - Strabismus 1989
  - Blepharospasm, Hemifacial Spasm 1989
  - Cervical dystonia 2000
  - Glabellar rhytides 2002
  - Primary axillary hyperhidrosis 2004
  - (20 indications in 75 countries)
- Myobloc
  - Cervical dystonia 2000

## Clinical Uses of BTX

- Movement disorders
- Spasticity
- Pain syndromes
- Ophthalmologic
- Otolaryngologic
- Autonomic
- Cosmetic
- Gastroenterologic
- Urologic

## Volume of sales of Botox

- 2005                    \$830,900,000
- 2004                    \$705,100,000
- 2003                    \$563,900,000
- 2002                    \$439,700,000
- 2001                    \$309,500,000
  
- Net sales from Allergan Annual Report 2005



## Movement Disorders

- Focal dystonias
  - Blepharospasm and other cranial dystonia, cervical dystonia, laryngeal dystonia, focal hand dystonia, foot dystonia
- Hemifacial spasm
- Tic
- Tremor
  - Essential tremor (head, arm)
  - Essential palatal tremor (ear click)
- Myoclonus
- Bruxism, myokymia

## Cervical Dystonia



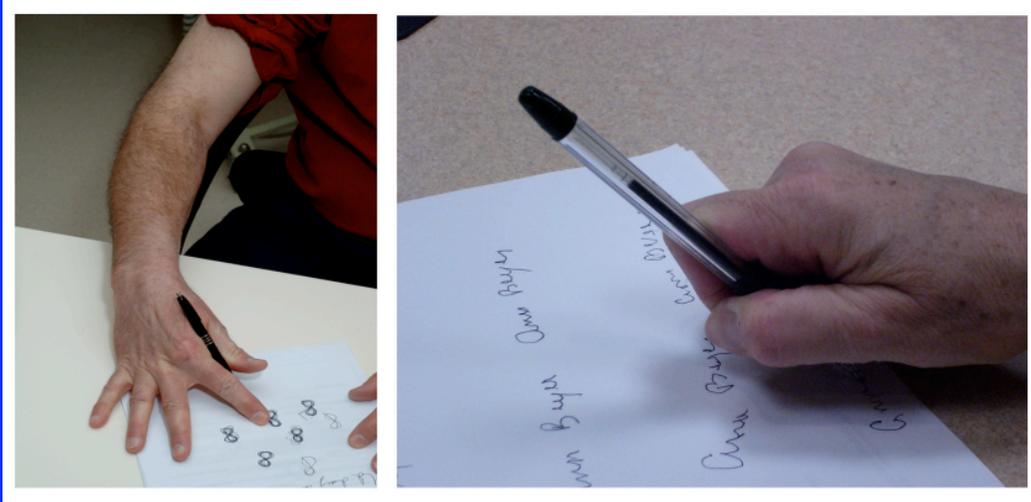
Courtesy of J. Jankovic  
From NTI Multispeciality Guide

## Blepharospasm



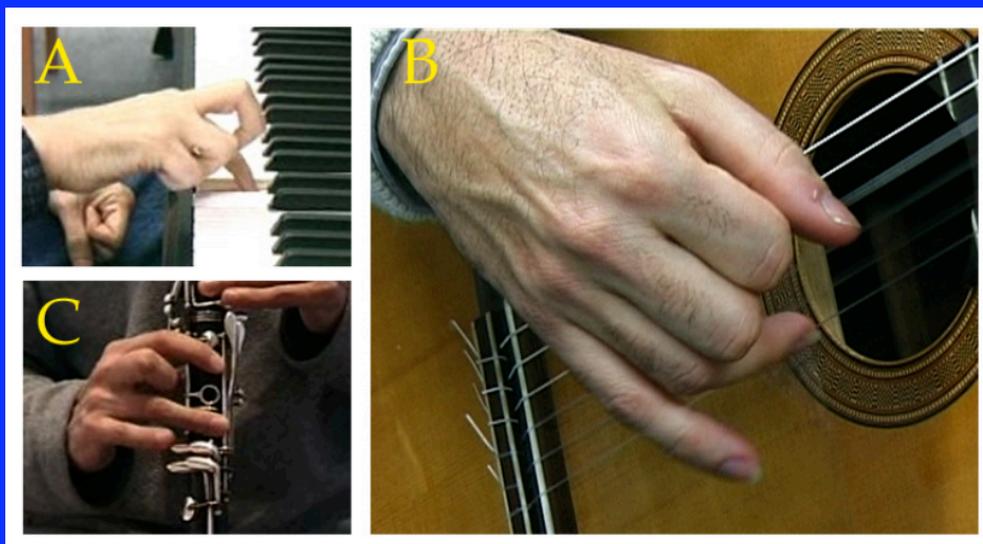
From [www.egms.de](http://www.egms.de)

## Writer's Cramp



Lin, Shamim & Hallett 2006

## Musician's Cramp



Lin, Shamim & Hallett 2006



Left hemifacial  
spasm

Devoize, JNNP 2001;70:516

## Spasticity

- Upper and lower limb
  - Stroke, multiple sclerosis, head injury
- Cerebral palsy



Right side  
spasticity due to  
cerebral palsy

[www.comewakening.com/spasticity.html](http://www.comewakening.com/spasticity.html)

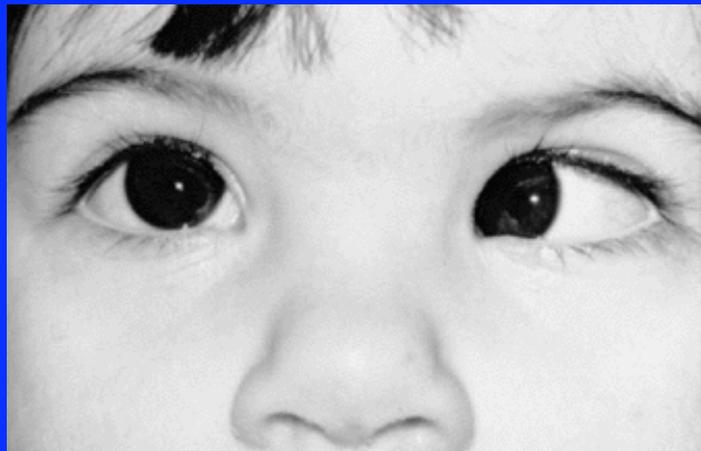
## Pain Syndromes

- Headache
  - Migraine
  - Tension headache, chronic daily headache
- Chronic low back pain
- Myofascial pain
- Arthritic pain

# Ophthalmologic

- Strabismus
- (Blepharospasm)
- Nystagmus
- Hyperlacrimation, hypolacrimation (dry eye)

## Strabismus



From American Academy of  
Ophthalmology Medical Library

## Otolaryngologic

- (Spasmodic dysphonia)

## Autonomic

- Hyperhidrosis
  - Axillary, palmar, gustatory sweating (Frey syndrome)
- Sialorrhea

## Axillary hyperhidrosis



Bhidayasiri & Truong 2005

## Palmar hyperhidrosis



Bhidayasiri & Truong 2005

# Cosmetic

- Wrinkles
  - Most commonly including the lateral canthal region (crows feet), glabellar folds, and forehead
- Wound healing

## Botox around the Eye



**BEFORE:** Deep 'crowsfeet' wrinkles about the eyes in a young woman, causing an aged appearance.



**AFTER BOTOX TREATMENT:** The smile lines have disappeared even with a wide smile, now producing a youthful appearance.

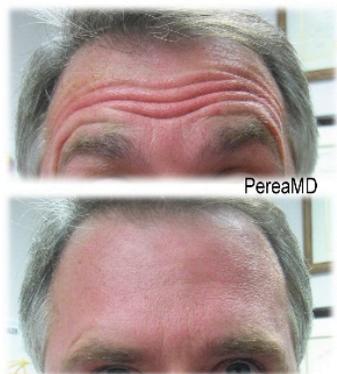
[www.drpercahealth.com/gpage3.html](http://www.drpercahealth.com/gpage3.html)

### Forehead Lines

**BEFORE BOTOX:**  
Forehead lines were extremely deep, causing an aging, worried, and rough appearance.

**AFTER BOTOX:**  
Within just one week, forehead lines disappeared, leaving a relaxed, youthful, and very natural appearance.

Headaches often improve with Botox treatment.



BOTOX Before (Above), After (Below)

Botox For Forehead wrinkles

[www.drpercahealth.com/gpage3.html](http://www.drpercahealth.com/gpage3.html)

### Botox for Frown Lines

**BEFORE:** This woman showed very deep furrows between the eyebrows (Glabella), and complained of frequent headaches.

**AFTER:** By one week after Botox to the frown lines, the deep glabellar furrows became smooth, even with any attempt to frown purposely. She is unable to frown, but there is no unusual sensation. Headaches improved dramatically after Botox treatment.



Before

PereaMD



AFTER Botox to frown lines (Glabella)

[www.drpercahealth.com/gpage3.html](http://www.drpercahealth.com/gpage3.html)

## Wound healing: BoNT injection



FIGURE 2. Left, A 44-year-old white woman 1 week after excision of a basal cell carcinoma of the right lateral aspect of the forehead. The longest postoperative excisional size was 2.7 cm. Fifteen units of botulinum toxin was injected, and layered closure was performed with 5-0 Monocryl subcutaneous and 6-0 Nylon simple running sutures. Right, The resulting scar 6 months after botulinum toxin treatment displays good color match and no hypertrophy or inversion.

Gassner et al. 2006

## Wound healing: Placebo injection

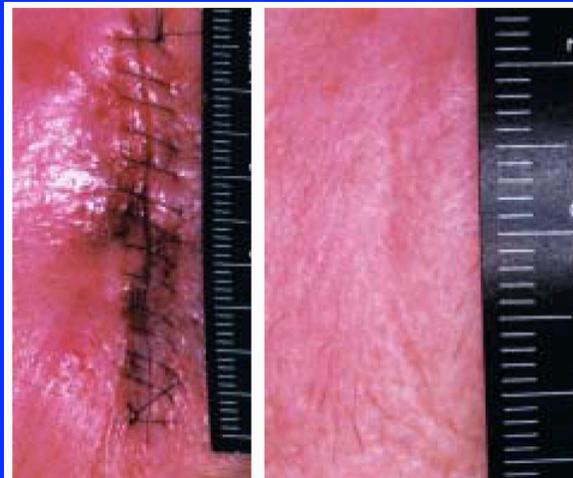


FIGURE 3. Left, A 67-year-old white woman 1 week after excision of a squamous cell carcinoma of the central forehead. Postoperative excisional size was 4.0 by 6.0 cm. Six milliliters of the placebo medication (1% lidocaine with 1:100,000 epinephrine) was injected, and layered wound closure was performed with 5-0 Monocryl and 6-0 running Nylon suture. Right, The resulting scar at 6 months after placebo treatment shows notable widening of the scar.

Gassner et al. 2006

## Gastroenterologic

- Achalasia
- Upper esophageal sphincter, cricopharyngeal achalasia
- Anismus and other obstructive constipation
- Anal fissure
- Sphincter of Oddi dysfunction
- Proctalgia fugax
- Obesity

## Urologic

- Detrusor-sphincter dyssynergia
- Hyperreflexive bladder
- Chronic pelvic pain, vaginismus
- Interstitial cystitis
- Benign prostatic hypertrophy

## Side-effects

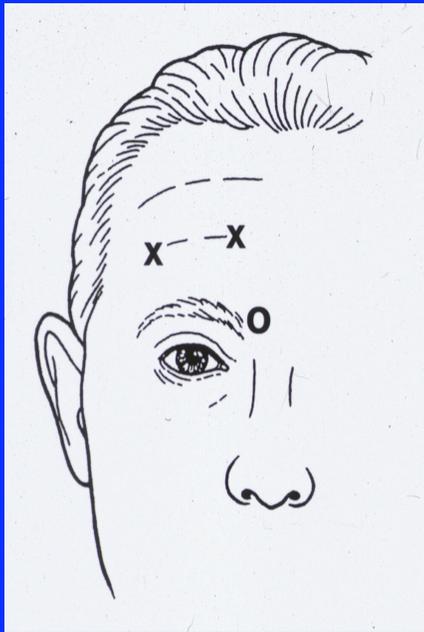
- Weakness
  - Local: most important is dysphagia
  - Systemic: minimal weakness, malaise
- Autonomic effects
  - Dry mouth, constipation, gall bladder dysfunction
- Local effects
  - Pain, hematoma, infection, rash
- Antibodies (subsequent resistance)

## Immuno-resistance Measures

- Mouse protection assay (MPA)
  - semiquantitative test deemed positive when the patient's serum neutralizes the effects of BTX injected intraperitoneally into mice
  - Specific but not sensitive
- Immunoprecipitation assay (IPA)
  - immunological technique based on the in vitro aggregation and precipitation of iodinated BTX and patient's serum antibodies
  - Sensitive, but not specific
- Human functional assays
  - Unilateral brow injection (UBI) or frontalis injection
  - Extensor digitorum brevis test (EDB test) (can be done clinically or with EMG)
  - Probably the most helpful clinically

# Unilateral Brow Injection (UBI)

Baylor College of Medicine

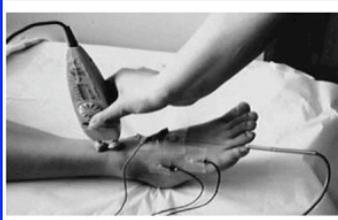


**O = 20 U BOTOX®  
or  
1,000 U MYOBLOC™**

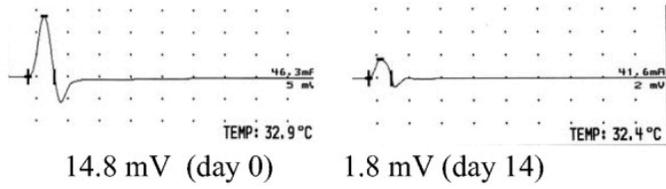
**Courtesy of Dr. J. Jankovic**



**Courtesy of Dr. J. Jankovic**



Movement Disorder Society



**Figure 1.** EDB cMAP is recorded on the EDB muscle with a supramaximal stimulation of the peroneal nerve. Test is performed before and 2 weeks after BTXA injection into the EDB muscle. Note different amplitude calibration on the two traces.

Cordivari et al. 2006

Of course, such a quantitative test could also be used as a measure of potency of a batch of toxin

## Conclusions

- The BoNTs have a wide range of indications and, for many, BoNT is the treatment of choice.
- The number of indications is growing rapidly.