BOTULINUM TOXIN THERAPY FOR THE TREATMENT OF UPPER AND LOWER LIMB SPASTICITY

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DISCLOSURE STATEMENT

I have no relevant financial relationship with any pharmaceutical company.

There are no conflicts of interest.

LEARNING OBJECTIVES

- Review clinical presentations of spasticity in the upper and lower limb.
  - Review anatomy of relevant musculature.
- Identify patients that are appropriate candidates for botulinum toxin (BoNT).
- Review pathophysiology of BoNT and mechanism of action.
- Develop familiarity with treatment expectations.

DISCUSSION OUTLINE

- Clinical findings in spasticity and clinical indication for BoNT injections.
- Brief history of the development of BoNT.
- Mechanism of action/pathophysiology of BoNT.
- Different forms/brands of BoNT.
- Injection technique.
- Potential complications of treatment with BoNT.
- Questions/Discussion.

LIMB SPASTICITY

- Upper motor neuron lesions resulting in chronic weakness and spasticity with possible joint contractures.
  - Stroke
  - Spinal cord injury
  - Multiple sclerosis/Neuromyelitis Optica (NMO)
  - Cerebral palsy
  - TBI
- Upper motor neuron lesions classically affect extensors > flexors in UEs and flexors > extensors in LEs.

MUSCLE INVOLVEMENT

Upper Limb

Pectoralis

Biceps Brachii*/Brachialis

Brachioradialis

Flexor Carpi Radialis*

Flexor Carpi Ulnaris*

Pronator Teres/(Pronator Quadratus)

Flexor Digitorum Profundus*

Flexor Digitorum Sublimis*

Lumbricals

Flexor Pollicis Longus*

Adductor pollicis*

Lower Limb

Gastrocnemius*/Soleus* complex

Tibialis posterior*

Thigh Adductors

Hamstrings

Extensor hallucis longus (“striatal toe”)

Flexor hallucis longus*

Flexor digitorum longus*

*Formal FDA labeling

ABNORMAL LIMB POSTURE

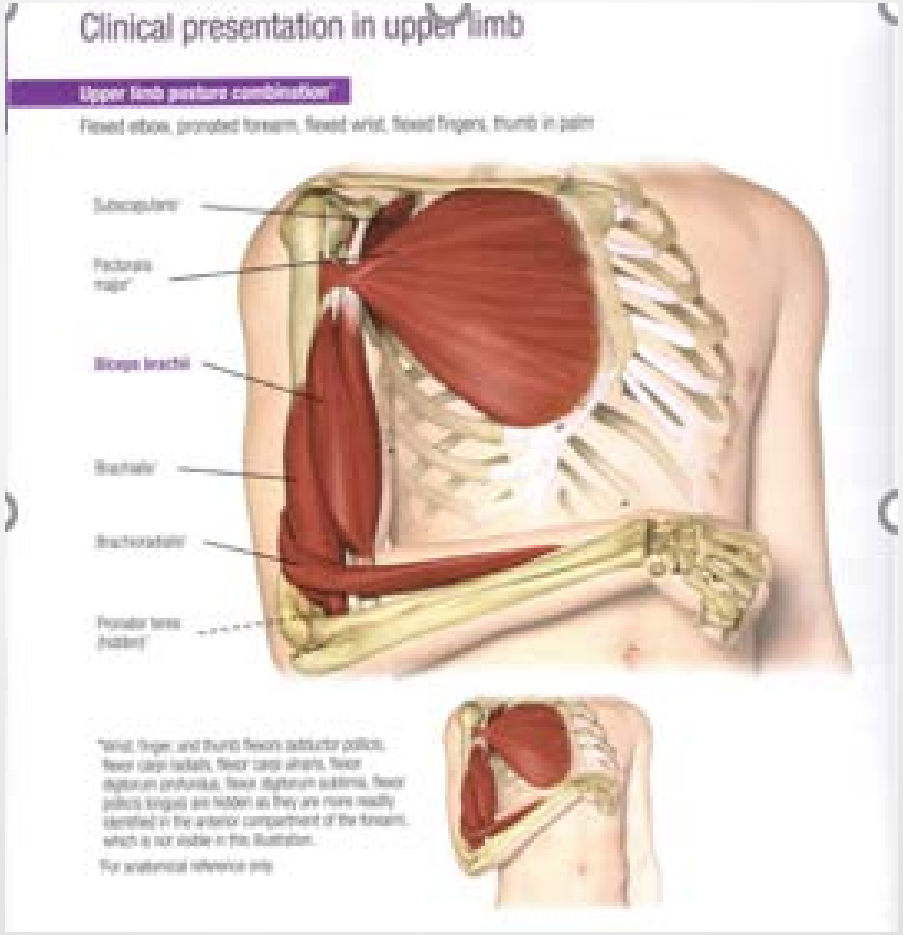
UPPER LIMB

- Adducted/Internally Rotated Shoulder
- Flexed Elbow
- Pronated Forearm
- Flexed Wrist
- Clenched Fist
- Thumb-in-Palm Deformity

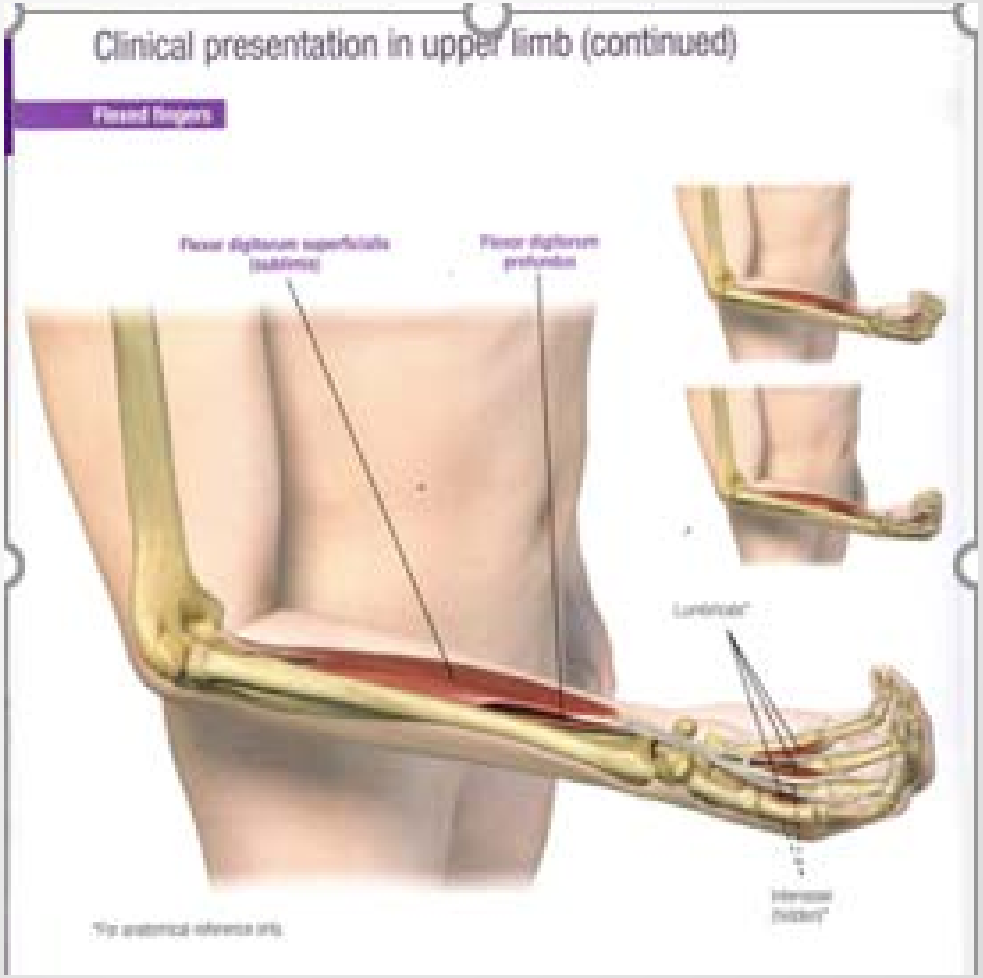
LOWER LIMB

- Adducted thigh
- Tight hamstring
- Tight heel cord
- Inverted foot
- Equinovarus foot

ABNORMAL LIMB POSTURE – UPPER LIMB

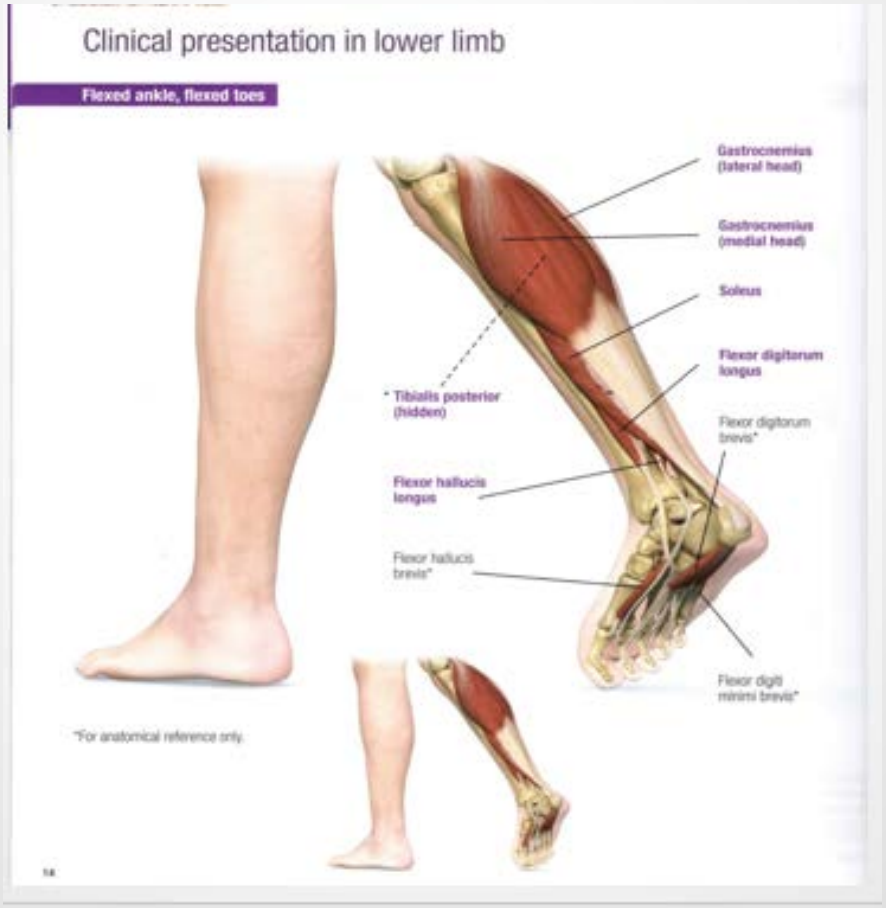


ABNORMAL LIMB POSTURE – UPPER LIMB

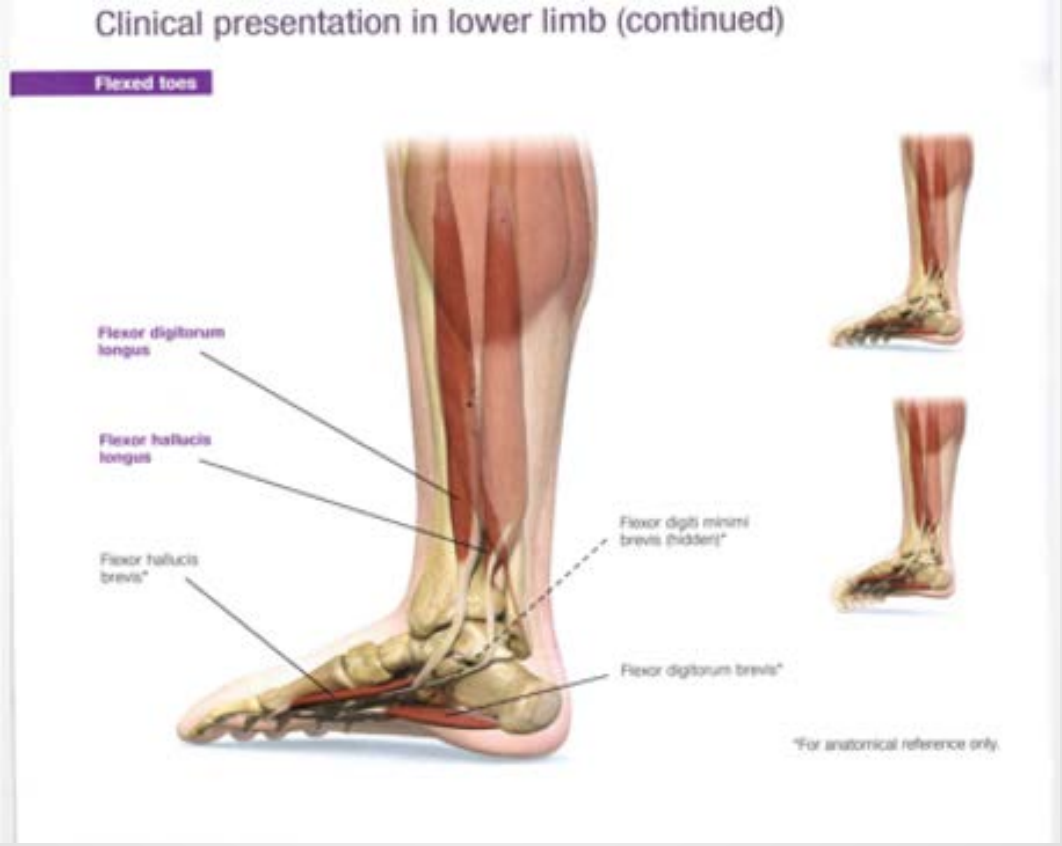


ABNORMAL LIMB POSTURE – UPPER LIMB

ABNORMAL LIMB POSTURE – LOWER LIMB



ABNORMAL LIMB POSTURE – LOWER LIMB



JOINT CONTRACTURES

- Joints that can develop contractures from spasticity:
  - Elbow
  - Wrist
  - Fingers
  - Ankle (shortened heel cords)
  - Knee (shortened hamstrings)
- Very chronic/long-stand Botulinum Toxin ing joint contractures may not respond well or completely to and may require surgery to correct.

TREATMENT CONSIDERATIONS

- Important to set expectations:
  - Botulinum Toxin injections will generally not improve motor function.
  - Must be coupled with Physical Therapy and Occupational Therapy, in some cases splinting or serial casting.
  - Treatment goals:
    - Alleviate spasticity-related symptoms
      - Pain, stiffness, spasms, dystonic movements.
    - Improving ROM
      - Prevention of contractures
      - Splint tolerance
    - Ease of caring for the affected limb
      - Maintenance of hygiene of hand, elbow, axilla
      - Maintenance of skin integrity, cutting fingernails
      - Dressing and positioning of the limb

BOTULINUM TOXIN

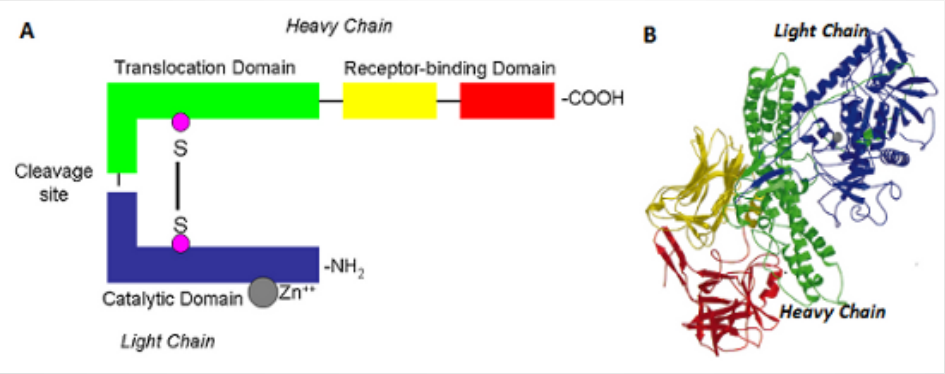
- BoNT is produced by *Clostridium botulinum*, a gram positive anaerobic bacterium.
- BoNT is broken into 7 neurotoxins (labelled A, B, C, D, E, F, G) which are antigenically distinct, but structurally similar.
  - Human botulism is caused mainly by types A, B, E.
- Clinical syndrome of botulism can occur after ingestion of contaminated food, from colonization of the infant GI tract, or from a wound infection.
  - Recognized since the 1800s as "sausage poison". A German physician in 1870 coined the name botulism (Latin form *botulus*, which means "sausage").
  - Suggestive accounts even from ancient times.

BOTULINUM TOXIN

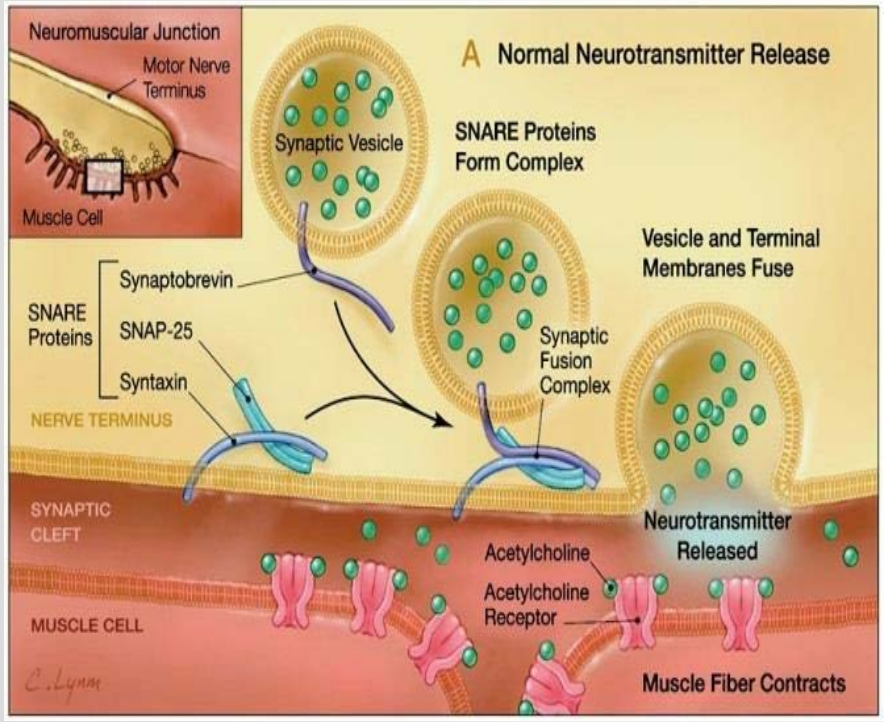
- Recognized since ~1950 that BoNT blocks neuromuscular transmission.
  - Postulated at this time that the toxin could have clinical applications.
- In clinical use since ~1980.
  - Initially used to treat strabismus by injection of the extraocular muscles.
- In 1989, botulinum toxin A was approved by the FDA for treatment of strabismus, blepharospasm, hemifacial spasm.
- Since this time, additional BoNT formulations (3 type A formulations, 1 type B formulation) and additional FDA approved indications with widespread clinical use.

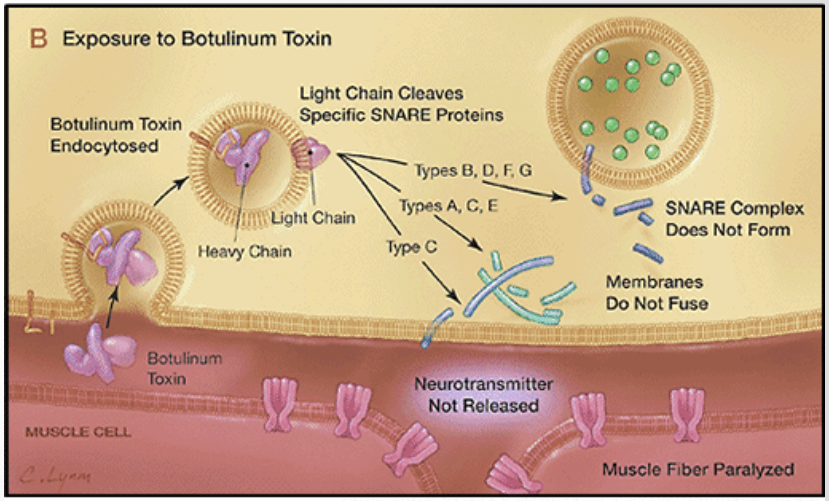
MECHANISM OF ACTION

- BoNT type A and type B are composed of a 150 kD polypeptide consisting of a light chain and a heavy chain joined by a disulfide bond (cleavage site).
  - Heavy chain is responsible for binding to the cholinergic nerve terminal receptors.
  - Light chain is internalized and exerts its effect by preventing the release of acetylcholine (ACh) from the nerve terminal by cleaving SNARE protein complex.
    - Type A toxin cleaves SNAP-25.
    - Type B toxin cleaves synaptobrevin (VAMP).



MECHANISM OF ACTION





JAMA. 2001;285:1059-1070. © American Medical Association

MECHANISM OF ACTION

- Effectively denervates the muscle fibers ("chemodenervation")
  - Effect and proportion of muscle fibers chemodenervated is dependent upon dose.
  - Denervation potentials will be seen on EMG in injected muscles.
- After chemodenervation, the motor nerve terminal forms new synapses (sprouting), although blocked synapses are eventually regenerated.
- *Local spread of toxin can lead to unwanted effects.
- *Minute amounts of botulinum toxin can be distributed with blood circulation.
  - Increased neuromuscular "jitter" in distant muscles on single fiber EMG has been reported.

MECHANISM OF ACTION

- Clinical effect in ~ 48-72 hours.
- Peak effect in about 2-4 weeks.
- Duration of effect about 10-12 weeks for muscle. More prolonged effect in glandular tissue and sweat glands.
- Injections are repeated every 12 weeks.
  - Repeating injections too frequently or at too high of a dose may increase risk of immunogenicity.
  - Some indications (e.g. sialorrhea or hyperhidrosis) can go longer between injections.
- Rate of immunogenicity is very low
  - ~1-1.5% cited, my clinical impression is even lower.

BOTULINUM TOXIN FORMULATIONS

- Botox (onabotulinumtoxinA)
  - Most widely used toxin.
- Dysport (abobotulinumtoxinA)
  - Purported to have longer duration of effect than Botox by ~ 7 days. Consider in Botox cases with early wearing off.
  - Dose conversion is ~ 2.5:1 to Botox.
- Xeomin (incobotulinumtoxinA)
  - Dose conversion is ~ 1:1 to Botox
- Myobloc (rimabotulinumtoxinB)
  - Clinical utility for cases of BoNT type A immunity (neutralizing Abs) and for sialorrhea.

BOTULINUM TOXIN RECONSTITUTION

- Botox, Dysport and Xeomin come in a single-use, vacuum-sealed vials.
  - Botox and Dysport must be refrigerated.
  - Xeomin can be stored at room temperature.
  - Must be reconstituted with sterile 0.9% normal saline.
  - Must be used within 24 hours of reconstitution.
  - More dilute – more potential spread.
    - Botox 2:1 (2 cc/100 Units or 0.1 cc/5 Units) for migraine.
    - Botox 1:1 (1 cc/100 Units or 0.1 cc/10 Units) for other indications.
- Myobloc comes in a single-use, sterile liquid formulation vials.
  - Myobloc must be refrigerated.
  - Myobloc does not require reconstitution.

BOTULINUM TOXIN DOSING

- BOTOX
  - 100 Unit vial
  - 200 Unit vial
- DYSPORT
  - 300 Unit vial
  - 500 Unit vial
- XEOMIN
  - 50 Unit vial
  - 100 Unit vial
  - 200 Unit vial
- MYOBLOC
  - 2500 Units/0.5 mL vial
  - 5000 Units/1 mL vial
  - 10000 Units/2 mg vial

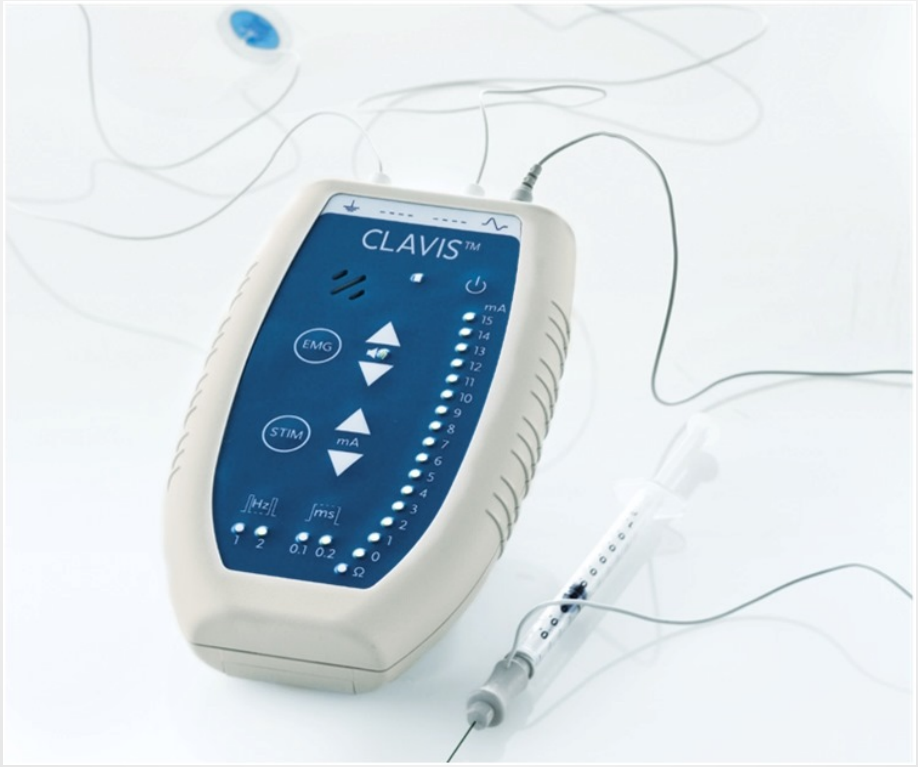
INJECTION TECHNIQUE

- Dose calculation
  - Charts are available with recommended dose ranges for different muscles.
  - Need to consider body weight, muscle mass, degree of spasticity/muscle tension or contraction.
- Administration
  - BoNT is administered by intramuscular injection with relatively contained diffusion and avid binding to endplates of the motor neuron and muscle spindle.
- Injection technique
  - Methods of target muscle localization include the anatomical method, electromyographic guidance, electrical stimulation, and ultrasound guidance.

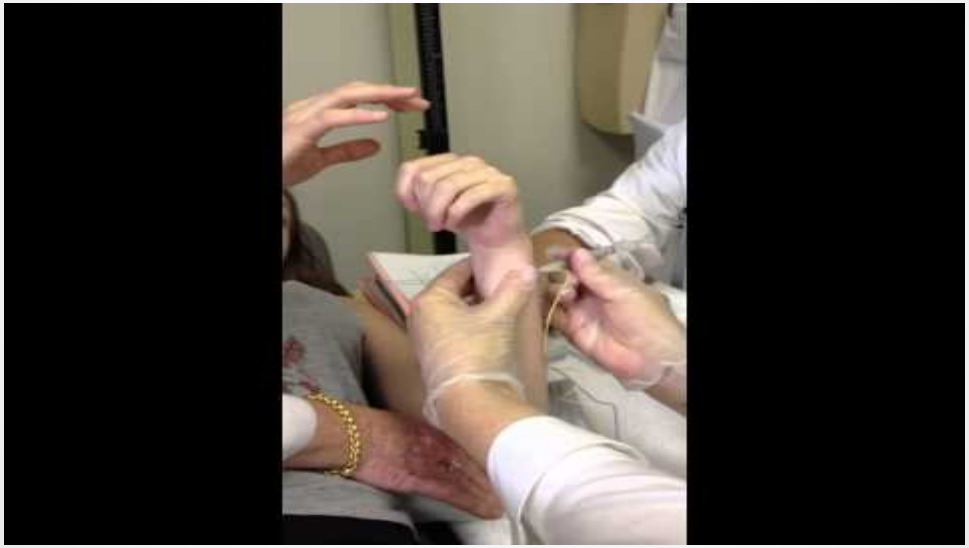
INJECTION TECHNIQUE

- I always utilize EMG guidance.
  - Sometimes stimulation is required, especially for finger flexors or thumb flexor for example.
- If severe lower limb spasticity is present or bilateral lower limb spasticity to where high enough doses of BoNT are not feasible, I would consider intrathecal baclofen pump (ITBP).
  - ITBP and Botox injections can be utilized concurrently.
- BoNT can also be used in conjunction with oral antispasmodic therapies (baclofen, tizanidine, etc.).

INJECTION TECHNIQUE



INJECTION TECHNIQUE



INJECTION TECHNIQUE

- Poor response to initial botulinum toxin
  - Inadequate muscle injection technique
  - Inappropriate muscle selection
  - Dose may be too low
- Secondary non-responder: relative or complete loss of efficacy at subsequent injections
  - Inadequate muscle injection technique
  - Inappropriate muscle selection
  - Dose may be too low
  - *Change in pattern of muscle involvement
  - *Soft tissue contracture
  - *Neutralizing antibodies may be present
    - Tests for nonresponse: frontalis test, antibody assays (limited sensitivity, specificity)

POTENTIAL COMPLICATIONS

- Injection site pain.
- Muscle weakness.
- Distal spread of toxin.
- Fatigue.
- Slightly increased incidence of upper respiratory infections in clinical trials.
- Immunogenicity
  - Incidence < 1%.

PHYSIOTHERAPY AFTER INJECTIONS

- Numerous clinical studies substantiate the beneficial effect of aggressive physiotherapy after BoNT therapy over BoNT alone.
  - This has been demonstrated in multiple sclerosis patients and stroke patients.
- In some cases splinting or serial casting may be appropriate, especially for the hand.

QUESTIONS/DISCUSSION