SPASTICITY MANAGEMENT:
AN OVERVIEW OF SYSTEMIC AND FOCAL OPTIONS

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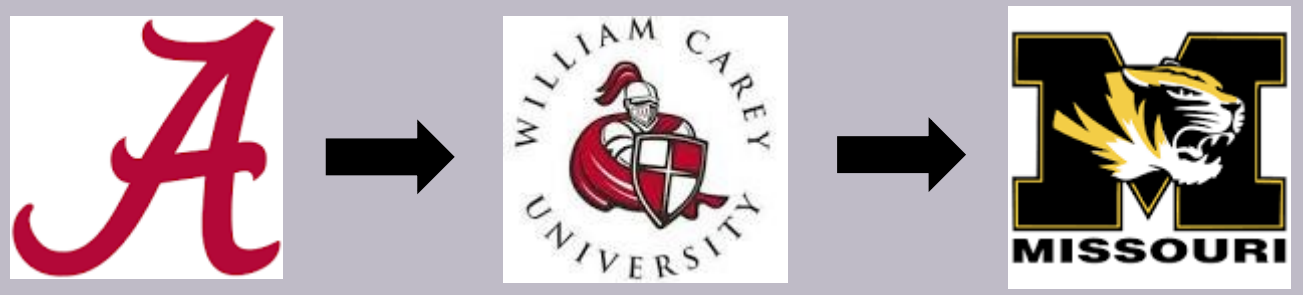
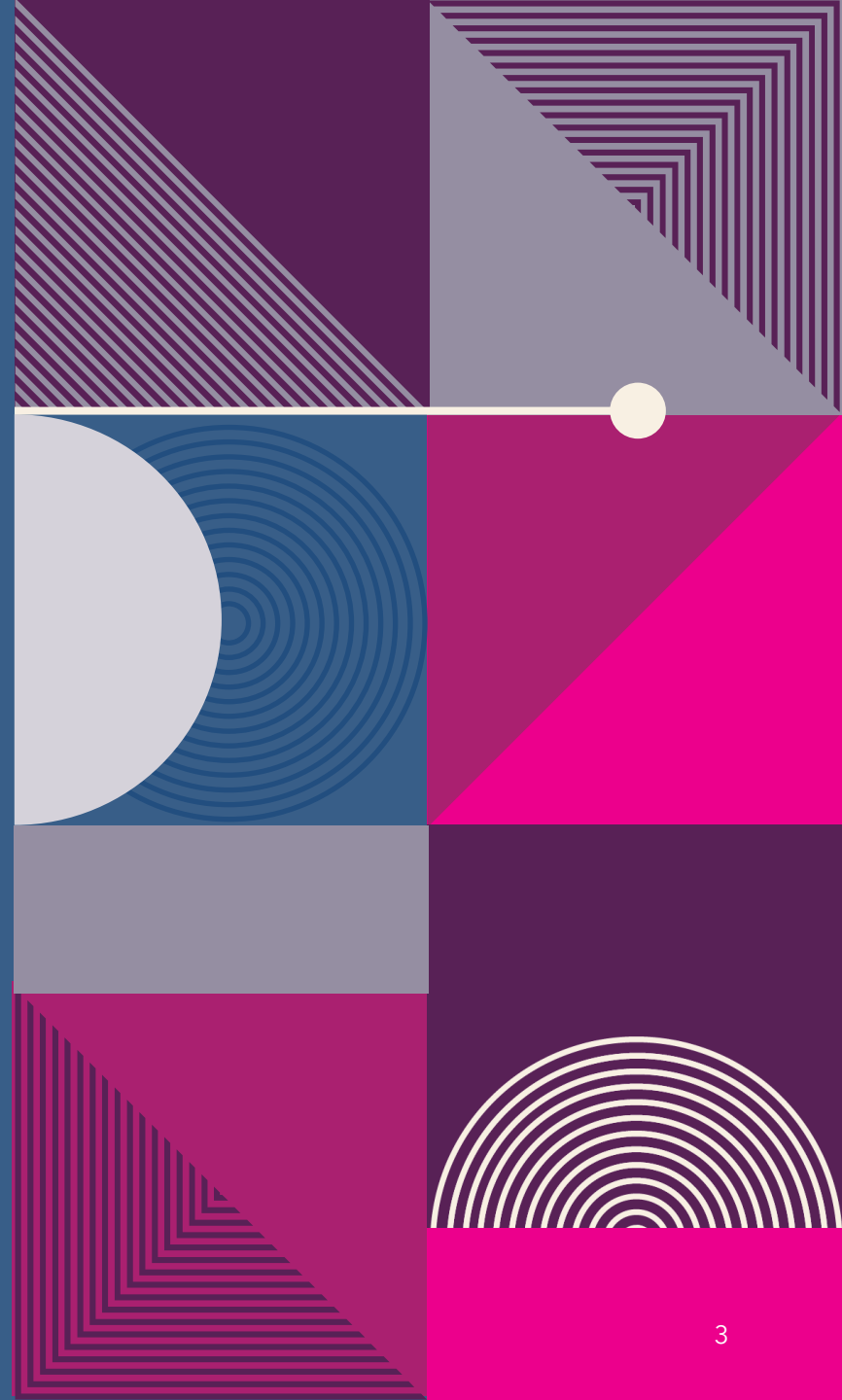
DISCLOSURES

- No disclosures to report



OBJECTIVES

- What is Spasticity?
- Synergistic Model of Spasticity Management
- Systemic Options
- Focal Options



WHAT IS SPASTICITY?

SPASTICITY

- A motor disorder characterized by a ***velocity-dependent*** exaggeration of stretch reflexes, resulting from abnormal intraspinal processing of primary afferent input.

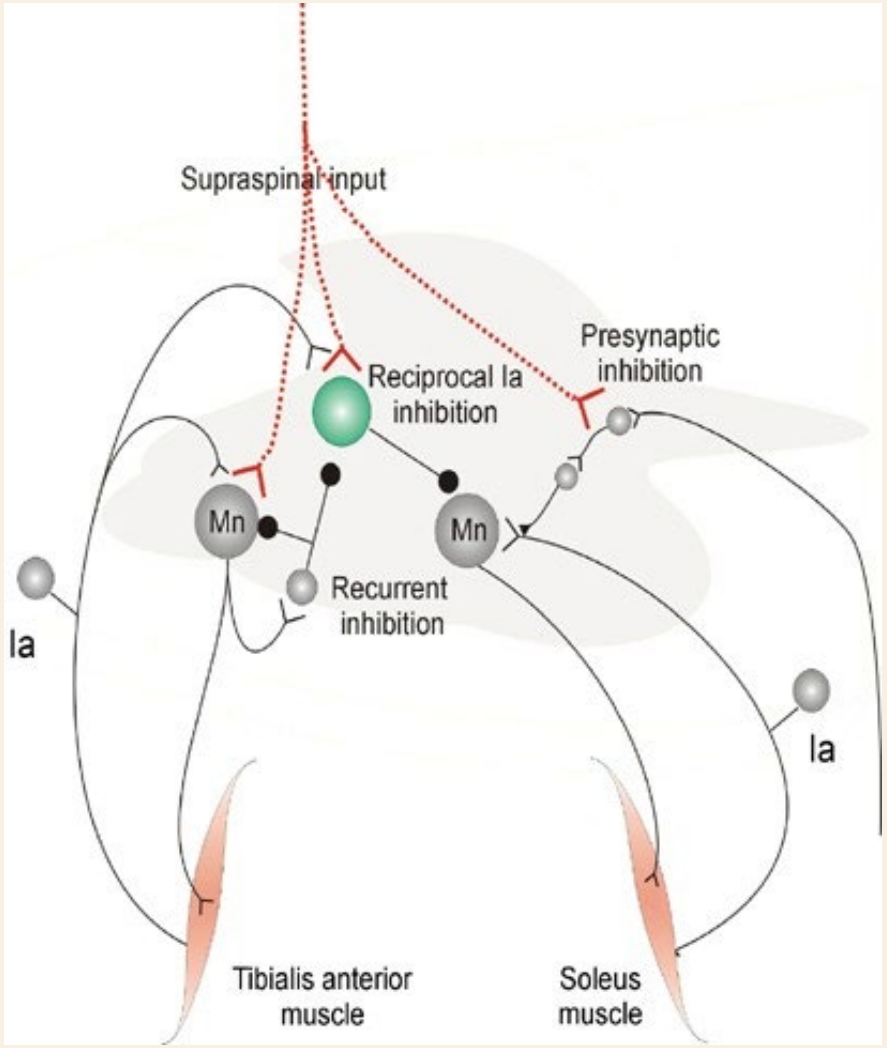
SPASTICITY

- Types:
  - **Generalized** = affects motor skills over widespread bodily regions
  - **Regional** = affects motor skills over a large region of the body, such as the torso or entire side of body
  - **Focal** = affects motor skills in a single body part, such as an arm or leg

SPASTICITY

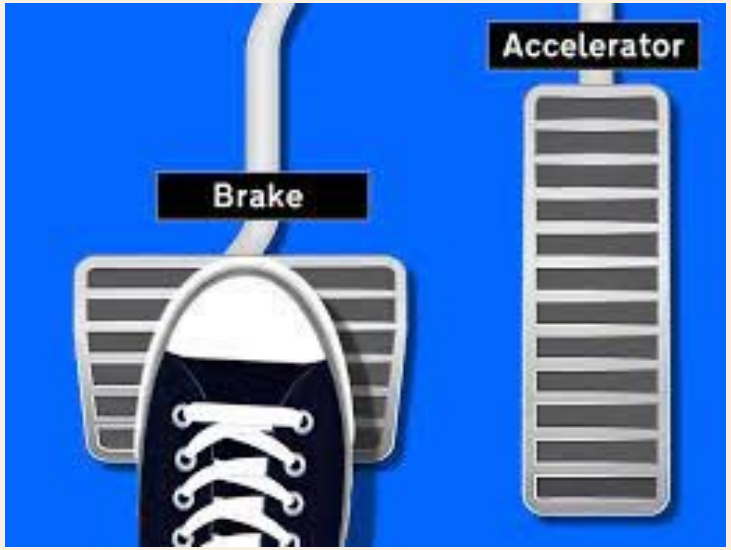
- Conditions:
  - **Stroke**
  - **Traumatic brain injury**
  - **Spinal cord injury**
  - **Cerebral palsy**
  - **Multiple sclerosis**

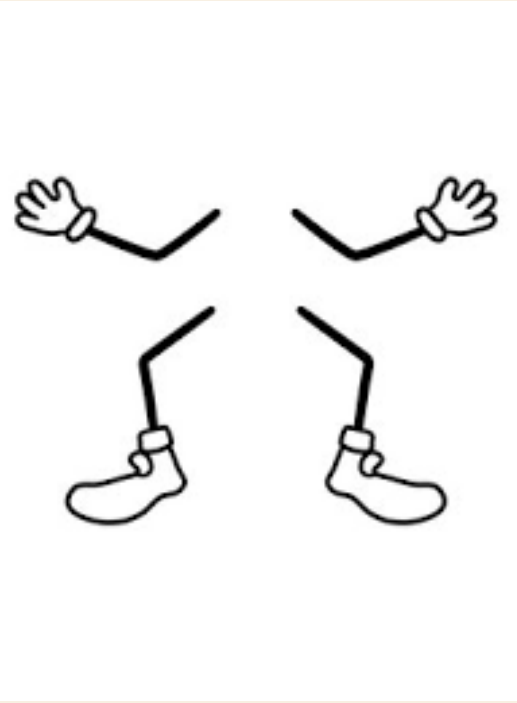
SPINAL PATHWAYS



Biering-Sørensen, F., Nielsen, J. & Klinge, K. Spasticity-assessment: a review. *Spinal Cord* **44**, 708–722 (2006). https://doi.org/10.1038/sj.sc.3101928

SPINAL PATHWAYS

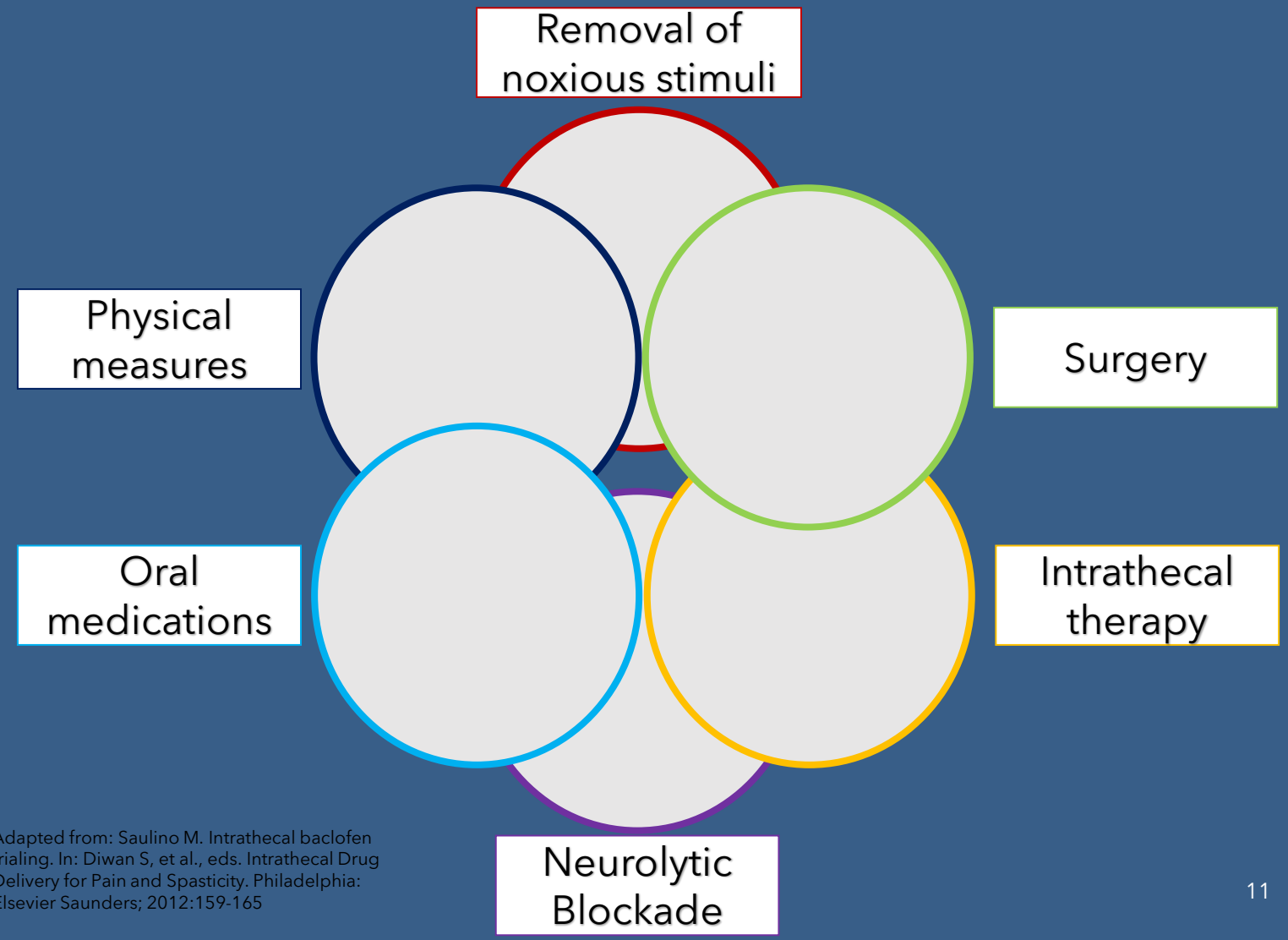




GOALS FOR TREATMENT

- **Technical goals:**
  - Increase range of motion
  - Reduce muscle tone
  - Reduce muscle spasms
- **Functional goals:**
  - Improve activities of daily living
  - Improve limb position
  - Improve walking and other movements
- **Preventive goals:**
  - Prevent immobility/contractures
  - Prevent pressure sores
  - Delay or prevent surgery
- **Other goals:**
  - Decrease caregiver burden

SYNERGISTIC MODEL OF SPASTICITY MANAGEMENT

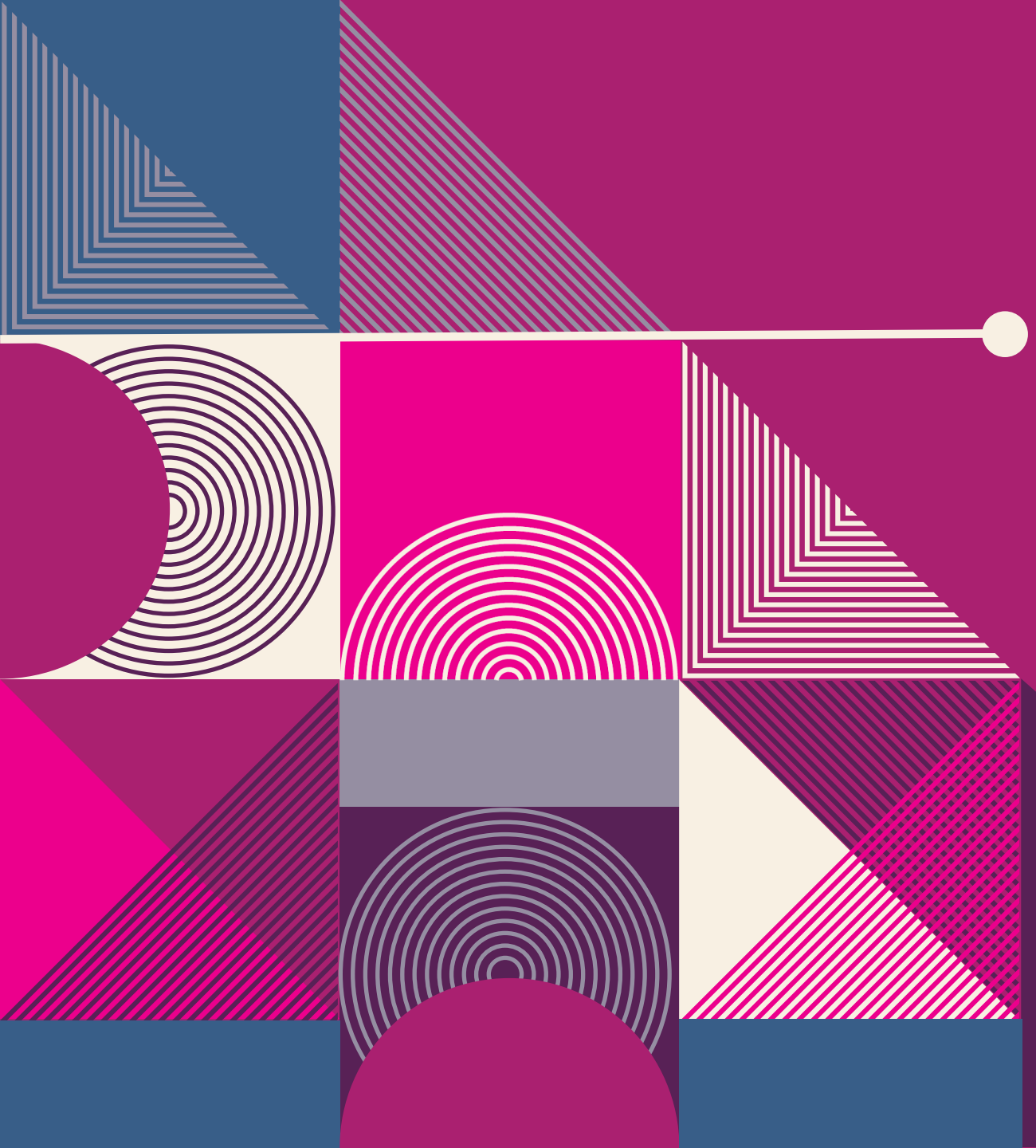


Adapted from: Saulino M. Intrathecal baclofen trialing. In: Diwan S, et al., eds. Intrathecal Drug Delivery for Pain and Spasticity. Philadelphia: Elsevier Saunders; 2012:159-165

GENERAL APPROACH

SYSTEMIC

FOCAL



SYSTEMIC OPTIONS

SYSTEMIC OPTIONS

- **Oral**
- **Intrathecal**
- Noninvasive neuromodulation (NINM)
  - Repetitive transcranial magnetic stimulation (rTMS)
  - Transcranial direct current stimulation (tDCS)

ORAL OPTIONS

ORAL OPTIONS

- **Baclofen** → GABA-B (1 and 2) agonist
- **Diazepam** → GABA-A agonist
- **Dantrolene** → ryanodine receptor antagonist *(peripherally acting)*
- **Tizanidine** → alpha-2 agonist
- **Cyclobenzaprine** → MOA poorly understood
- **Methocarbamol** → general CNS depression
- **Gabapentin** → mimics GABA, alpha-2-delta-1 subunit voltage-gated Ca2+ channels
- **Cyproheptadine** → antihistamine and serotonin antagonist *(off label - SCI only)*
- **Trihexyphenidyl** *(Artane)* → anticholinergic *(initial therapy for Parkinsonism)*

BACLOFEN

- MOA: inhibits the transmission of both monosynaptic and polysynaptic reflexes at the spinal cord level, possibly by hyperpolarization of primary afferent fiber terminals, with resultant relief of muscle spasticity
- GABA-B
- **Lioresal** – extended release
  - Dosing: 5 mg three times daily
  - Titration: can increase by 5 mg per dose every 3 days
  - Do not exceed 80 mg daily (20 mg four times daily)

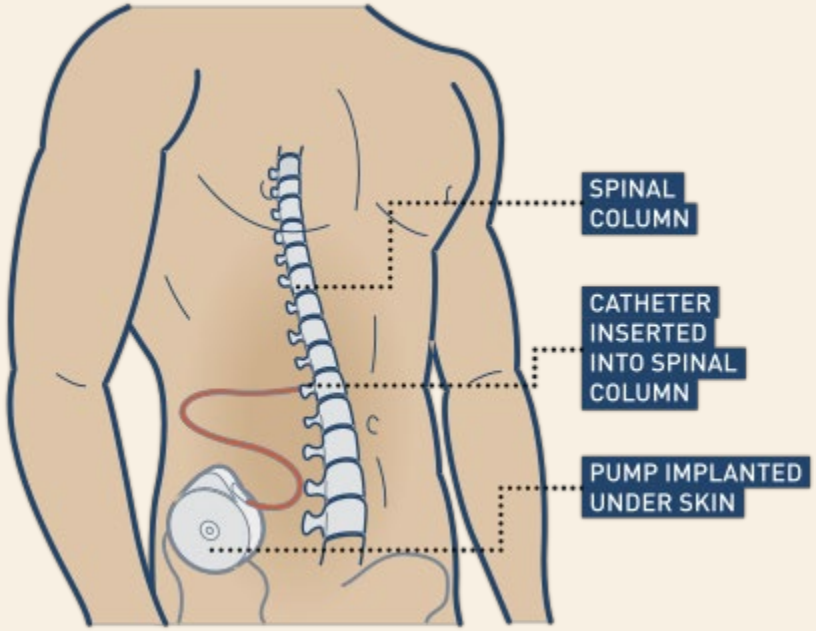
- **Lyvispah** – instant release

LYVISPAH™
(baclofen) oral granules

INTRATHECAL OPTIONS

INTRATHECAL OPTIONS

- Baclofen (Lioresal; Gablofen)



ITB MEDICATIONS

LIORESAL

- 2 concentrations
- 500 / 2,000

GABLOFEN

- 3 concentrations
- 500 / 1,000 / 2,000
- Sterile prefilled syringe

Boster AL, et al … recommend initiating therapy with 500 mcg/mL concentration to provide maximum flexibility for dosing in the lower range without having to dilute the drug.

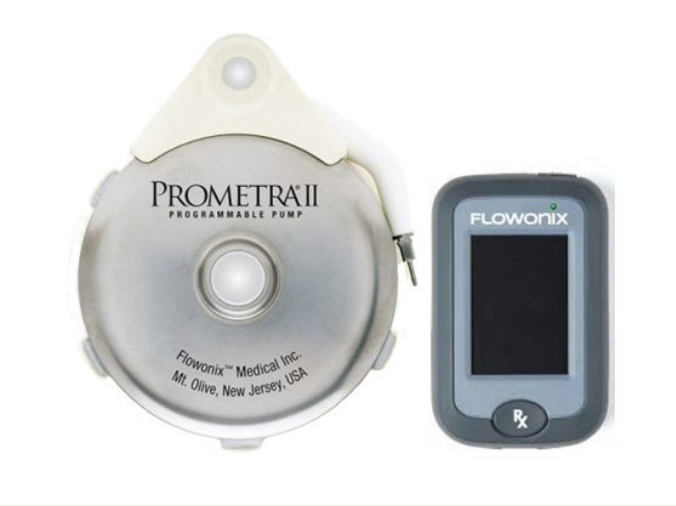
1.Boster AL, Adair RL, Gooch JL, et al. Best practices for intrathecal baclofen therapy: dosing and long-term management. *Neuromodulation*. 2016;19(6):623-631.

ITB PROGRAMABLE PUMPS

- ❑ Both are programmable devices using a tablet and Bluetooth connection
- ❑ Mechanics of each pump differ

MEDTRONIC SYNCHROMED II

FLOWONIX PROMETRA II



ITB TRIAL TEST DOSE

- 50 mcg bolus
  - 25 mcg in very small children or patients who rely on spasticity for mobility
- Patients unresponsive to standard dose may require 75 mcg or 100 mcg; 24 hours should elapse between bolus doses
- Effects within 30 minutes → max effect 4 hours
- Spasticity measures should be assessed at least twice within four hours

Boster AL, Bennett SE, Bilsky GS, Gudesblatt M, Koelbel SF, McManus M, Saulino M. Best Practices for Intrathecal Baclofen Therapy: Screening Test. Neuromodulation. 2016 Aug;19(6):616-22. doi: 10.1111/ner.12437. Epub 2016 Jul 19. PMID: 27434115.

ITB TRIAL MEASURES

MODIFIED ASHWORTH SCALE

- Measures increase in muscle tone
- **0** = no increase in tone
- **1** = slight increase with catch and release
- **1+** = slight increase with catch followed by minimal resistance through < 50% of ROM
- **2** = more marked increase through > 50% of ROM
- **3** = considerable increase in tone
- **4** = rigid

TARDIEU SCALE

- Measures joint angles
- **R1** = angle of muscle reaction
- **R2** = angle of full range of passive motion

TARDIEU VS ASHWORTH

- Mehrholz J, et all … "in patients with severe brain injury and impaired consciousness the ***Modified Tardieu Scale provides higher test retest and inter-rater reliability*** compared with the Modified Ashworth Scale and may therefore be a more valid spasticity scale in adults."

Mehrholz J, Wagner K, Meissner D, Grundmann K, Zange C, Koch R, Pohl M. Reliability of the Modified Tardieu Scale and the Modified Ashworth Scale in adult patients with severe brain injury: a comparison study. Clin Rehabil. 2005 Oct;19(7):751-9. doi: 10.1191/0269215505cr889oa. PMID: 16250194.

ITB Trial
Dose: 50 / 75 / 100 mcg

Before

Tardieu Scale:

	RIGHT		LEFT	
	R1	R2	R1	R2
Shoulder Abduction				
Elbow Extension				
Wrist Extension				
Finger Extension				
Hip Abduction				
Hip External Rotation				
Hip Internal Rotation				
Knee Extension				
Popliteal Angles				
Ankle Dorsiflexion				
Ankle Plantarflexion				

Modified Ashworth Scale:
1:
1+:
2:
3:
4:

Mobility/Ambulation:

After

Tardieu Scale:

	RIGHT		LEFT	
	R1	R2	R1	R2
Shoulder Abduction				
Elbow Extension				
Wrist Extension				
Finger Extension				
Hip Abduction				
Hip External Rotation				
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Modified Ashworth Scale:
1:
1+:
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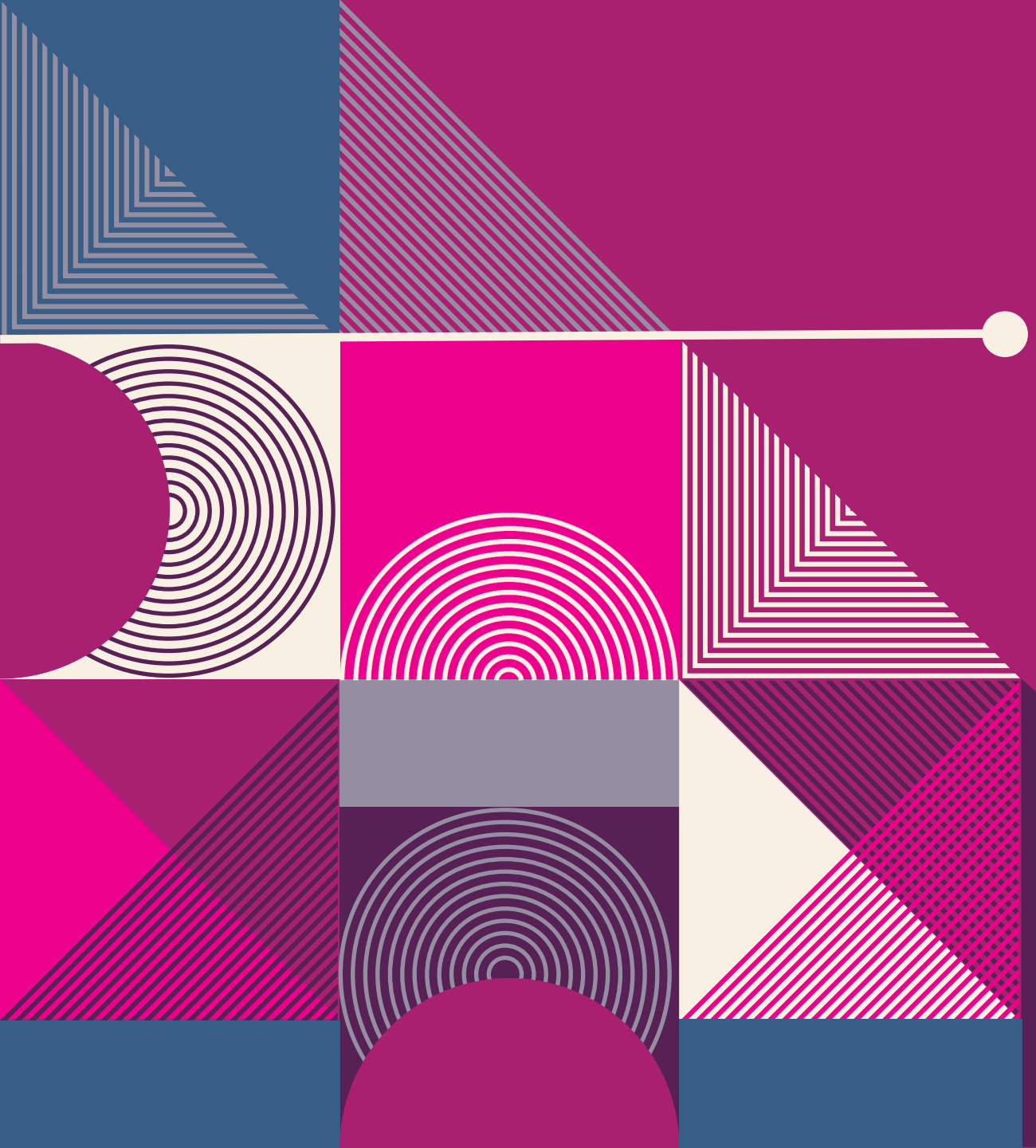
Mobility/Ambulation:



FOCAL OPTIONS

FOCAL OPTIONS

- ❑ Therapies and Modalities
  - ❑ PROM
  - ❑ Cold therapy
  - ❑ Splinting/bracing

- ❑ **Injections**
  - ❑ Neurotoxin
  - ❑ Neurolysis

- ❑ Surgical
  - ❑ Tendon release

FOCAL INJECTIONS

- **Neurotoxin**
  - Botulinum toxin
- **Neurolysis**
  - Phenol

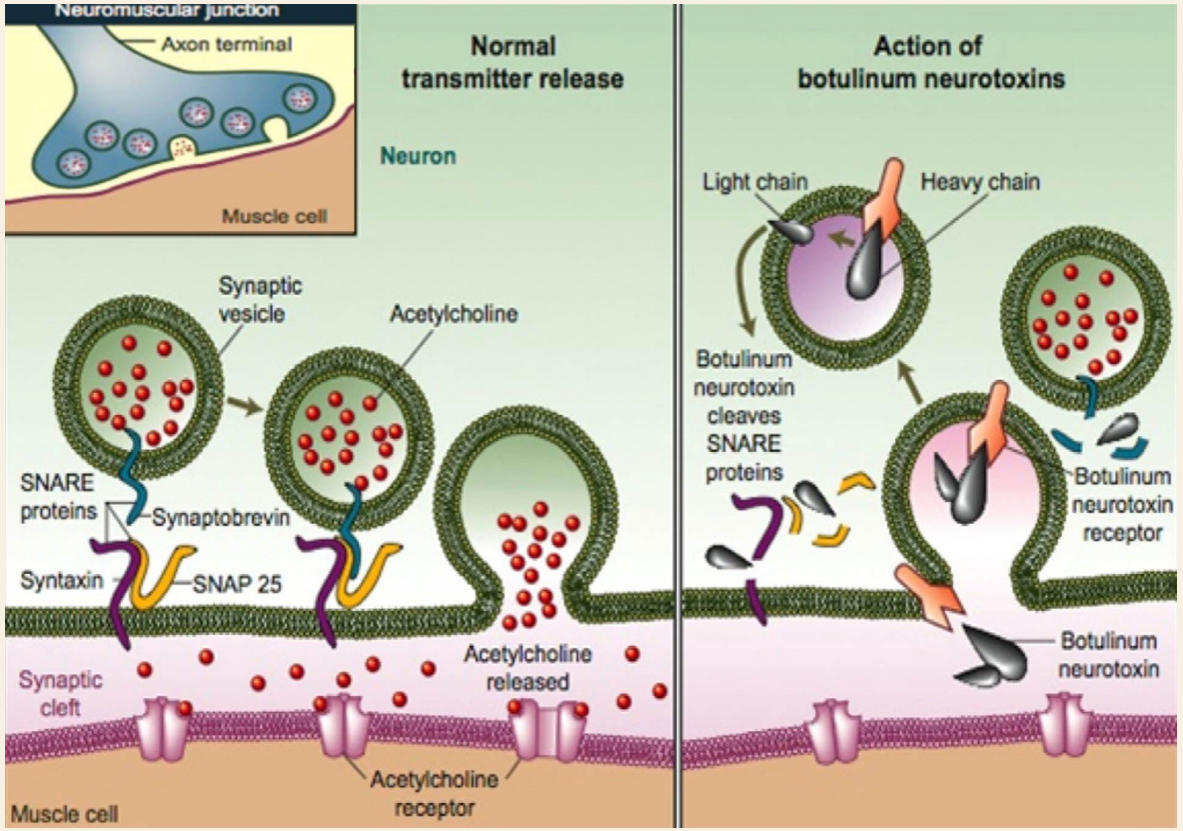
HISTORY OF BOTULINUM TOXIN

HISTORY OF BOTULINUM TOXIN

- First historical description reported in 1735
- 1793 several persons died after eating "Blunzen" – pork stomach filled with blood and spices
- German physician J.C. Kerner – first to study botulism and names the new toxin **"sausage poison"**
- 1895 E. Van Ermengem isolated the bacterium *Clostridium botulinum*, from samples of a piece of ham that had poisoned people at a funeral
  - Named the toxin "Bacillus Botulinus"
    - Botulus – meaning sausage in Latin
- 1944 E. Schantz cultured *Clostridium botulinum* and isolated the different stereotypes of the toxin
- 1980 first utilized in humans therapeutically – strabismus
- 1989 FDA approved onabotulinumtoxinA for treatment of strabismus, blepharospasm and hemifacial spasm in children younger than 12 years of age

Franca K, Kumar A, Fioranelli M, Lotti T, Tirant M, Roccia MG. The history of Botulinum toxin: from poison to beauty. Wien Med Wochenschr. 2017;167(8):46 8. DOI: 10.1007/s10354-017-0553-7 PMID: 28299552.

BOTULINUM TOXIN



BOTULINUM TOXIN

- Neurotoxin produced by *Clostridium botulinum*
  - 8 antigenically distinguishable exotoxin serotypes
    - A, B, C1, C2, D, E, F, and G

- MOA: Affects the **PRE-SYNAPTIC** membrane of the neuromuscular junction → prevents calcium-dependent release of acetylcholine → state of denervation

- Muscle inactivation persists until new fibrils grow from the nerve and form junction plates on new areas of the muscle-cell walls

Nigam PK, Nigam A. Botulinum toxin. Indian J Dermatol. 2010;55(1):8-14. doi: 10.4103/0019-5154.60343. PMID: 20418969; PMCID: PMC2856357.

BOTULINUM TOXIN TYPES

BOTOX

- ❑ Onabotulinumtoxin A
- ❑ Units: 100 / 200
- ❑ Strength: 1:1
- ❑ Approval: **Upper and lower** limb spasticity

DYSPORT

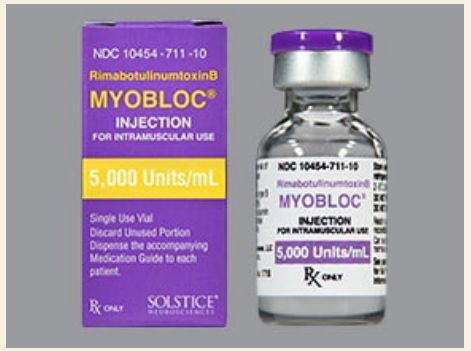
- ❑ AbobotulinumtoxinA
- ❑ Units: 300 / 500
- ❑ Strength: 1.2–1.4:1
- ❑ Approval: **Upper and lower** limb spasticity

XEOMIN

- ❑ IncobotulinumtoxinA
- ❑ Units: 50 / 100 /200
- ❑ Strength: 1:1
- ❑ Approval: **Upper** limb spasticity

NEUROBLOC / MYOBLOC

- ❑ RimabotulinumtoxinB
- ❑ Units: 2500 / 5000 / 10,000
- ❑ Strength: 1:50-1:100
- ❑ Not approved for spasticity



Strength = Botulinum toxin A : product

BOTULINUM TOXIN TYPES

BOTOX

- Active neurotoxin is **BTX-A**
- The original product
- Purified by repeated precipitation and re-dissolution
- 1997 formulation change → reduced amount of immunogenic protein content

DYSPORT

- Active neurotoxin is **BTX-A**
- Purified by a column separation method
- Appears to have a greater spread effect clinically → more diffuse distribution of clinical effects
- Dose ratios between Dysport and Botox = 3:1

XEOMIN

- Active neurotoxin is **BTX-A** stripped from any complexing proteins
- Purer formulation has been suggested to lead to greater efficacy with reduced risk of sensitization or antibody formation

NEUROBLOC / MYOBLOC

- Only **BTX-B** approved in US
- First toxin approved for cervical dystonia
- More rapid onset of action and greater area of diffusion, however painful (pH 5.5-6.5) and shorter duration of effects
- Units are significantly less effective when compared to BTX-A units

Walker TJ, Dayan SH. Comparison and overview of currently available neurotoxins. J Clin Aesthet Dermatol. 2014 Feb;7(2):31-9. PMID: 24587850; PMCID: PMC3935649.

BOTULINUM ADVERSE EFFECTS

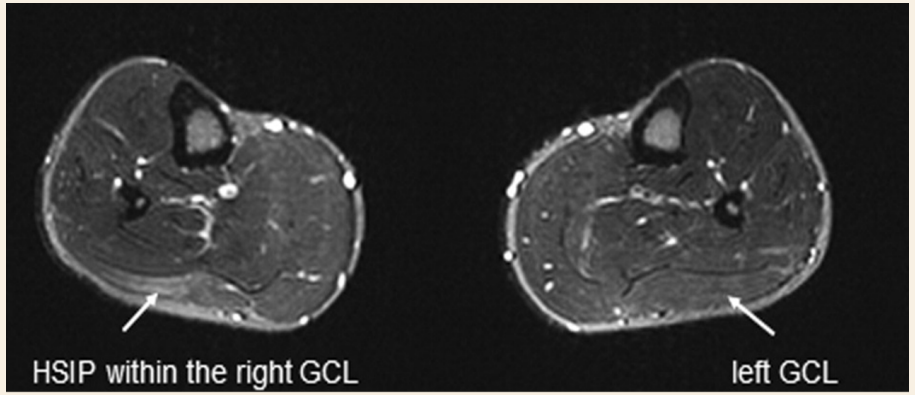
- One of the most lethal toxins on the planet
  - Lethal dose (LD50) is 1.3-2 ng/kg (IM/IV) and 10-13 ng/kg (inhaled)

- Between 2009-2013, 285 adverse events were reported to Health Canada
  - 18% were hospitalized, 8% died
  - Weakness
  - Dysphagia
  - Respiratory problems
  - Eye related complications
  - Bowel/bladder
  - Infection

Phadke, C., Balasubramanian, C., Holz, A., Davidson, C., Ismail, F., & Boulias, C. (2016). Adverse Clinical Effects of Botulinum Toxin Intramuscular Injections for Spasticity. *Canadian Journal of Neurological Sciences / Journal Canadien Des Sciences Neurologiques, 43*(2), 298-310. doi:10.1017/cjn.2015.314

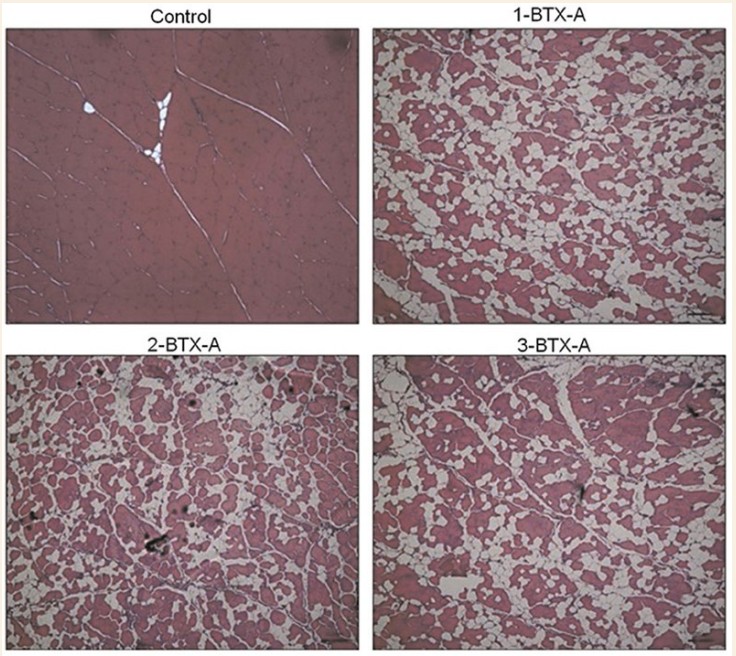
BEWARE OF THE LASTING EFFECTS

1 YEAR AFTER INJECTION INTO LATERAL GASTROCNEMIUS OF HEALTHY VOLUNTEER



HSIP = high signal intensity pattern

6 MONTHS POST 1, 2 AND 3 INJECTIONS OF BTX- A

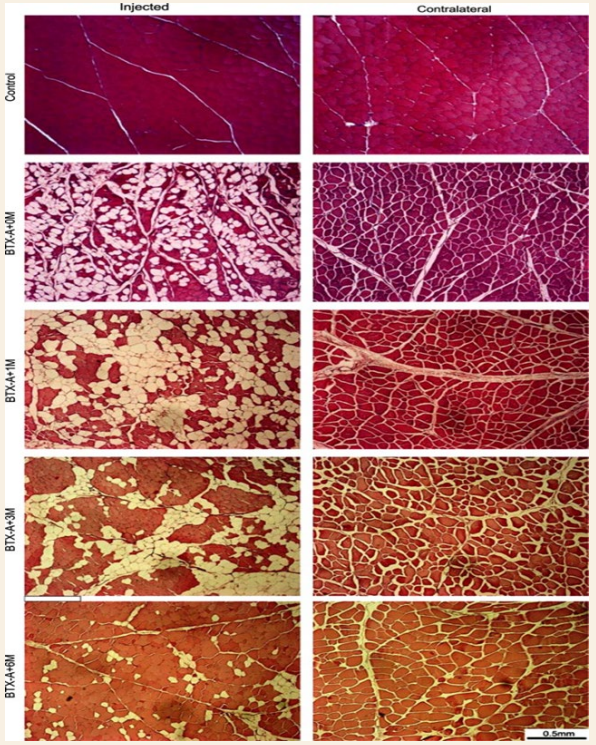


Schroeder AS, Ertl-Wagner B, Britsch S, Schröder JM, Nikolin S, Weis J, Müller-Felber W, Koerte I, Stehr M, Berweck S, Borggraefe I, Heinen F. Muscle biopsy substantiates long-term MRI alterations one year after a single dose of botulinum toxin injected into the lateral gastrocnemius muscle of healthy volunteers. Mov Disord. 2009 Jul 30;24(10):1494-503. doi: 10.1002/mds.22661. PMID: 19489066.

BEWARE OF THE LASTING EFFECTS

DO SKELETAL MUSCLE PROPERTIES RECOVER FOLLOWING REPEAT ONABOTULINUM TOXIN A INJECTIONS?

- "… BTX-A injections can cause severe adverse effects in injected and non-target muscles."
- "… target and non-target muscles did not fully recover within six month recovery period following our BTX-A protocol."



quadriceps muscles on New Zealand white (NZW) rabbits

Fortuna R, Horisberger M, Vaz MA, Herzog W. Do skeletal muscle properties recover following repeat onabotulinum toxin A injections? J Biomech. 2013 Sep 27;46(14):2426-33. doi: 10.1016/j.jbiomech.2013.07.028. Epub 2013 Jul 26. PMID: 23953503.

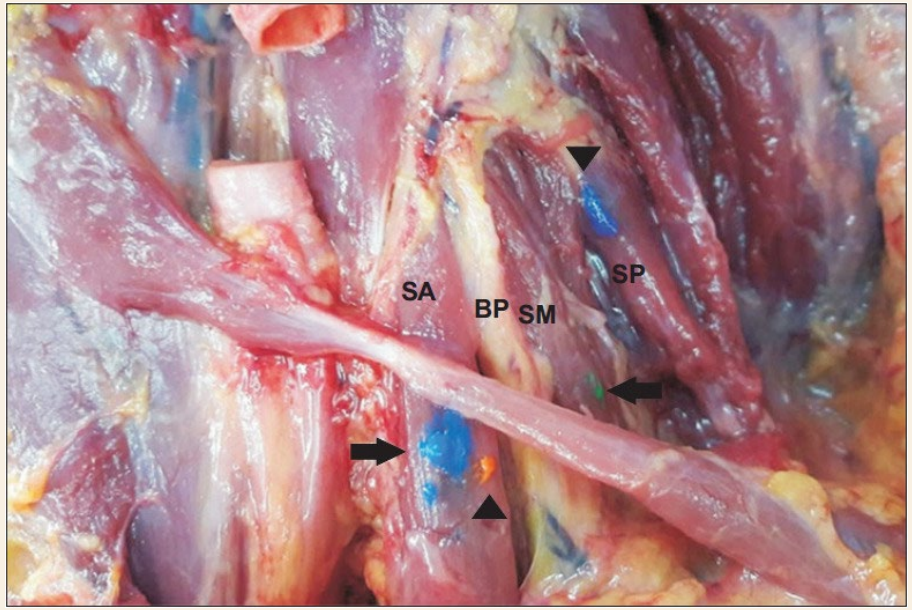
GUIDANCE OPTIONS

- ❑ **Palpation**
- ❑ **Ultrasound**
- ❑ **Electromyography**
- ❑ **Stimulation**

PALPATION GUIDED INJECTION

ACCURACY OF ULTRASOUND-GUIDED AND NON-GUIDED BOTULINUM TOXIN INJECTION INTO NECK MUSCLES INVOLVED IN CERVICAL DYSTONIA: A CADAVERIC STUDY

- 2 physicians injected ultrasound-guided and non-guided injections to each side of the cadaver's neck muscles (sternocleidomastoid, upper trapezius, levator scapulae, splenius capitis, scalenus anterior, and scalenus medius)
- The overall accuracies of the ultrasound-guided and non-guided injections into the six muscles were 97.2% and 62.5%, respectively ($p<0.001$).



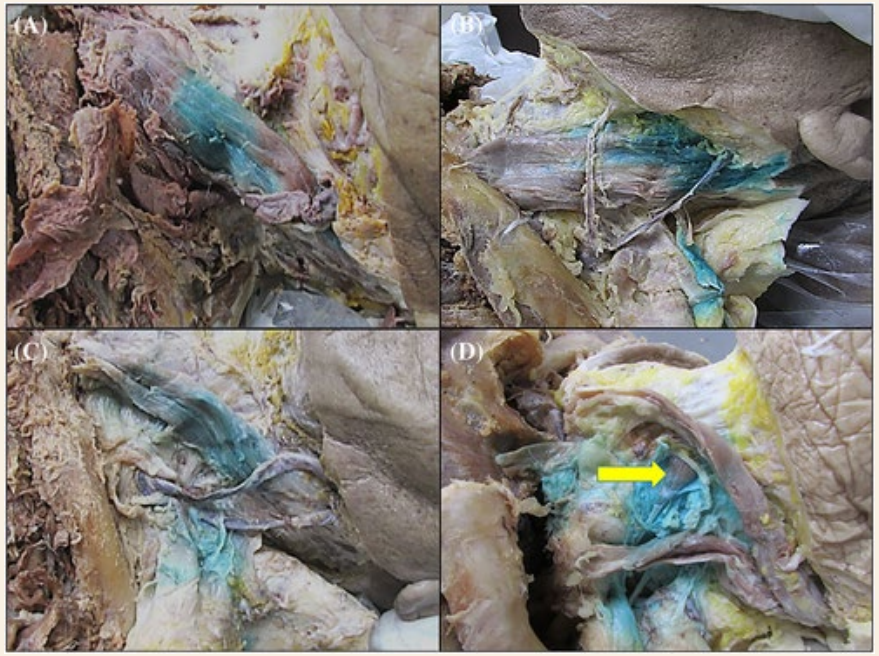
Dissected cadaver with ultrasound-guided injection (blue and green dye, arrow) and non-guided injection (orange and purple dye, arrow head). The purple dye that targeted the scalenus medius muscle was misinjected into the scalenus posterior muscle. SA, scalene anterior; BP, brachial plexus; SM, scalene medius; SP, scalene posterior.

Ko YD, Yun SI, Ryoo D, Chung ME, Park J. Accuracy of Ultrasound-Guided and Non-guided Botulinum Toxin Injection Into Neck Muscles Involved in Cervical Dystonia: A Cadaveric Study. Ann Rehabil Med. 2020 Oct;44(5):370-377. doi: 10.5535/arm.19211. Epub 2020 Sep 28. PMID: 32986942; PMCID: PMC7655231.

ULTRASOUND GUIDED INJECTION

ULTRASOUND-GUIDED INJECTION OF THE STERNOCLEIDOMASTOID MUSCLE: A CADAVERIC STUDY WITH IMPLICATIONS FOR CHEMODENERVATION

- Physician with 15+ years of experience performed injections with US-guidance.
- An injection was considered successful when the dye was confined to the SCM and superficial structures (A, B, and C). In one case of a 3.5-mm-thick SCM, the dye reached the omohyoid muscle and was deemed unsuccessful (D). *Yellow arrow = omohyoid muscle; SCM = sternocleidomastoid muscle.
- **"Accurate targeting of the motor endplate zone improves the effectiveness of intramuscular botulinum toxin injection."**



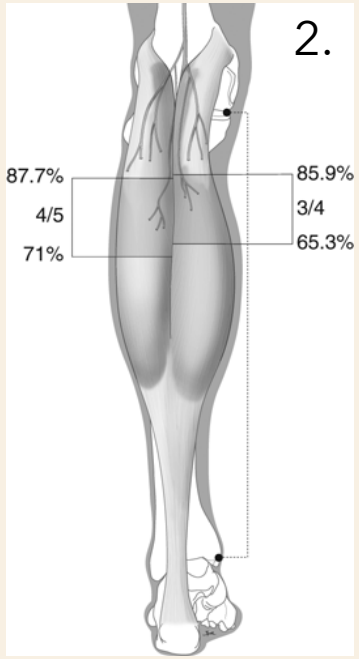
*Yellow arrow = omohyoid muscle;
SCM = sternocleidomastoid muscle.

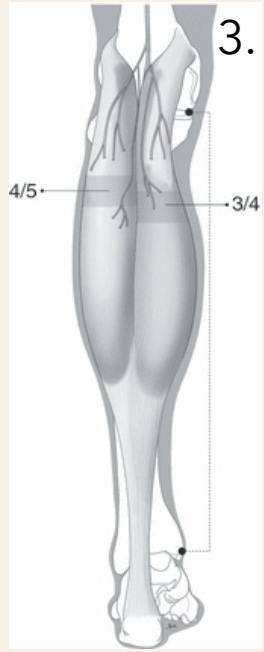
Kim, B.S., Kim, D.S., Kang, S., Kim, J.Y., Kang, B., Rhyu, I.J. and Yoon, J.S. (2021), Ultrasound-Guided Injection of the Sternocleidomastoid Muscle: A Cadaveric Study with Implications for Chemodenervation. PM&R, 13: 503-509. https://doi.org/10.1002/pmrj.12463

ELECTROMYOGRAPHY / STIMULATION GUIDED INJECTION

LOCALIZATION OF THE MOTOR ENDPLATE ZONE IN HUMAN SKELETAL MUSCLES OF THE LOWER LIMB: ANATOMICAL GUIDELINES FOR INJECTION WITH BOTULINUM TOXIN

- **1.** Gastrocnemius muscle (muscle belly; proximal, up; distal, down; no markings were made by Christensen about left–right or medial–lateral) after cholinesterase staining. Dots represent MEPs, according to Christensen.
- **2.** Gastrocnemius on a left leg, posterior view. MEP area according to Parratte et al.17
- **3.** Optimal injection area for gastrocnemius muscle. Left leg, posterior view.





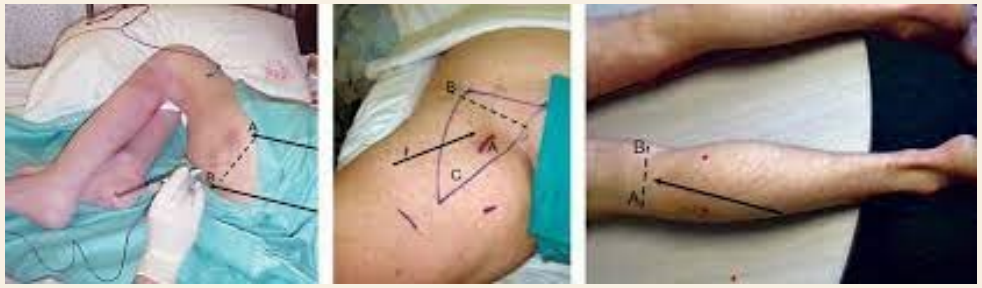
VAN CAMPENHOUT, A. and MOLENAERS, G. (2011), Localization of the motor endplate zone in human skeletal muscles of the lower limb: anatomical guidelines for injection with botulinum toxin. Developmental Medicine & Child Neurology, 53: 108-119. https://doi.org/10.1111/j.1469-8749.2010.03816.x

ELECTROMYOGRAPHY / STIMULATION GUIDED INJECTION

DANTEC CLAVIUS HANDHELD

NEUROLYSIS INJECTIONS

- **Phenol**
  - Chemical composite agent
  - Typical concentration: 6%
  - MOA: denatures proteins
    - Effects are a combination of neurotoxicity and ischemia
    - Leads to non-selective nerve destruction, muscle atrophy, and necrosis of surrounding tissues
      - Proper guidance is important!



PHENOL

- Onset is within minutes → about 70% of total response
- Remaining response (30%) occurs over the next 30 days
  - Wallerian degeneration

- Nerve selection is important → motor heavy/specific
  - Musculocutaneous
  - Pectoral
  - Obturator
  - Tibial
  - Sciatic (hamstring selective)

IN REVIEW

KEYS TO SUCCESS

- Set expectations
  - 50% improvement in pain
  - 50% improvement in function
- Considerations
  - Length of therapy
  - Patient/caregiver travel
- Approach
  - Conservative versus aggressive

THANK YOU

Ochsner Health System