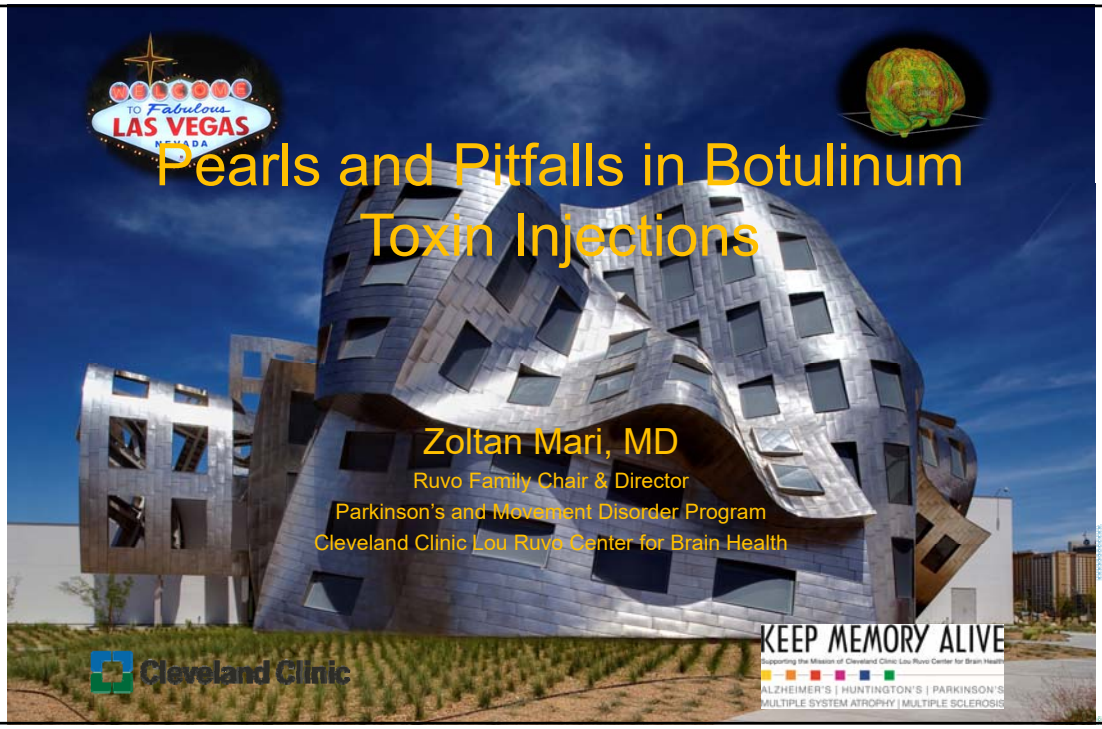


Outline

1. **Beware! BoNT is a poison!**
2. **Brief historical overview**
3. **Review of BoNT mechanism of action**
4. **Dosing BoNT**
5. **Cervical dystonia treatment with BoNT**
6. **BoNT controversies, questions, pitfalls, and pearls**

"Sausage Poisoning"

1st Pitfall!

Botulinum toxin (BoNT) is a powerful poison – the most potent naturally occurring known poison!

While botulism is rare and proper use of therapeutic BoNT brands should never cause it, please keep in mind that errors may lead to fatal consequences.

Justinius Kerner 1786–1862

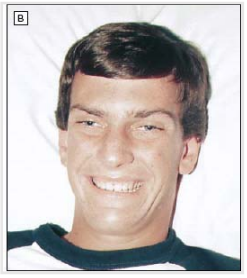
Das
Fettgift
oder
die Fettsäure
und
ihre Wirkungen auf den thierischen Organismus,
ein Beytrag
zur Untersuchung des in verdorbenen Würsten giftig wirkenden Stoffes,
von
Dr. Justinus Kerner,
Oberamtsarzt zu Weinsberg.
Stuttgart und Tübingen,
in der J. G. Cotta'schen Buchhandlung.
1822.

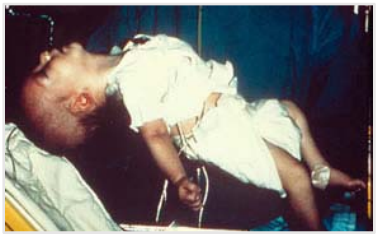
Kerner's second monograph on "fatty poison" (1822)

Erbguth FJ. *Mov Disord.* 2004;19:S2-S6.

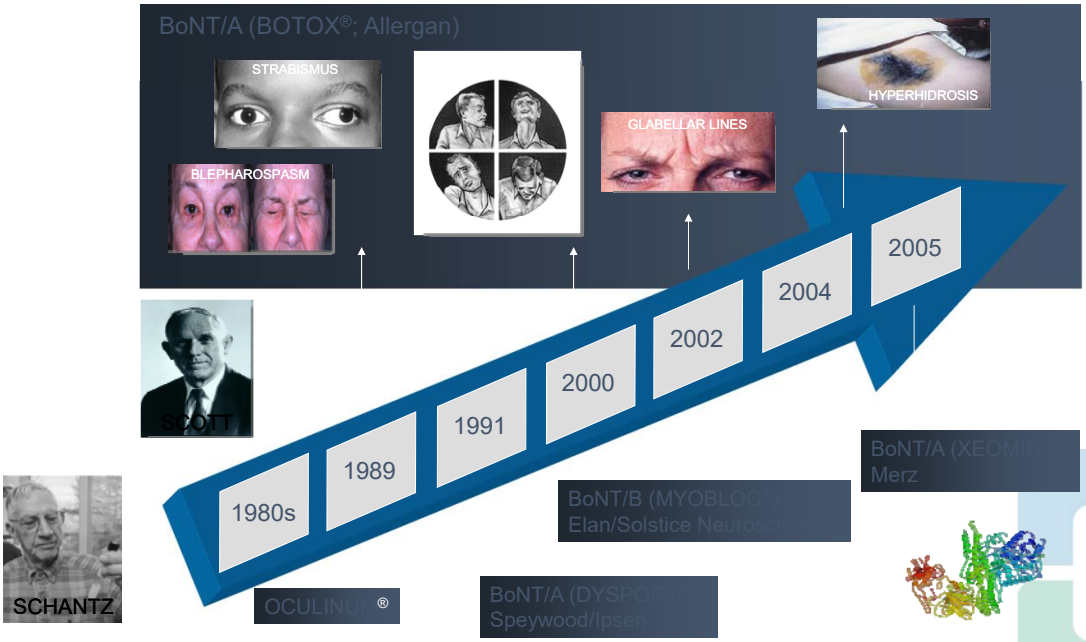
Botulism

- Symmetric cranial neuropathies
  - Diplopia/blurred vision
  - Ptosis
  - Dysphagia
  - Dysarthria
  - Dry mouth
  - Mydriasis
- Flaccid paralysis
  - Respiratory failure





Brief Historical Overview of Botulinum Toxin Clinical Development

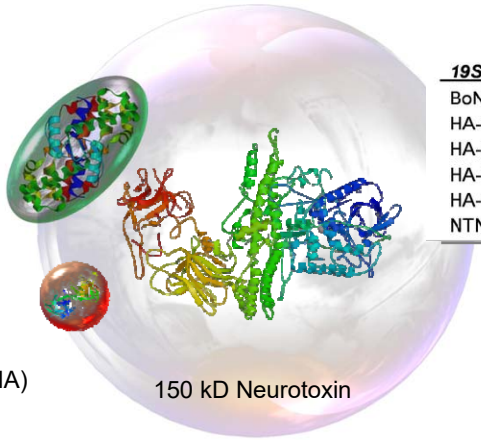


Botulinum Toxins

- 7 distinct serotypes of toxin
  - A, B, C, D, E, F, G
  - Serotypes A and B available for human use
- Botulinum toxin complex
  - Hemagglutinin and nonhemagglutinin proteins
  - Neurotoxin

Botulinum Toxin Structure

Non-toxic, non-hemagglutinin (NTNH)



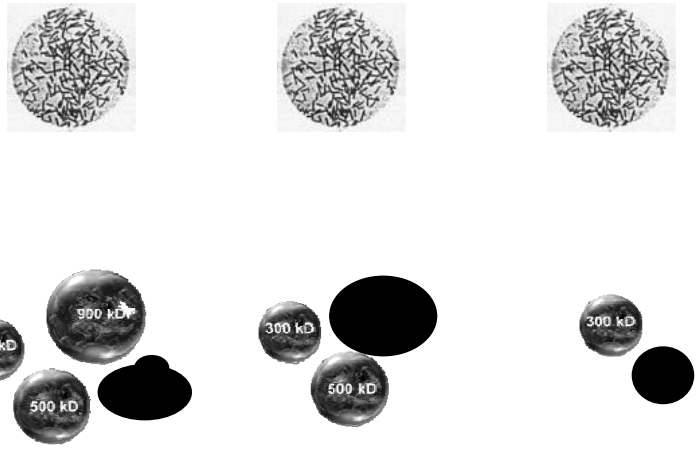
Hemagglutinin (HA)

150 kD Neurotoxin

19S Protein	Molar Ratio
BoNT/A	1
HA-52	2
HA-35	8
HA-19/20	3
HA-15	3
NTNH	1

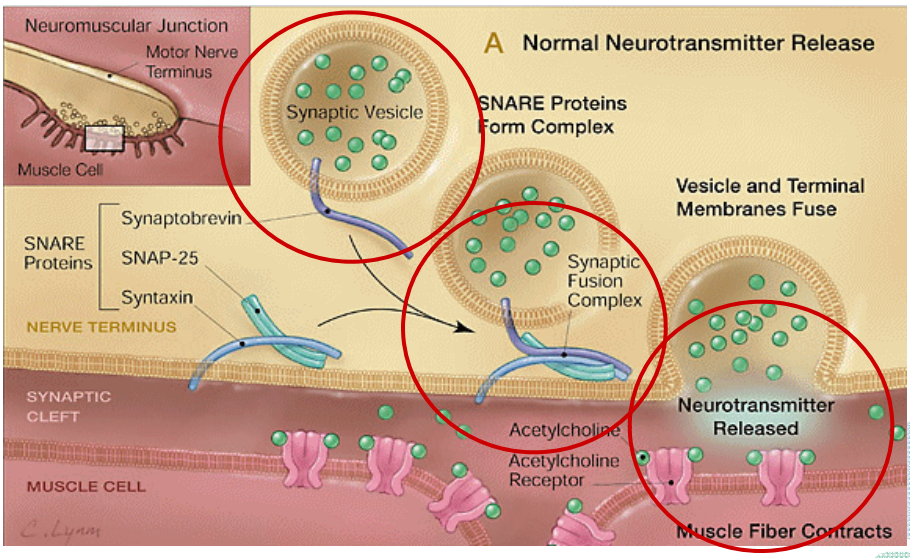
[1]Hathaway. In: Hauschild AHW, ed. Clostridium Botulinum: Ecology and Control in Foods New York, NY: Marcel Dekker, Inc.;1993;54:pp 3-20.
[2]Inoue et al. Infect Immun 1996;64:1589-1594.
[3]Lacy et al. Nat Struct Biol 1998;5:898-902 (with permission).

Clostridia produce different size progenitor toxin complexes

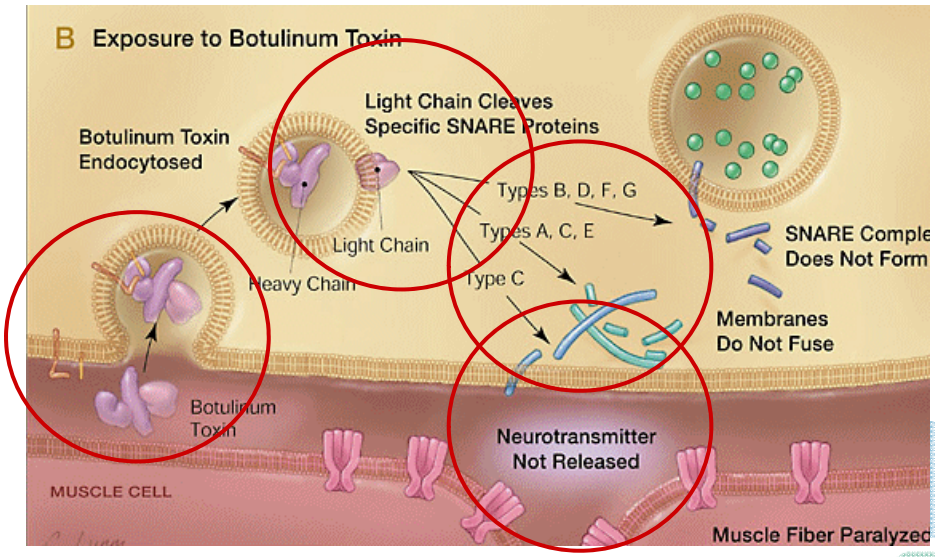


[1]Hathaway. In: Hauschild AHW, ed. Clostridium Botulinum: Ecology and Control in Foods New York, NY: Marcel Dekker, Inc.;1993;54:pp 3-20.

Normal Neuromuscular Function



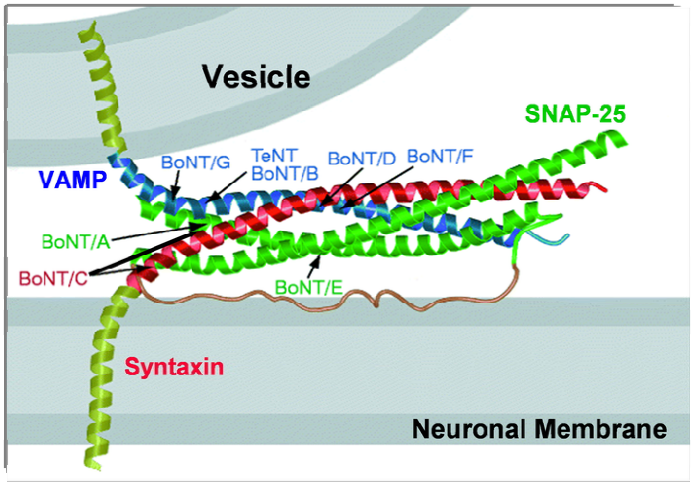
Botulinum Toxin Mechanism of Action



Botulinum Toxin Mechanism of Action
Neuromuscular Junction

VIDEO

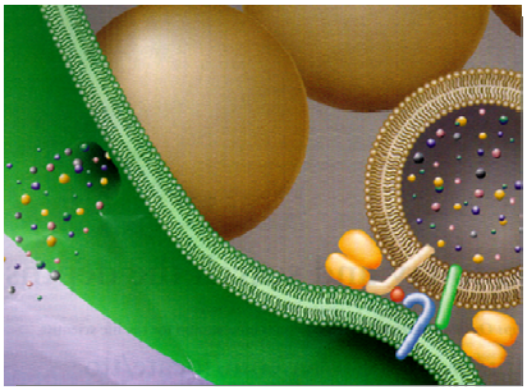
SNARE* Protein Target Sites For Botulinum Toxin Serotypes



SNARE: Conserved Throughout the PNS

SOMATIC

AUTONOMIC



Botulinum Toxin

- Most potent and persistent neurotoxin known
- Nanogram amounts are sufficient to be lethal
- Listed among the 6 highest risk threat agents of bioterrorism by the Centers for Disease Control and Prevention

Know Your Botulinum Toxin!

Be familiar with the brand of BoNT
Storage, vial size, dosing, serotype

LABEL SYRINGE WITH TYPE AND CONCENTRATION

Botulinum toxin dosing

Commercially available toxins (in the US)

Generic name	Brand name Vial sizes	Dose in CD (Units)
onabotulinumtoxinA	Botox 100/200U	100-300
abobotulinumtoxinA	Dysport 300/500U	500-1,000
incobotulinumtoxinA	Xeomin 50/100U	100-300
rimabotulinumtoxinB	Myobloc 2500/5000/10000	2,500-10,000

Comparative studies have not demonstrated superiority of one brand over another.

Toxin Dosing

Increase the dose

+ Heavy weight
+ Large muscle bulk
+ Severe disease
+ Low concern for weakness

– Low weight
– Small muscle bulk
– Mild disease
– High probability of weakness
– Too much weakness from previous injection

Decrease the dose

Botulinum toxin brands are *unique* drugs

- There is no interchangeable dosing.
- When starting a new brand, base dosing on the package insert and studies of that brand
- Consider changing from one brand to another:
  - if there is resistance to one serotype
  - based on patient need or insurance
- Avoid “rotating” brands and serotypes

Cervical Dystonia: Characteristics

1. Most common form of focal dystonia
   - Affects 9 to 30 persons per 100,000 population
   - 1.3 to 2 times as common in women as in men
   - Median age of onset, 41 years
2. Sensory tricks—provides partial, temporary relief[1]
3. Prognosis: stabilization is common; remission rate is 10% to 20%; progression to segmental rate is 20%[2]
4. Misdiagnosis, underdiagnosis are common[3]

1. Dashtipour K, Lew M. *Handbook of Dystonia*. 2007: 137-154.
2. Jankovic J. *Dystonia: Etiology, Clinical Features, and Treatment*. 2004; 159-166.
3. Dressler D. *Botulinum Toxin Therapy*. 2000: 39-125.

Cervical Dystonia: Other Characteristics

1. Commonly associated with asymmetric muscle hypertrophy
   --seen especially in the sternocleidomastoid
2. Postural tremors seen in 30%
   --"No-no" vs. "yes-yes" tremor
3. Neck pain in > 70% *(Chan et al 1991)*
4. Usually remains focal; Uncommon for generalized dystonia to start in the neck

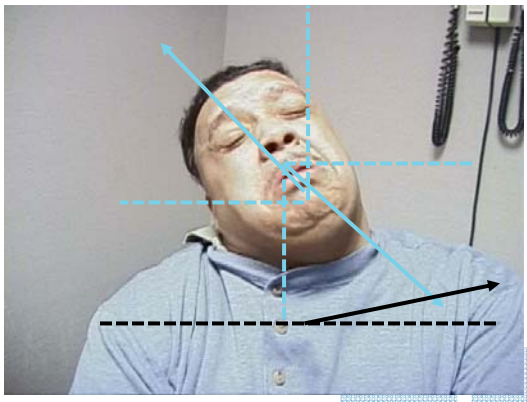
1. Dashtipour K, Lew M. *Handbook of Dystonia*. 2007: 137-154.
2. Jankovic J. *Dystonia: Etiology, Clinical Features, and Treatment*. 2004; 159-166. 3. Dressler D. *Botulinum Toxin Therapy*. 2000: 39-125.

Describing a patient with cervical dystonia

- Where is the head tilted? How much?
- Where is the chin deviated? How much?
- Is there retrocollis or anterocollis?
- Is the shoulder elevated?
- Is the head shaking?

Best description:

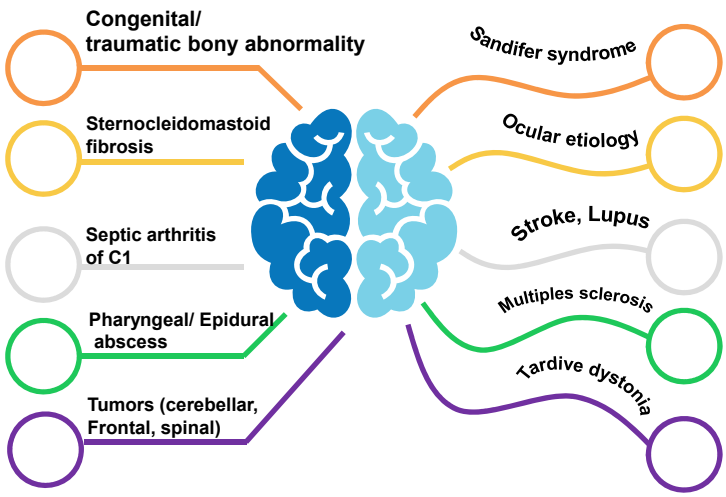
about a 45 degree head tilt to the right;
45 degree chin deviation to the left;
15 degree left shoulder elevation;
with mild retrocollis; no head shakes



Cervical dystonia: etiopathogenesis

- Etiology remains unknown
- Post-traumatic cervical dystonia
  - No relief with sleep
  - No sensory tricks
  - Fixed; tendency for laterocollis
  - Resistant to treatment
- Many other causes of secondary dystonia
- Putaminal lesions cause contralateral dystonia

Examples of "secondary" CD



Idiopathic Cervical Dystonia:
rotational torticollis is common

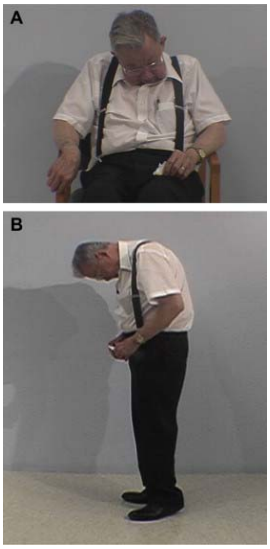
PATIENT
VIDEOS

Tardive Cervical Dystonia:
typically presents with retrocollis

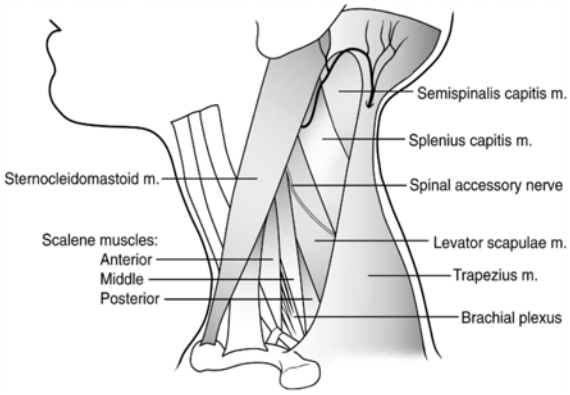
PATIENT
VIDEO

Multiple Systems Atrophy:
typically presents with anterocollis

- Flexion of neck, with chin to chest
- Often involves anterior muscles



Cervical Dystonia:
Injection Anatomy



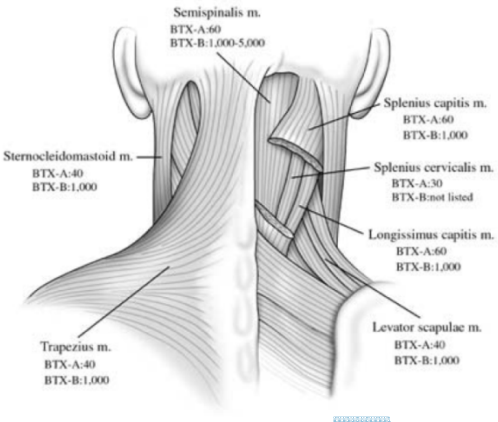
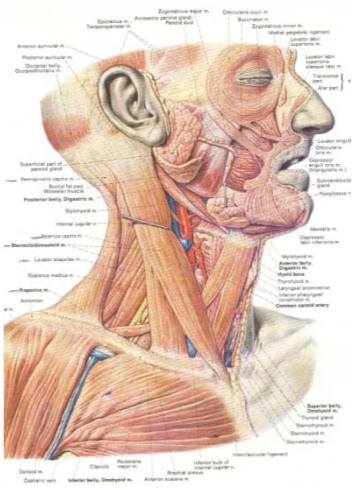


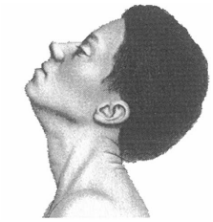
Image credit: WEMOVE website (www.wemove.org, http://www.mdvu.org/library/anatomicals/illustrations). Reprinted with permission of WEMOVE, New York, NY.

Structures to avoid

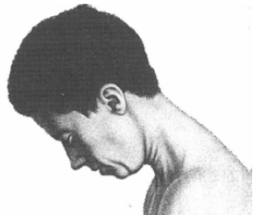
- Brachial plexus
- Carotid sheath
- Greater occipital nerve
- Larynx and trachea
- Pharynx and esophagus
- Thyroid gland
- Pleura and apex of the lung



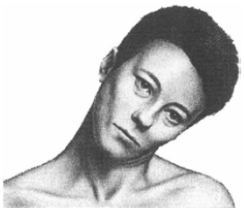
Basic Injection Patterns



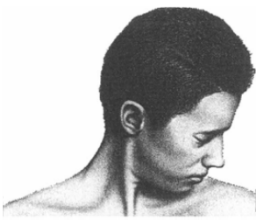
Retrocollis



Anterocollis



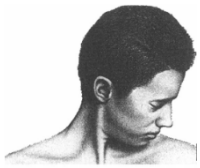
Laterocollis

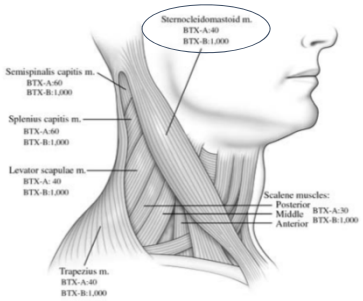


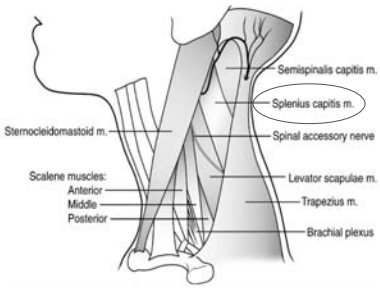
Rotational torticollis

Image adapted from Benecke R, et al. Cervical and axial dystonia. In: Moore P, Naumann M, eds. *Handbook of Botulinum Toxin Treatment.* Malden, MA: Blackwell Science Ltd; 2003:158-194. Reproduced with permission of Blackwell Publishing, Ltd.

Torticollis



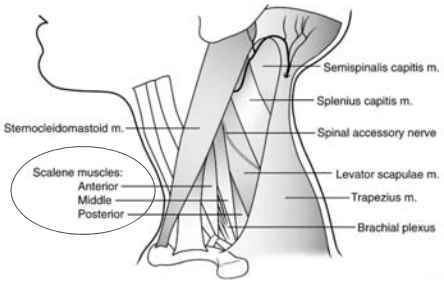




- Contralateral sternocleidomastoid
- Ipsilateral splenius capitis

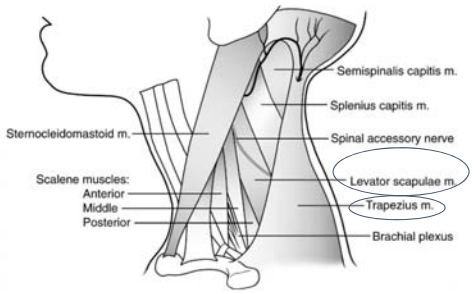
Laterocollis

- Ipsilateral scalenes
- Optional:
  - Ipsilateral levator scapulae
  - Ipsilateral splenius capitis
  - Ipsilateral sternocliedomastoid

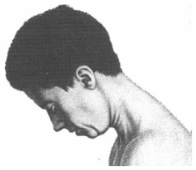


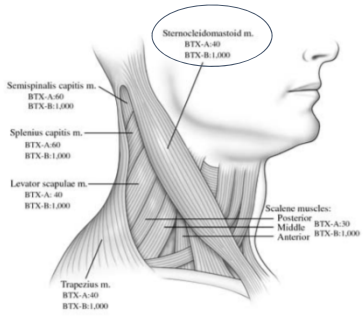
Shoulder elevation

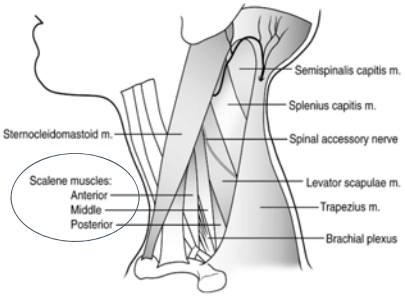
- Ipsilateral levator scapulae
- Ipsilateral upper trapezius



Anterocollis

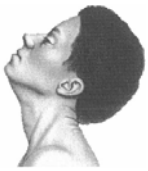


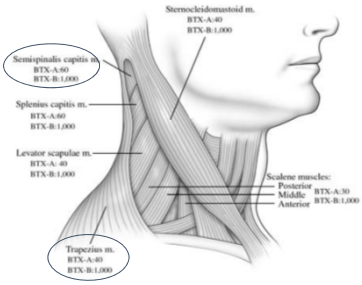


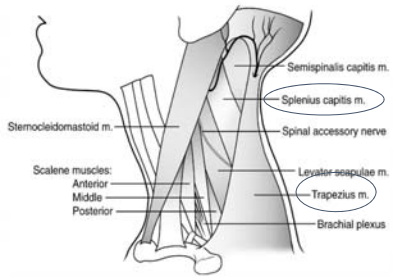


- Bilateral SCM
- Bilateral anterior scalene
- Optional: Bilateral levator scapulae

Retrocollis



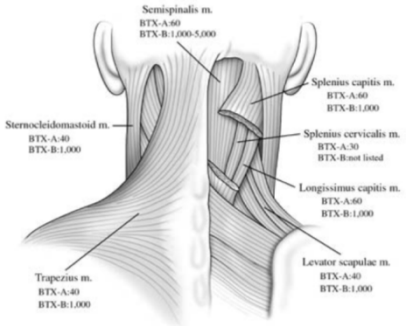




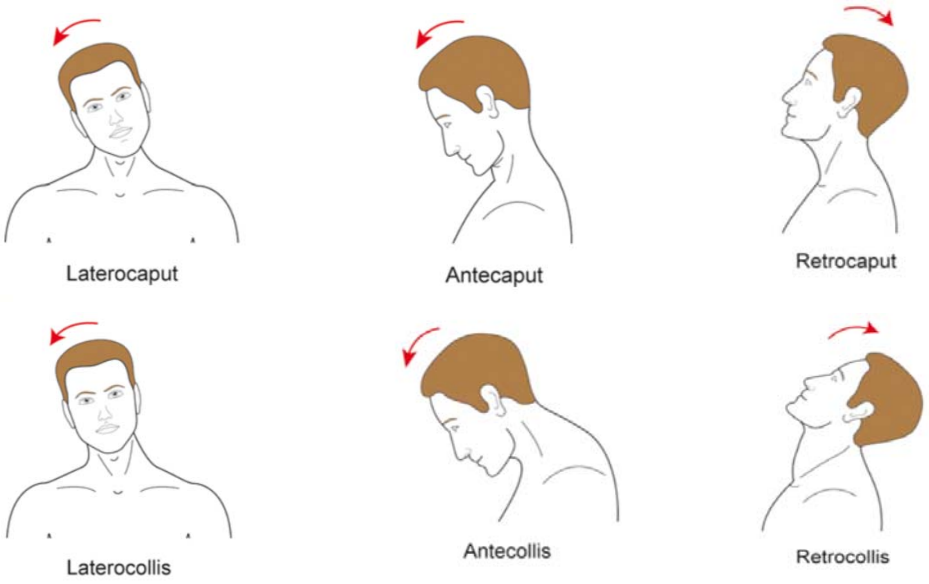
- Bilateral splenius capitis
- Optional: Bilateral trapezius
- Optional: Bilateral semispinalis capitis

Head tremor

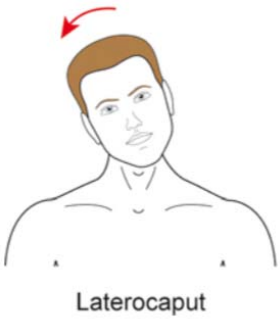
- Need to inject both the ‘main’ and ‘compensatory’ muscles
- 2-3 : 1 dosing ratio between main and compensatory muscles

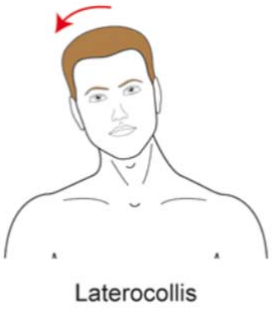


Complex Injection Patterns



Complex Injection Pattern #1





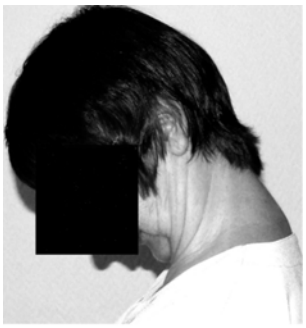
Ipsilateral:

- Splenius capitis
- Sternocleidomastoid
- Trapezius pars descendans

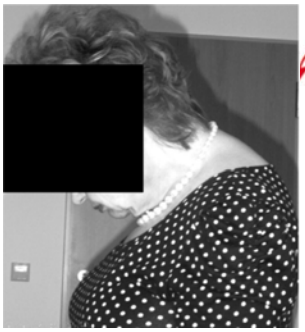
Ipsilateral:

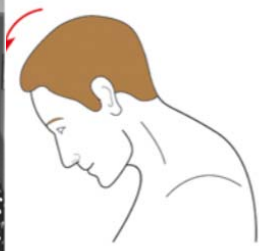
- Scalene
- Splenius cervicis
- Levator

Complex Injection Pattern #2



Antecaput





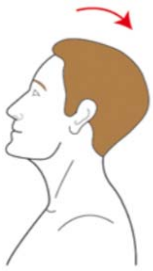
Antecollis

Bilateral:
1. Sternocleidomastoid
2. Submentalis complex?
3. Levator?

Bilateral:
1. Scalene
2. Levator

J. Finsterer et al. / Journal of the Neurological Sciences 355 (2015) 37–43

Complex Injection Pattern #3



Retrocaput

Retrocollis

Bilateral:

- Splenius capitis
- Semispinalis capitis
- Trapezius pars descendans

Bilateral:

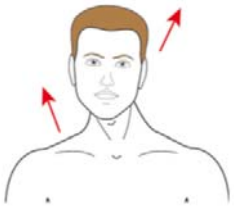
- Semispinalis cervicis

Very Complex Injection Pattern #1: Lateral Shift

Left Laterocaput

Right:

- Scalene
- Splenius cervicis
- Levator



Lateral shift

Left

- Splenius capitis
- Sternocleidomastoid
- Trapezius pars descendans

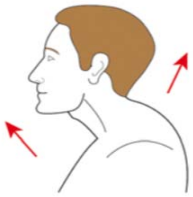
Right Laterocollis

Very Complex Injection Pattern #2: Sagittal Shift

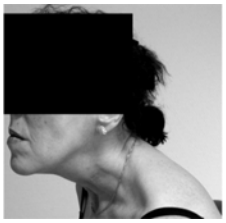
Anterocollis

Bilateral:

1. Scalene
2. Levator



Sagittal shift



Retrocaput

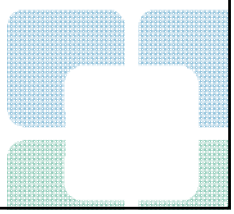
Bilateral:

1. Splenius capitis
2. Semispinalis capitis
3. Trapezius pars descendans

Clinical Issues: Cervical Dystonia

Treatment goals – establish priority of patient problems:

A. Pain
B. Muscle tension
C. Rotation, tilt, extension, shift. Flexion is hard to treat.
D. Tremor/nystagmoid jerking ("dystonic tremor")
E. Secondary phenomena (radiculomyelopathy)

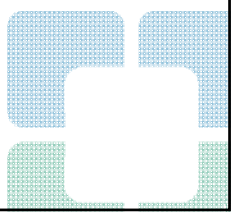


Clinical Issues: Cervical Dystonia

- Muscles injected include SCM, trapezius, splenius capitis, levator scapulae, scalenus medius, longissimus capitis, semispinalis capitis. Muscle contraction and muscle hypertrophy are clues.

Reasonable starting scheme:

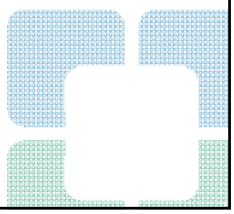
L Rotation	L Tilt	Retrocollis
R SCM	L SCM	L&R Splenii
L Trapezius	L Splenius	L&R Trapezii
L Splenius	L Levator	
	L Trapezius	



Clinical Issues: Cervical Dystonia

- To treat shift of the head, treat as if there were tilt in the opposite direction. (Why? I don't know.) For example:

R shift, treat for:	Anterior shift, treat for:
L Tilt	Retrocollis
L SCM	L&R Splenii
L Splenius	L&R Trapezii
L Levator	

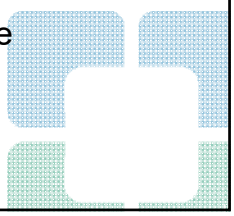


Clinical Issues: Cervical Dystonia

Tremor may require injection of agonist/antagonist pairs.

Painful muscle spasm can be treated with relatively small doses wherever it occurs. However, you must inject the correct muscles, and this is not always easy! Tender muscle is a good clue!

REMEMBER: The physiology of dystonia is co-contraction of agonist and antagonist muscles. Many patients have dystonic contractions of bilateral neck muscles, so that painful muscle spasms may occur on the "wrong" side (eg, someone with L rotation may have pain in the R splenius capitis).

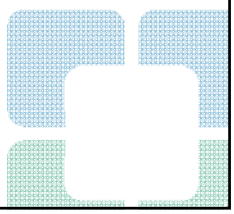


Clinical Issues: Cervical Dystonia

Starting doses/concentration/volume of injection/sites

Caveat: None of these is scientifically determined and probably not the same for all patients. However, the following do work:

- Concentration: 25 to 100 units/cc. I usually use 50 units/cc.
- Volume per injection site: 0.1 cc to 0.5 cc. Principle: Reduce volume for patients bothered by pain (give the same dose by adjusting the concentration). More volume->affects more endplates but increased risk of spread to unintended muscles.
- Sites: Diagrams to follow.



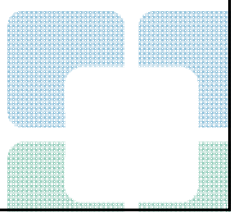
Clinical Issues: Cervical Dystonia

Starting doses/concentration/volume of injection/sites

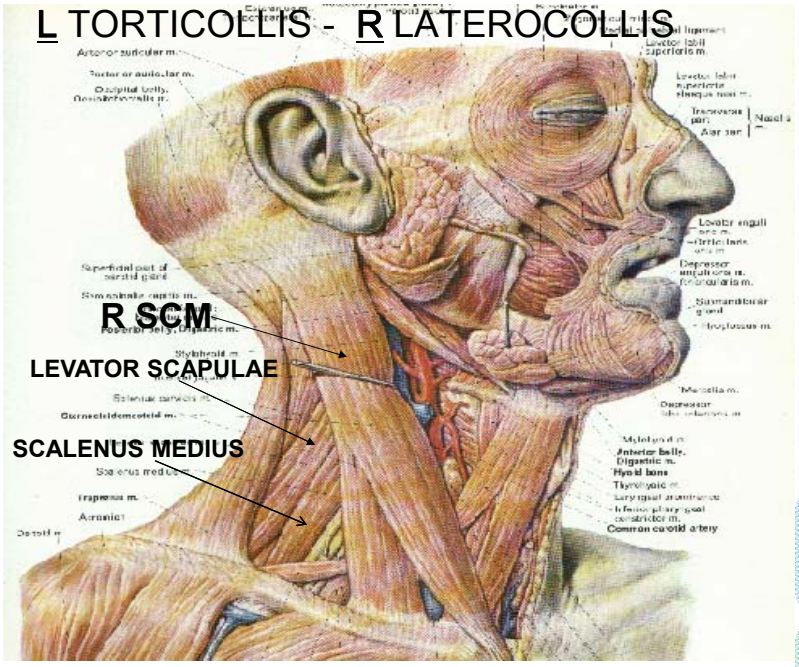
Dose per muscle:

- SCM: 25 u in 0.5 cc, single injection in upper 1/3 muscle
- Splenius: 25 u in 0.5 cc; if muscle is hypertrophied, 25 u X 2
- Trapezius: 25 u in 0.5 cc X 3 spaced along the vertical portion of the muscle
- Scalenus medius/levator scapulae: 12.5 u in 0.25 cc SC only if muscle is hypertrophied

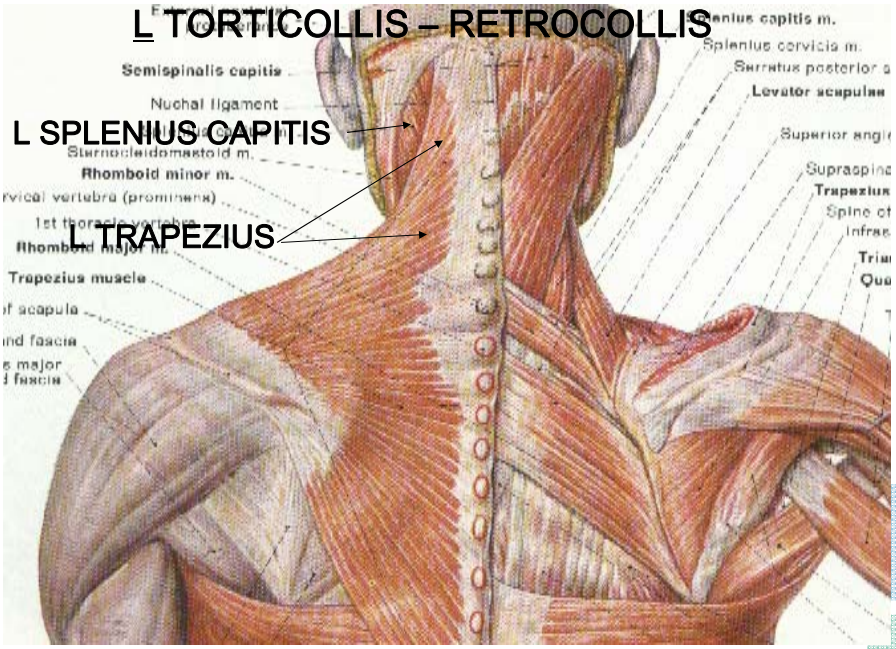
Diagrams to follow.

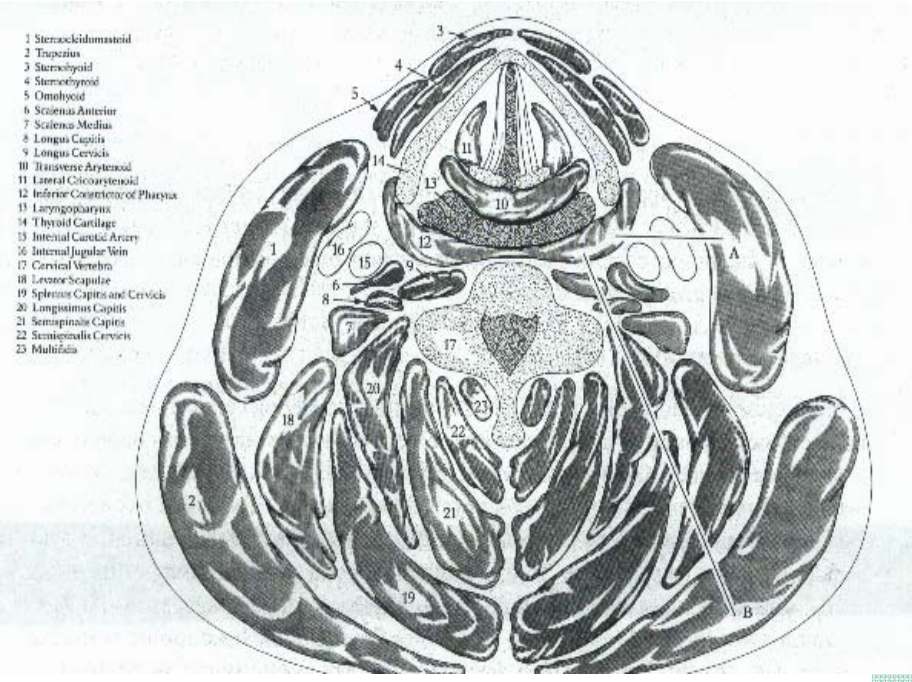


L TORTICOLLIS - R LATEROCOLLIS



L TORTICOLLIS – RETROCOLLIS





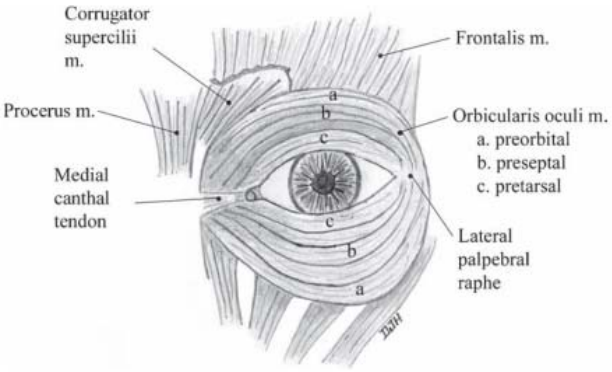
Blepharospasm

Squinting
frontalis
corrugator supercilli
orbicularis occuli (preseptal and pretarsal)

Increased blink rate
orbicularis occuli (pretarsal)

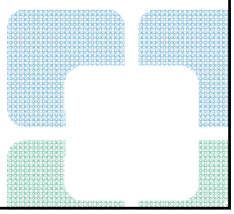
Involuntary closure of the eyelids
orbicularis occuli (pretarsal)

Apraxia of eyelid opening
orbicularis occuli (preseptal)



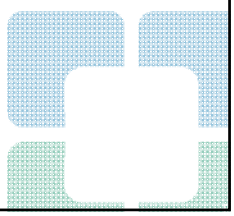
Blepharospasm: Injection Technique

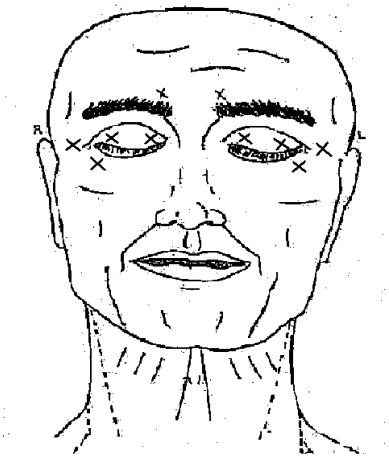
1. Point the tip of needle away from midline to minimize ptosis.
2. Avoid intradermal injections; injections should be subcutaneous or intramuscular.
3. Many patients need injections over the pretarsal component of the orbicularis oculi. This can be accomplished safely by retracting the lid and inserting the needle over the orbital ridge.



Blepharospasm: Injection Technique

4. The risk of ptosis seems to be lower with a smaller volume of toxin: use double the concentration and half the volume to give the same dose.
5. Lower lid injections are necessary in a minority of patients (estimated 20%).
6. Some patients will benefit from ptosis crutches for ptosis after injections.



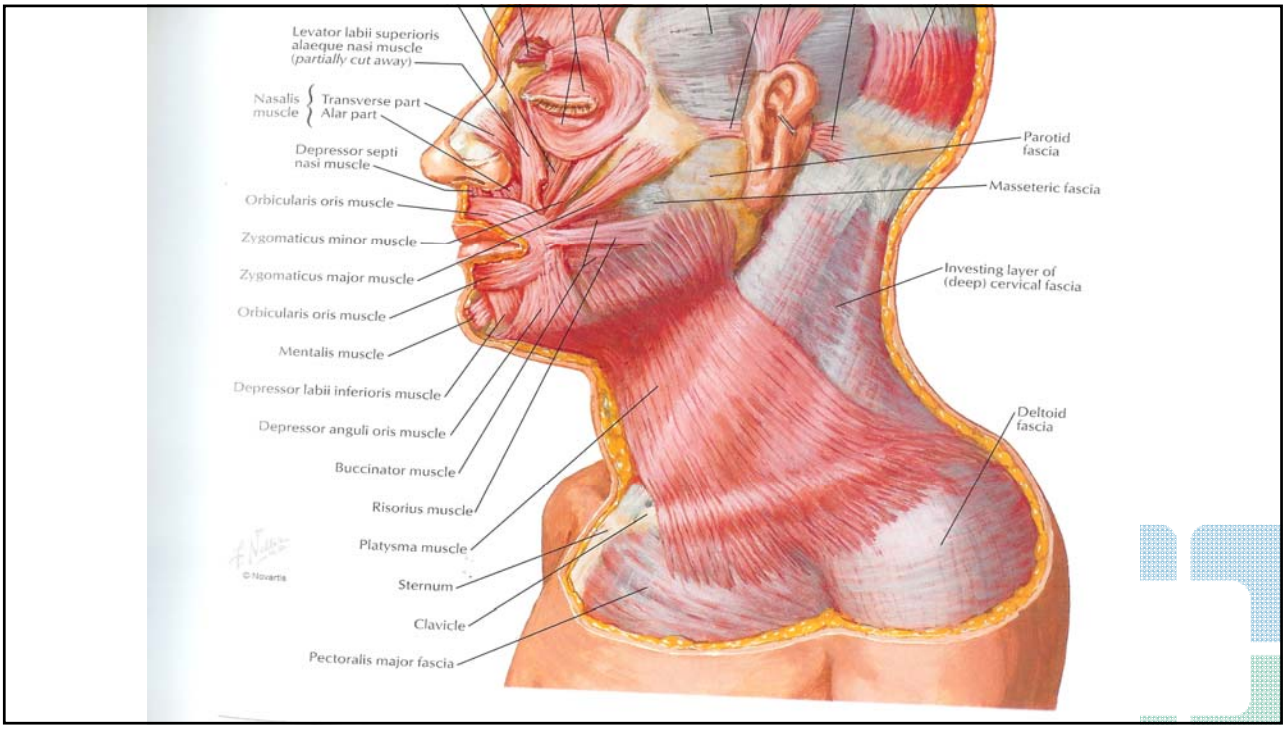


BLEPHAROSPASM

BLEPHAROSPASM

Meige Syndrome: Methods

1. I find it helpful to use EMG guidance for some facial muscles (hollow-core, unipolar EMG needle allows recording, and injection with a single stick).
2. Start with low doses to avoid weakness of the injected and nearby muscles:
   1. Zygomaticus major/risorius 1.25 U/side
   2. Masseter 25 U/side
   3. Platysma 5 U at 3 sites/side
   4. Temporalis 12.5 U/side
3. You will probably have to increase these doses at subsequent injection sessions.



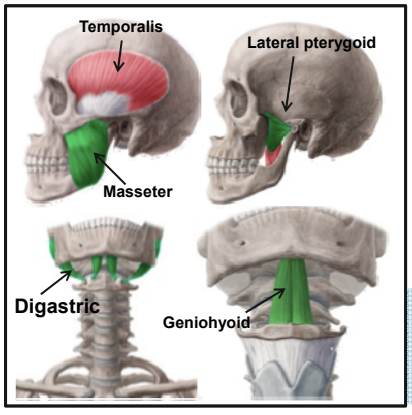
Oromandibular dystonia

Jaw closing dystonia
Bilateral masseters, temporalis

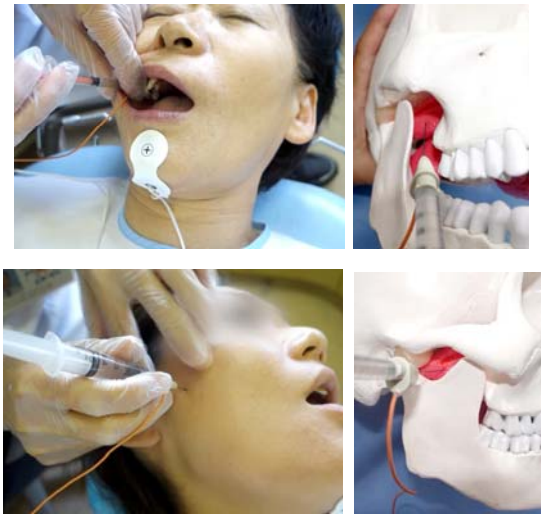
Jaw opening dystonia
Bilateral lateral pterygoids
Bilateral digastrics, omohyoids, geniohyoids

Jaw deviation dystonia
Contralateral lateral pterygoids

Tongue protrusion dystonia
genioglossus, hypoglossus



Oromandibular dystonia Injection Technique



Clinical Issues

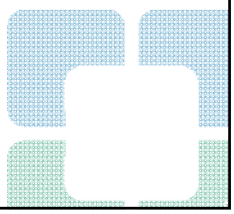
- Methods for administration
- Safety
- Penetration into central nervous system
- Brand and serotype equivalency
- Immunogenicity

Methods of Administration

Outcomes

Response assessed by patient

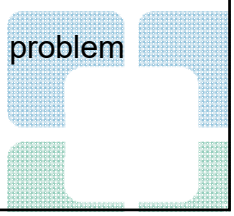
- Normalization of posture
- Functional improvement
- Relief of discomfort



Treatment Principles

General principles:

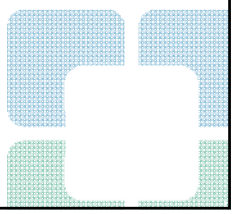
1. Start low, go slow: A small number of patients are much more/less sensitive than average.
2. Videotape all patients before the first injection.
3. See all new patients once shots have taken effect (3-4 weeks later). Remember: BTX injections cause muscle atrophy proportional to the dose (with ceiling effect).
4. Treat symptoms, not signs.
5. See patients when they report problems unless the cause of the problem is clear.



Treatment Principles

"Boosters":

1. To minimize side effects and risk of immunity, you want to keep the dose as low as possible.
2. Patients may have very different sensitivities to BTX.
3. However, if you use a low dose at the first session, most patients will need more.
4. Your options are to make patients wait 3 months (which patients hate and makes them discouraged) or to give a booster.
5. What to do?



Blepharospasm: Initial Doses

CONCENTRATION: 25 U to 50 U/cc depending on age (older-> more concentrated, smaller volume)

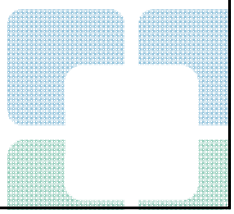
SITES: (Diagram to follow)

- Orbicularis oculi: 5-6 sites/eye, 2.5 U/site
- Frontalis, procerus, levator labii superioris, levator anguli oris, levator labii superioris alaeque nasi, etc

DECREASED INITIAL DOSE:

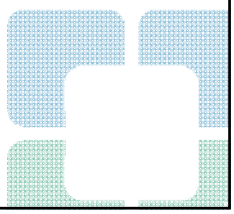
Advanced age
Prior myectomy

Nerve damage (hemifacial spasm, Guillain-Barre, ptosis)



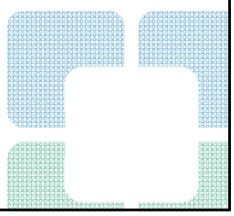
Clinical Issues

- Methods for administration
- Safety
- Penetration into central nervous system
- Brand and serotype equivalency
- Immunogenicity



Cervical Dystonia: Adverse Effects

1. Dysphagia: Mainly levator scapulae/scalenus medius, deep portions of the splenius capitis and lower 2/3 of the SCM. Depends on the site and volume of injection.
2. Excess weakness of injected muscles: Usually resulting in extensor weakness of the neck.
3. Pain: Sometimes in uninjected muscles (?dystonic recruitment of new muscles?)
4. Increase in distant dystonic contractions.



Cervical Dystonia: Adverse Effects

1. Dry mouth
2. Herpes Zoster
3. Allergic reactions: Usually rashes. Possibly more severe allergic reactions (rare)
4. Flu-like syndrome (rare)
5. Botulism-like illness (almost unheard of in this country)

Blepharospasm: Adverse Effects

COMMON:

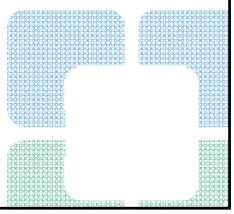
1. Blepharoptosis
2. Ecchymoses
3. Increased/decreased tearing
4. Dermatochalasis

UNCOMMON SIDE EFFECTS:

1. Diplopia
2. Exposure keratopathy
3. Entropion/ectropion
4. Acute angle glaucoma

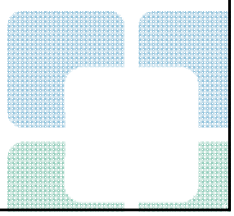
Evidence of Spread of Botulinum Toxins Beyond Local Injection Site

- Systemic spread
  - Increased jitter in distant muscles
  - Dysphagia following CD injections
  - Dry mouth following injection of BoNT-B into limb muscles
- Direct or indirect central effects
  - Altered plasticity



Safety

- If injections administered properly, most adverse events are mild and transient
  - Caution in frail individuals
- Although may have some central nervous system penetration of toxin, clinically evident adverse events have not been observed (more about this later)



Serious Adverse Effects

- More common with therapeutic than cosmetic use
- Not necessarily related to toxin (eg, MI, seizure)
- Probably related
  - Weakness, dysphagia, flu-like syndromes, injection site trauma
- 50 deaths with neurological Sx (1992-2009)
  - Deaths from: dysphagia, weakness, encephalitis, MI, respiratory arrest, CVA, PE, pneumonia, other.

Severe Nervous System Complications After Botulinum Type A Therapy: Three Case Reports With Reviews of FDA-Reported Nervous System Adverse Effects

Anna H. Hristova, MD, Lenore N. Joseph, MD, Swati A. Sathe, MD, James B. Wade, PhD

INTRODUCTION

The short-term safety of botulinum toxin type A (BoNT/A) has been established in numerous double-blind trials, but as many authors have pointed out, long-term drug safety is an unresolved issue [1-3]. We report 3 cases of central nervous system complications with encephalitic clinical features that occurred shortly after treatment of focal dystonia with BoNT/A. The goal of this study is to raise awareness and increase the vigilance of health care providers regarding the possible occurrence of adverse events that may be related not directly to the toxin but to other mechanisms that have not yet been well studied. We suggest an algorithm for safer toxin use until further research is conducted. We also offer a summary of toxin-related nervous system adverse events reported to the U.S. Food and Drug Administration (FDA) between September 1992 and May 2009.

Physical Medicine and Rehabilitation
1934-1482/12/$36.00 Vol. 4, 613-623, August 2012

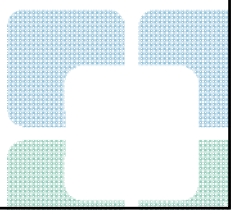
Table 5. *Deaths after botulinum toxin type A therapy reported to the Food and Drug Administration, 1992 to 2009*

Cause of Death	No. Reports	% of Total
Neurological symptoms	50	40.6
Dysphagia, dysphonia, dry mouth*	15	
Weakness paralysis, asthenia, botulism, diplopia, gait problems	12	
Encephalitis, coma, brain edema, encephalopathy, lethargy, stroke, mental status changes, feeling abnormal	12	
Status epilepticus and seizures	7	
Guillain-Barré, autonomic neuropathy, delayed gastric emptying	4	
Cardiac	15	12.1
Pulmonary	12	9.7
Infectious	11	8.9
Pyrexia	3†	
Pyrexia only	1	
Pyrexia with sudden death	2	
Sudden death	1‡	
Drug overdose or interaction	6	4.9
Anaphylactic shock	2	1.6
Fetus	2§	1.6
Cause not listed	21	17.1
Total	123	

*Usually associated with aspiration pneumonia.
†Total cases where pyrexia was reported: 8.
‡Total cases when sudden death was part of the report: 6.
§One abortion and one intrauterine death.

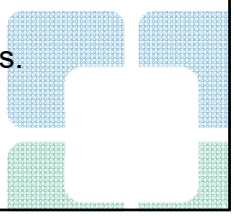
Safety

- FDA safety review in 2008: Deaths reported in children receiving high doses for CP (40 units/kg); risk complicated by underlying disorders and use of anesthesia
- Black box warning required (April 2009)
  - Risk of adverse events with toxin spread beyond injected site
- Developed non-proprietary names to emphasize difference between marketed products
- Risk Evaluation and Mitigation Strategy
  - Information of risk for distant spread
  - Medication guide



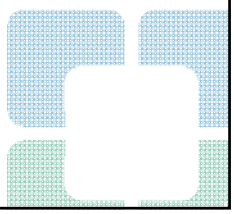
Black Box Warning

- The effects of (brand name) and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening, and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity, but symptoms can also occur in adults, particularly in those patients who have underlying conditions that would predispose them to these symptoms.



Is Electromyography Useful?

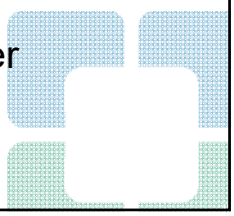
- Significantly increases the magnitude of improvement at the same dose of BoNT
  - Used complementary to clinical examination
  - Blinded evaluations show significance for both patient and physician assessments
    - Comella, 1992
- Targeting muscle is not accurate without EMG guidance
  - Van Gerpen, 2000
- Sternocleidomastoid "missed" in 20%; splenius capitis and deeper muscles missed up to 60% of the time without EMG guidance
  - Brans, 1996
- Accuracy in forearm approximately 37% without EMG
  - Molloy, 2002



Is Electromyography Useful?

Why I use EMG infrequently:

1. EMG selection of muscles can be misleading because the pattern of muscle contraction changes when you stand, walk, run, etc.
2. EMG does not allow you to determine the appropriate dose to inject.
3. It is hard to gauge depth with EMG guidance and find the same deep muscle 3 months after a successful injection.



Methods of Administration

- Appropriate dilutions
- Dose into specific muscles
- Number of injection sites into each muscle
- Use of EMG or ultrasound
- Outcomes
  - Clinically important measures
  - Scales with demonstrated reliability, validity, and responsiveness

Outcomes

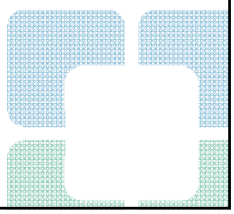
Response Assessed by Patient

Visual Analog Scale
No improvement Complete Improvement
0% 100%

Outcomes

Response Assessed by Examiner

- **Scales with demonstrated reliability, validity, TWSTRS (CD)**
  - **Blepharospasm rating scale**
  - **Spasticity scales (modified Ashworth)**



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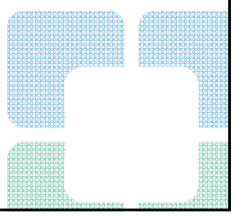
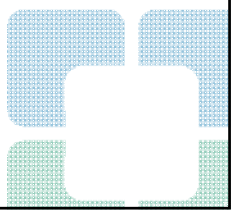


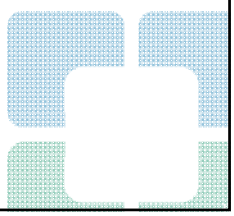
Evidence of Central Effects

- Effects on spinal cord circuitry
  - Reduced presynaptic inhibition between flexor and extensor forearm muscles following injection for limb dystonia/tremor
- Effects on brainstem
  - Changes in abducens motoneurons with lateral rectus muscle injections
  - No effects on blink reflex recovery, brainstem auditory evoked potentials
- Cortical effects
  - Conflicting evidence of altered central plasticity and excitability following injections



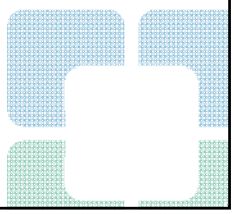
Central Effects: Clinical Implications

- Central effects difficult to interpret clinically
  - Primary clinical effect is denervation
  - Altered central plasticity due to altered sensory input (effects on gamma neurons?)
  - Retrograde axonal transport with central BoNT activity
- "Lack of adverse central effects suggest that physicians can continue to use BoNT safely as therapy."



Clinical Issues

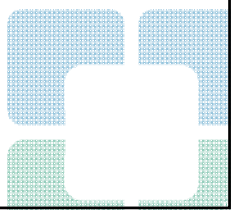
- Methods for administration
- Safety
- Penetration into central nervous system
- Brand and serotype equivalency
- Immunogenicity



All brands and types of botulinum toxin can be used interchangeably.

A. Yes

B. No



Can BoNT Brands and Serotypes Be Used Interchangeably?

- 4 brands of BoNT available for clinical use
  - 3 are BoNT-A (Botox® [onabotulinumtoxinA], Dysport® [abobotulinumtoxinA], Xeomin® [incobotulinumtoxinA])
  - 1 is BoNT-B (Myobloc® [rimabotulinumtoxinB]/NeuroBloc® [botulinum toxin type B])
- Each brand of BoNT except Xeomin® (incobotulinumtoxinA) is a complex mixture of components with BoNT being the therapeutically active component, but . . .
  - Each of these components influences therapeutic efficacy, adverse-effects profile, and antigenicity
- Comparative studies have not established simple dose equivalency calculations that can be used in a clinical setting
- Clinicians should consider each brand and serotype individually.

Can BoNT Brands and Serotypes Be Used Interchangeably?

No?

- When starting a new brand, base dosing on the package insert and studies of that brand
- Consider changing from one brand to another:
  - If there is resistance to 1 serotype (A vs B)
  - Based on patient need or insurance
    - Avoid "rotating" brands and serotypes

Can BoNT Brands and Serotypes Be Used Interchangeably?

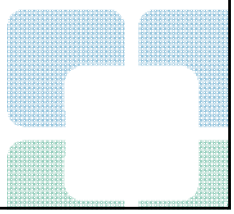
What do we know about relative doses?

1. 50 u of Myobloc® (RimabotulinumtoxinB) produced about the same degree of weakness as 1 u of Botox® (OnabotulinumtoxinA; actually 66.7 u B to 1 u A in quantitative EMG studies).

2. Double-blind study showed 2500 u Myobloc® (RimabotulinumtoxinB) equivalent to 250 u Botox® (OnabotulinumtoxinA) for sialorrhea (10 u B to 1 u A).*

3. Xeomin® (IncobotulinumtoxinA) and Botox® (OnabotulinumtoxinA) are approximately equipotent in clinical trials although Xeomin® (IncobotulinumtoxinA) less potent in preclinical studies.

4. There is considerable variation in the relative potency of Dysport® (AbobotulinumtoxinA) and Botox® (OnabotulinumtoxinA).



Clinical Issues

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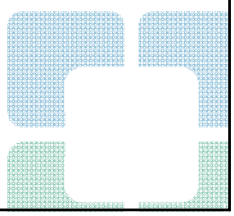
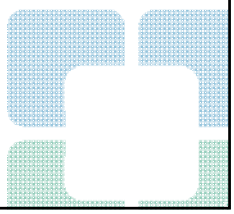


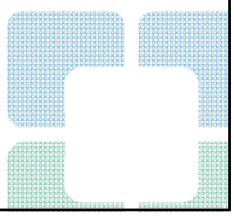
Failure to Benefit Rarely Due to Antibodies

- Common reasons for lack of efficacy
  - Injection into the wrong muscles
  - Inadequate dosing
  - Unrealistic patient expectations
  - Stress-induced exacerbation
- Uncommon reasons for lack of efficacy
  - Change in dystonia
  - Immunoresistance



Failure to Benefit Rarely Due to Antibodies

- Nonetheless: It is likely that some dose/frequency of injections with each serotype will produce antibodies.
- Unfortunately: We do not know what the risk is at any given dose/frequency!



Factors Associated with Immunoresistance

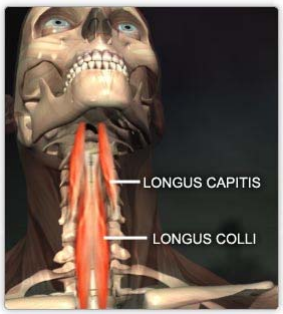
- Protein content of BoNT (eg, amount of denatured protein)
  - Complexing proteins
  - Hemagglutinin and nonhemagglutinin
- More frequent injections
  - Intervals less than 3 months
- "Booster" injections
- Large doses/cumulative doses
- Genetic predisposition

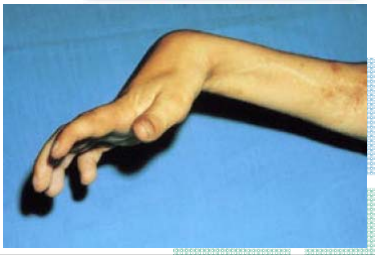
Unilateral Brow Injection (UBI) for BoNT Resistance

- Injection of small amount of BoNT into corrugator on 1 side
- Re-evaluate at 4 weeks
- Assess symmetry of corrugator contraction by comparison of brow furrows

Failure of therapy: Primary Non-response

1. Muscles are not accessible for injection (e.g. anterocollis)
2. Structural abnormality (e.g. fibrosis or contracture of muscle; skeletal abnormality)
3. Side effects negate the benefits (e.g. head drop or dysphagia)
4. Suboptimal muscle selection or dosing





Failure to benefit

- **Common reasons for lack of efficacy**
  - Injection into the wrong muscles
  - Inadequate dosing
  - Unrealistic patient expectations
  - Stress-induced exacerbation
- **Uncommon reasons for lack of efficacy**
  - Change in dystonia
  - Immune-resistance

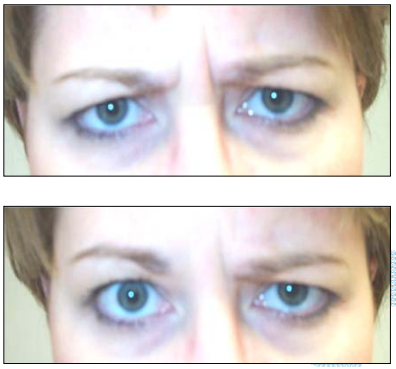
Failure of therapy: Immune-resistance

1. Previous benefit
2. Loss of benefit for at least 2 injections
3. On 4-week follow up: lack of muscle atrophy, no EMG devervation
4. 1-2 % of chronically treated cervical dystonia

Factors Associated With Immune-resistance

- More frequent injections
  - Intervals less than 3 months
- "Booster" injections
- Large doses/cumulative doses
- Genetic predisposition
- ? Protein content of BoNT
  - Complexing proteins
    - Hemagglutinin and non-hemagglutinin

Unilateral Brow Injection for Neurotoxin Resistance



What to do in immune-resistant patient

- Evaluate at 4 weeks following failed injection
- Switch to different serotype of toxin
  - Typically, serotype A to serotype B
  - Switching to another brand of A likely not successful
- If immune-resistant to both serotypes, consider other alternatives
  - Selective peripheral denervation
  - Deep brain stimulation
  - Medications

Post-injection expectations

- 70% of patients will get about 70% improvement
- Toxin will take effect in about 7 days
- Duration of effect is about 3 months
- Side effects: highest in children; high dose; low muscle mass
  - Dysphagia (high risk in bilateral sternocleidomastoid injections; scalene injections)
  - Pain and muscle weakness (high risk if the dose is too much)
  - Dry mouth (may be slightly higher with Botulinum Toxin Type B)
  - Fatigue (could represent “distant spread”)

Treatment goals

- Establish clear treatment goals
  - Reduction of pain
  - Improvement in posture/movement
  - Increase in function
  - Enhancement of QOL
- Discuss with patient!

Key Points

- BoNT works through reversible chemodenervation.
- Botulinum has a long history of efficacy and safety when used appropriately.
- BoNT used in practice requires careful explanation to patients of expectations, risks, and reporting of adverse events.
- The clinical importance of central nervous system penetration of BoNT requires further evaluation.
- Each BoNT brand and serotype should be considered a unique drug.

Final tips

- Be careful with certain muscles
  - Levator palpebrae, orbicularis oris, sternocleidomastoid, scalenes, quadriceps
- Take advantage of muscles with dual roles
  - sternocleidomastoid, splenius, trapezius, biceps, brachialis
- Timing of pain is important
- Do not inject compensatory muscles
- Be on the same page with your nurse