Overview of Botulinum toxins

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"Sausage Poisoning"

Justinius Kerner
1786-1862

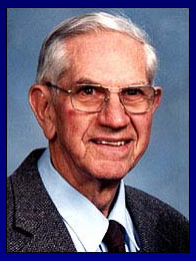

Das
Fettgift
oder
die Fettsäure
und
ihre Wirkungen auf den thierischen Organismus,
ein Beytrag
zur Untersuchung des in verdorbenen Würsten giftig wirkenden Stoffes,
von
Dr. Justinus Kerner,
Oberamtsarzt zu Weinsberg.
Stuttgart und Tübingen,
in der J. G. Cotta'schen Buchhandlung.
1822.

Ergbuth, 2004

Kerner's 2nd monograph on "fatty poison" (1822)

The pioneers of botulinum toxin therapeutics

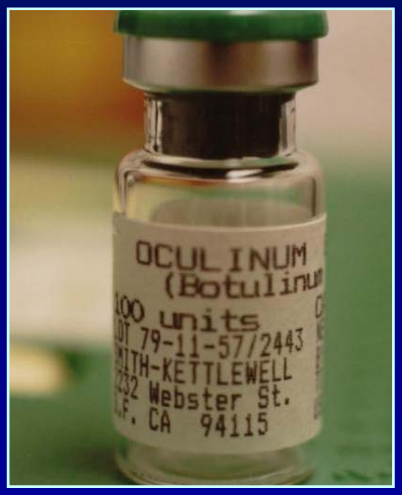
Allan Scott, MD



Edward Schantz, PhD

Botulinum toxin: First clinical preparation

- 1979: Original batch BoNTA (Oculinum)
  - 150 mg was used for more than 250,000 injections in humans.
  - Approximately 20% developed resistance



Objectives

- Describe the structure and mechanism of botulinum toxins
- Distinguish between the brands and serotype
- Outline efficacy and safety data
- Describe basic treatment principles

Botulinum Toxin

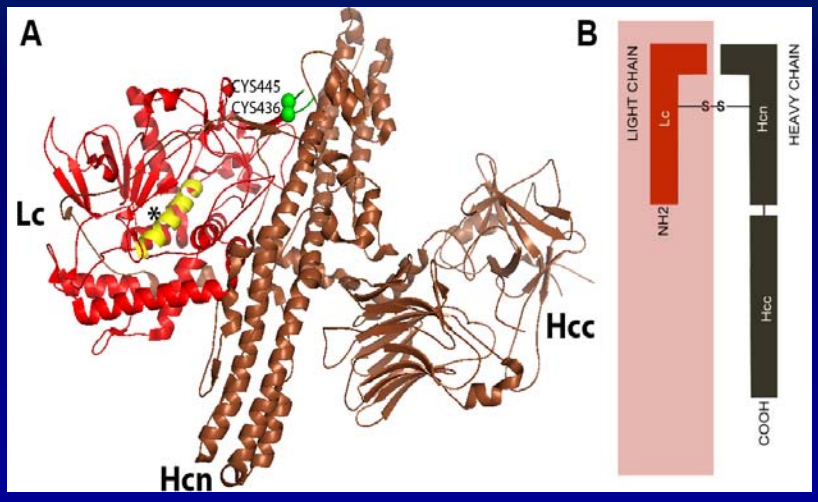
- Most potent neurotoxin known
- Nanogram amounts sufficient to be lethal
- Listed among 6 highest risk threat agents of bioterrorism by the Centers for Disease Control and Prevention (CDC)

Botulinum Toxin

- Produced by clostridium botulinum
- 7 distinct serotypes of toxin
  - A, B, C, D, E, F, G
    - Subtypes distinguished through genetic sequencing
  - Serotypes A and B available for human use
  - Serotype X recently identified
    - Cleaves VAMP 1,2,3 as others, but also VAMP 4,5,Ykt6
- Botulinum toxin complex
  - Hemagglutinin and non-hemagglutinin proteins
  - Neurotoxin

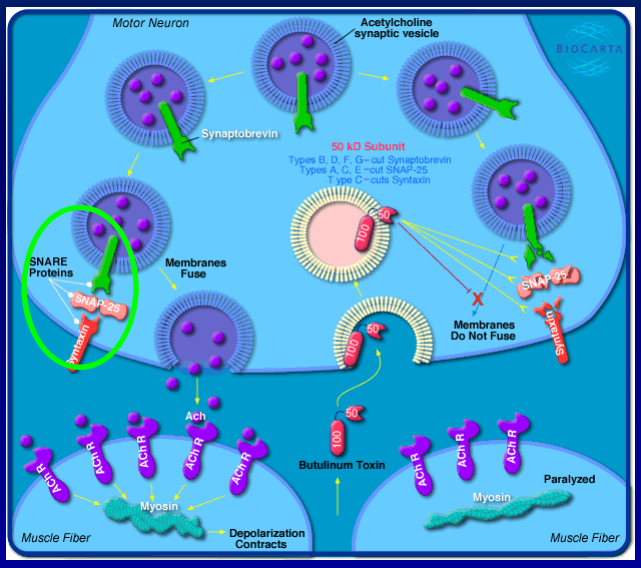
Zhang S et al. Nat Comm 2017

Botulinum Neurotoxin: A Marvel of Protein Design

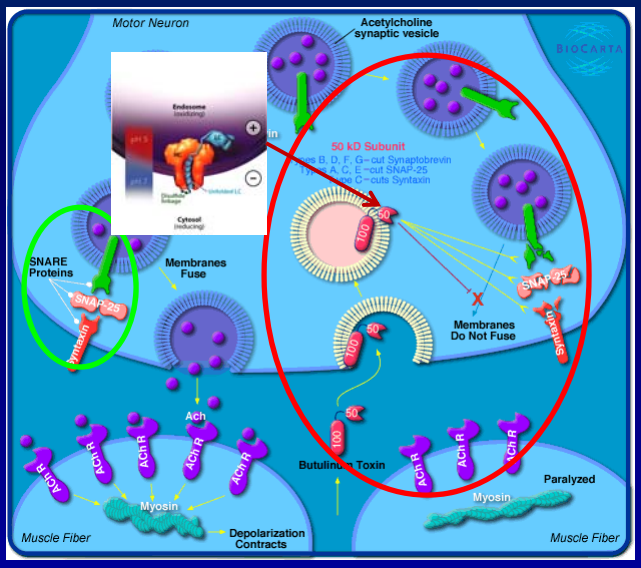


Chen et al. Toxins 2012, 1196-1222
Montal. Annu. Rev. Biochem. 2010. 79:591–617

BoNT Mechanism of Action



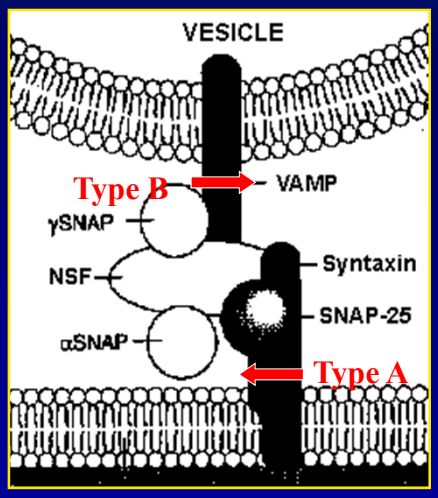
BoNT Mechanism of Action



Montal M. Ann Rev Biochem 2010

Botulinum Toxin Serotypes: Cleavage of SNARE Proteins

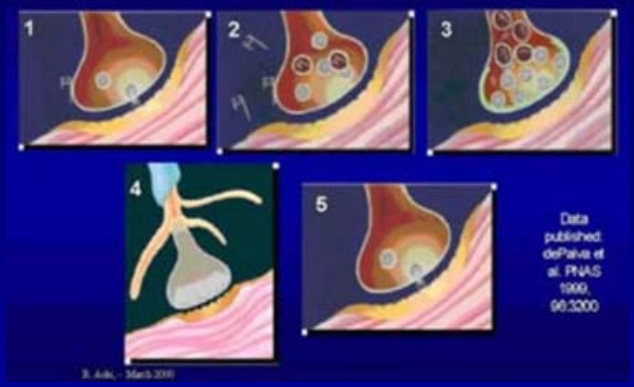
Toxin Type	Substrate
BTX A	*SNAP-25*
BTX B	*VAMP/Synabtobrevin*
BTX C	Syntaxin SNAP-25
BTX D	VAMP/Synaptobrevin
BTX E	SNAP-25
BTX F	VAMP/Synaptobrevin
BTX G	VAMP/Synaptobrevin



BoNT

- Interrupts neuromuscular transmission
  - Muscle weakness
- Local effect: predominant in the injected muscle
- Reversible
  - Recovery of NMJ in approximately 3-6 months

Recovery of NMJ following BoNT



Newer concepts of BoNT mechanism

- May not be only a peripheral effect
- Central effects important (muscle afferents)
  - Normalization of altered brain network activity
  - Normalization of left/right asymmetries of white matter microstructure (fractional anisotropy)

Brodoehl et al. Neuroimage Clin 2019
Blood A et al. Fron Neruol 2019

SPECIAL ARTICLE

Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache

Report of the Guideline Development Subcommittee of the American Academy of Neurology

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ABSTRACT

Objective: To update the 2008 American Academy of Neurology (AAN) guidelines regarding botulinum neurotoxin for blepharospasm, cervical dystonia (CD), headache, and adult spasticity.

Methods: We searched the literature for relevant articles and classified them using 2004 AAN criteria.

Results and recommendations: Blepharospasm: OnabotulinumtoxinA (onaBoNT-A) and incobotulinumtoxinA (incoBoNT-A) are probably effective and should be considered (Level B). AbobotulinumtoxinA (aboBoNT-A) is possibly effective and may be considered (Level C). CD: AboBoNT-A and rimabotulinumtoxinB (rimaBoNT-B) are established as effective and should be offered (Level A), and onaBoNT-A and incoBoNT-A are probably effective and should be considered (Level B). Adult spasticity: AboBoNT-A, incoBoNT-A, and onaBoNT-A are established as effective and should be offered (Level A), and rimaBoNT-B is probably effective and should be considered (Level B), for upper limb spasticity. AboBoNT-A and onaBoNT-A are established as effective and should be offered (Level A) for lower-limb spasticity. Headache: OnaBoNT-A is established as effective and should be offered to increase headache-free days (Level A) and is probably effective and should be considered to improve health-related quality of life (Level B) in chronic migraine. OnaBoNT-A is established as ineffective and should not be offered for episodic migraine (Level A) and is probably ineffective for chronic tension-type headaches (Level B). *Neurology*® 2016;86:1818–1826

Practice Guideline Summary

Table 2 Evidence-based conclusions and recommendations for the efficacy of various botulinum neurotoxin formulations by indication

Indication	Level A[a] effective	Level B[b] probably effective	Level C[c] possibly effective	Level U[d] insufficient evidence	Level A[e] ineffective	Level B[f] ineffective
Blepharospasm		OnabotulinumtoxinA, incobotulinumtoxinA	AbobotulinumtoxinA	RimabotulinumtoxinB		
Cervical dystonia	AbobotulinumtoxinA, rimabotulinumtoxinB	OnabotulinumtoxinA, incobotulinumtoxinA				
Upper limb spasticity[g]	AbobotulinumtoxinA, onabotulinumtoxinA,[h] incobotulinumtoxinA	RimabotulinumtoxinB				
Lower limb spasticity	OnabotulinumtoxinA, abobotulinumtoxinA			IncobotulinumtoxinA, rimabotulinumtoxinB		
Chronic migraine	OnabotulinumtoxinA[i]					
Episodic migraine					OnabotulinumtoxinA	
Tension-type headache						OnabotulinumtoxinA

Abbreviations: aboBoNT-A = abobotulinumtoxinA; incoBoNT-A = incobotulinumtoxinA; onaBoNT-A = onabotulinumtoxinA; rimaBoNT-B = rimabotulinumtoxinB.

Simpson et al. Neurology 2016

Clinical applications for BoNT

Dystonia
- Blepharopsasm*
- Hemifacial spasm*
- Cervical dystonia*
- Spasmodic dysphonia
- Limb dystonia
- Oromandibular dystonia

Strabissmus*

Spasticity
- Upper limb
- Lower limb

Other neurological disorders
- Tic disorders
- Tremor
- Camptocormia
- Pisa syndrome
- Stuttering
- Restless leg syndrome
- Synkinesias
- Nystagmus
- Bruxism

Depression

Pain
- Chronic migraine*
- Osteoarthritis
- Plantar fasciitis
- Temporomandibular joint disorders
- Neuropathic pain
- Lower back pain

Secretory disorders
- Sialorrhea*
- Rhinorrhea
- Frye's syndrome
- Axillary hyperhidrosis*
- Palmar hyperhydrosis

Genital-urinal disorders
- Detrusor over activity with/without neurologic condition
- Pelvic pain
- Erectile dysfunction
- Vulvodynia
- Vaginismus

Cardiac disorders
- Atrial tachycardia/fibrillation

Gastrointestinal disorders
- Gastroparesis
- Delayed gastric emptying
- Achalasia
- Anal fissures

Cosmetic
- Glabellar rhytides*
- Horizontal lines on the forehead*
- Lateral canthal lines (crow's feet)*
- Depressed brow Hypertrophic orbicularis oculi muscle
- Rhytides from upper nasalis muscle contraction
- Nostril flare
- Drooping nasal tip
- Nasolabial folds
- Vertical perioral rhytides
- Mouth frown
- Gummy smile
- Melomental folds (marionette lines)
- Mental crease
- Peau d'orange chin
- Masseteric hypertrophy
- Horizontal neck lines Platysmal bands on the neck

Samizadeh S, De Boulle K. Clin Cosmetic Invest Derm 2018
Carruthers J, Carruthers A. Uptodate 2018
Fonfria et al. Toxins 2018

FDA approvals for Botulinum toxins

- Blepharospasm
- Cervical dystonia
- Strabissmus
- Chronic sialhorrhea in PD
- Upper and lower limb spasticity
- Chronic migraine
- Hyperhydrosis
- Detrusor overactivity
- Cosmetic indications
  - Glabellar lines, canthal lines

Newer versions of BoNT with pilot clinical data

- BoNT Type E
  - Rapid onset (days)
  - Short duration of effect (4 weeks)
- DaxibotulinumtoxinA with novel excipient
  - Long duration of effect

Mechanism proposed for BoNTE

- Similarities to BoNT A
  - Binds to SV2 on presynaptic terminal
  - Internalized via synaptic vesicles
  - Translocates active protease subunit into cytosol
  - Cleaves SNAP-25 (different location than BoNTA)
- Differences from BoNT A
  - BoNT E light chain translocates more rapidly into the neuron cytosol
  - BoNT E light chain protease activity cleared rapidly in intoxicated neurons

Wang et al. J Biolog Chem 2008
Kumaran D et al. J Mol Biol 2009
Keller et al. Bioche 2004

Potential benefits of rapid onset, short duration BoNT

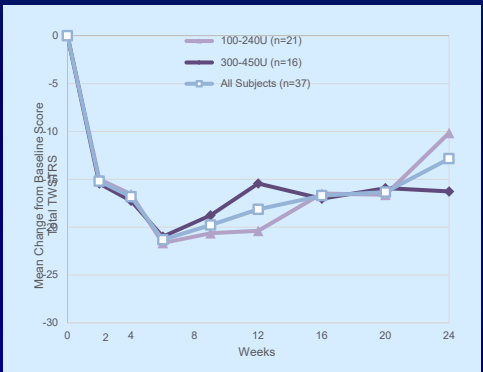
- Rapid onset treatment of muscle related pain (spasms/contractions)
- Potential to be a longer-acting, non-opioid without the side effects and addictive potential of opioids
- Short duration treatment effect allowing "test" of pattern of injection before injection of longer duration BoNT
- Short term "booster" improvement for suboptimal results from longer duration BoNT without the overlap at next injection visit
  - ? Immunoresistance
- Contribute to healing after injury, reduce scar formation by reducing muscle activity

Possible longer duration BoNTA DaxibotulinumtoxinA

- Purified 150 kDa BoNTA without accessory proteins
  - TransMTS® carrier peptide (RTP004)
    - Novel excipient
    - May reduce spread of toxin, extend the half life of effect
- Safety and tolerability study completed
  - 34 CD patients enrolled, 25 followed to week 24
  - Low dose (100-240U), High dose (300-450U)

Jankovic et al. Move Disord Clin Prac 2018

DaxibotulinumtoxinA for cervical dystonia Results of open label tolerability study



- Side effects:
  - Dysphagia 14% all mild
  - Muscle weakness 5% (1 mild, 1 moderate)
  - Neck pain 3%

Jankovic et al. Move Disord Clin Prac 2018

Potential benefits of longer duration toxin

- Less waning of effect between injections
  - Improved patient satisfaction
  - Longer optimal benefit
- Fewer injections over time
  - Less inconvenience for patients
  - Less expense?
  - Less likelihood of development of neutralizing antibodies?

Other BoNT A

- PrabotulinumtoxinA (FDA approved for cosmetic only)
- Evosyal
- Linurase
- Chinese BTX-A
  - Chintox
  - Prosigne
  - Lantox
  - Redux
- Neuronox/Meditoxin/Botulift

Can BoNT Brands and Serotypes Be Used Interchangeably?

No!

- Botulinum brands are unique drugs. There is no interchangeable dosing.
- *When starting a new brand, base dosing on the package insert , clinical studies, and the patient*
- Consider changing from one brand to another:
  - if there is resistance to one serotype
  - based on patient need or insurance
    - co-pay programs
- Avoid “rotating” brands and serotypes

Treatment Principles

- Know functional neuroanatomy
- Select appropriate muscles
- Dosing for each muscle
- Target injection into intended muscles
- Follow up for benefit and side effects

Treatment goals

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

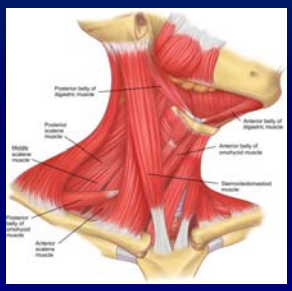
Safety: Black Box Warning

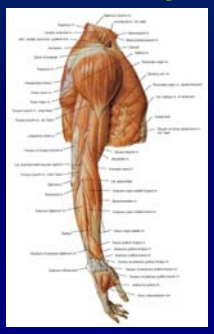
- The effects of all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects
- Swallowing and breathing difficulties can be life threatening, and there have been reports of death.
- Risk probably greatest in children treated for spasticity, but also occur in adults
  - particularly patients with underlying conditions predisposing them to these side effects

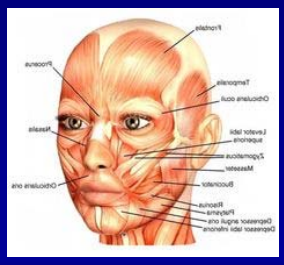
Basic treatment principles

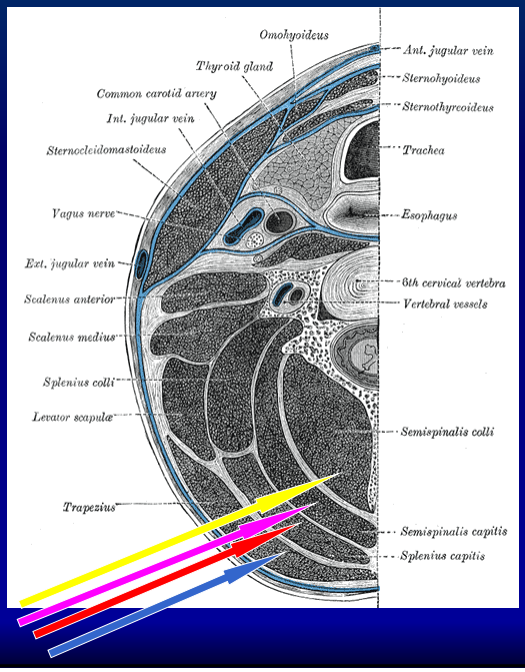
- Muscle selection
- Muscle localization for injection
  - Clinical, Electromyography, Ultrasound
- Dose into each muscle
- Number of injection sites per muscle
- Outcomes
  - Benefit/side effects
  - Use of scales, global impressions.

Know functional anatomy









Is Electromyography Useful?

- Increases the magnitude of improvement at the same dose of BoNT in single blind study
  - » 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

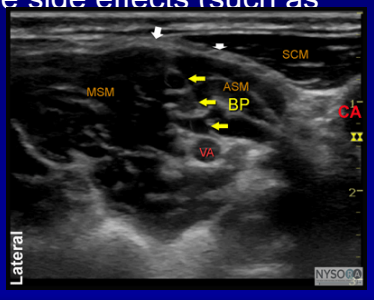
Ultrasound Guidance

- Direct visualization of muscles for injection
  - Used complementary to clinical examination
  - Offers comparable benefit as EMG when injected for spasticity (both EMG and USG better than surface landmarks)
    - » Picelli 2013
- May better limit spread, decrease side effects (such as dyphagia

Caveats

Ultrasound equipment is expensive

Requires specific training



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
  - Immunoresistance (? < 2% patients)

Manage patient expectations

- Symptom treatment, not a cure
  - Will not improve 100%
  - May take an injection or two to find right muscle pattern and dose
- Profile of Clinical Response
  - Onset : 3-10 days
  - Peak effect: 2-4 weeks
  - Duration of benefit:
    - 10-16 weeks

Online Survey through international dystonia foundations

- 1071 self-identified as CD
- 907 receiving BoNT
  - 56% fairly/very satisfied
  - 25% fairly/very dissatisfied
    - 46% no benefit
    - 33% adverse events

Comella, Bhatia et al, J Neurol 2014

BoNT in a real world setting

- Why do patients discontinue?
  - Lack of efficacy
    - Dose/muscle selection; complex CD
  - Adverse effects
  - Expense
  - Unrealistic expectations
  - Inconvenience

Comella and Bhatia. J Neurol 2015
Brashear et al. Mov Disord 2000
Jinnah et al J Neurol 2016

Botulinum toxin: health care coverage

- Preauthorization from health care coverage often required prior to treatment
- Diagnosis code, procedure code, drug code
- Consider drug company reimbursement programs for support of patient expenses (deductible, co-pay) if not Medicare in the US

Overview
Botulinum toxins

- Treatment of choice for focal dystonia, spasticity and other disorders
- Can improve posture, pain, quality of life, activities of daily living if injected appropriately

Future directions for botulinum toxins

- New formulations of botulinum toxin
  - Shorter duration toxins
  - Longer duration toxins
  - Fewer adverse effects
  - “Designer” toxins
- Improved muscle targeting
  - Muscle imaging
  - Ultrasound
- New indications