Botulinum Toxin for Movement Disorders: Physiology, Pharmacology and Evaluation of Patients

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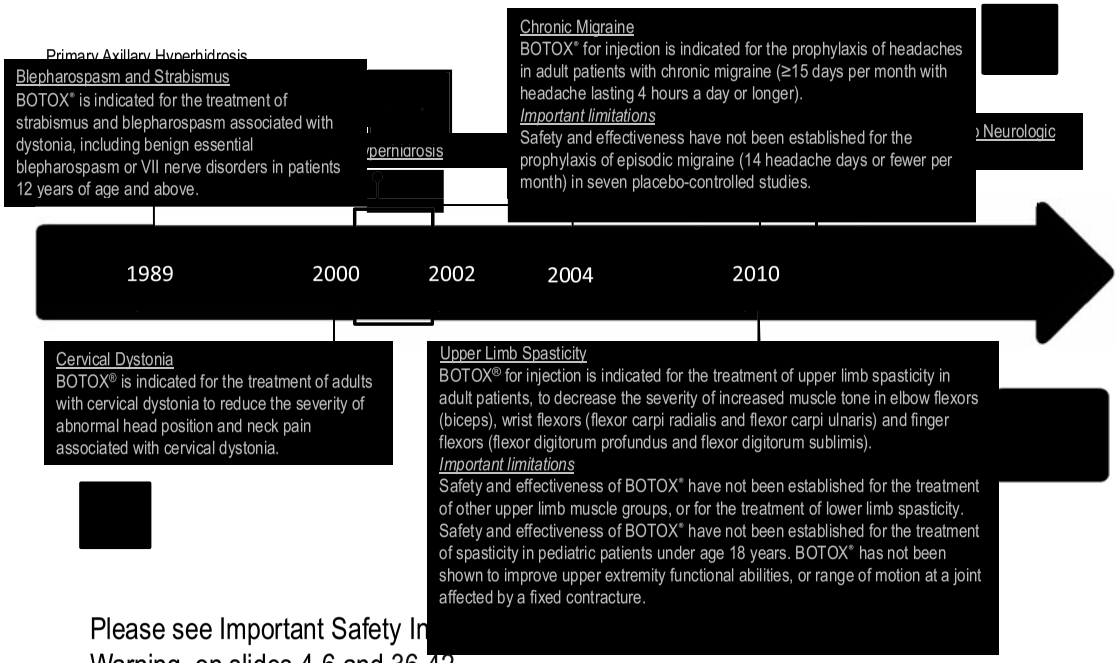
OBJECTIVES

- Review the pharmacology of botulinum toxin
- Review mode of action of botulinum toxin
- Be aware of diffusion characteristics of various formulations of botulinum toxin
- Know strategies to evaluate the patient that requires botulinum toxin or other form of spasmolysis/neurolysis.


• Hypersecretion of body fluids
• Ulcers from malignant diseases
• Skin alterations after burning
• Delusions; rabies; plague
• Tuberculosis (consumption)
• Yellow fever
Erbguth *Neurology*. 1999; 53:1850

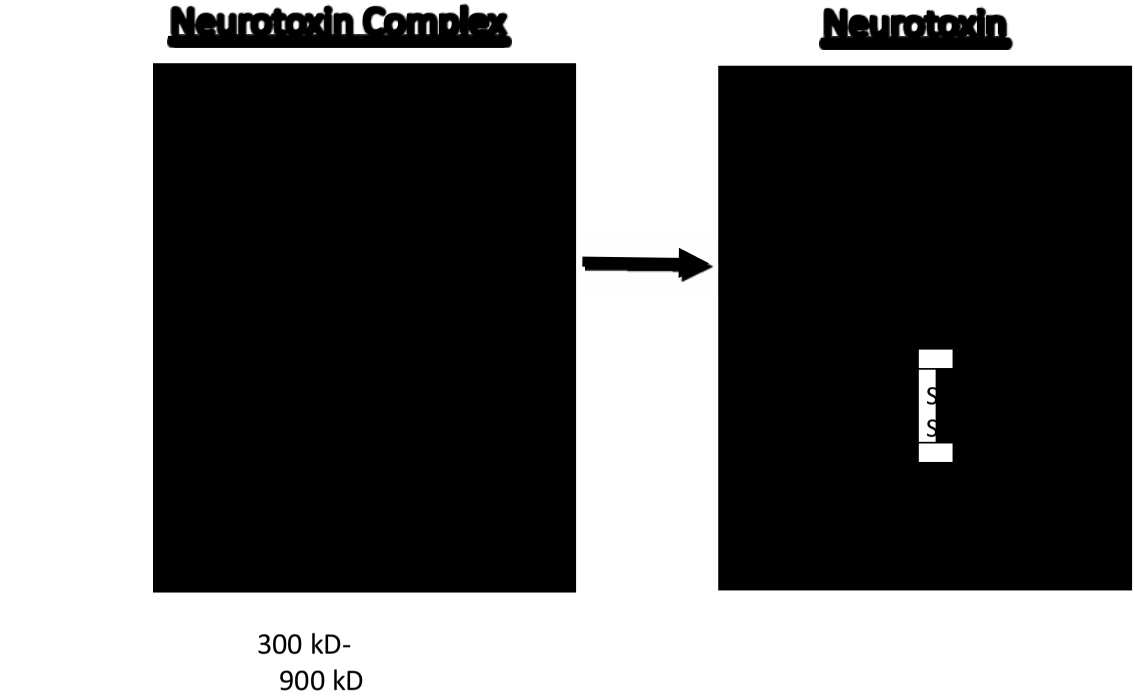
Erbguth *Neurology*. 1999; 53:1850

Therapeutic Indications[1]: Timeline of FDA Approvals



Please see Important Safety In
Warning, on slides 4-6 and 36-42.

1. BOTOX® (onabotulinumtoxinA) Prescribing Information. Irvine, CA: Allergan, Inc.; 2011.



Botulinum Neurotoxin Serotypes Differ by Weight and Composition

- Type A only one to form the 900 KD complex
- Types A, B, C_1, HA (hemagglutinin) positive D, form 500 KD and 300 KD complexes
- Types E, F, and HA–negative D, form only the 300 KD complex
- Type G forms a 500 KD complex

COOH NH_2

Light Chain Heavy Chain

NH_2

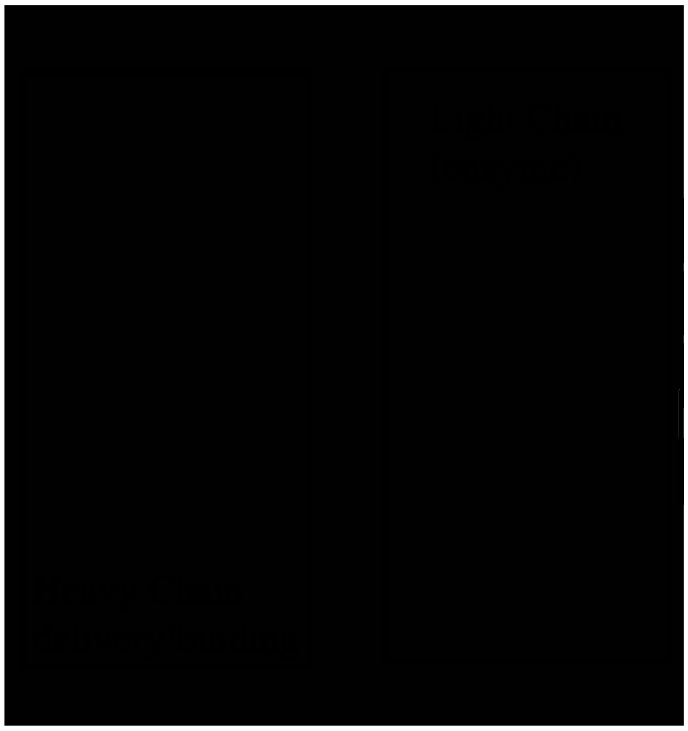
NH_2

COOH

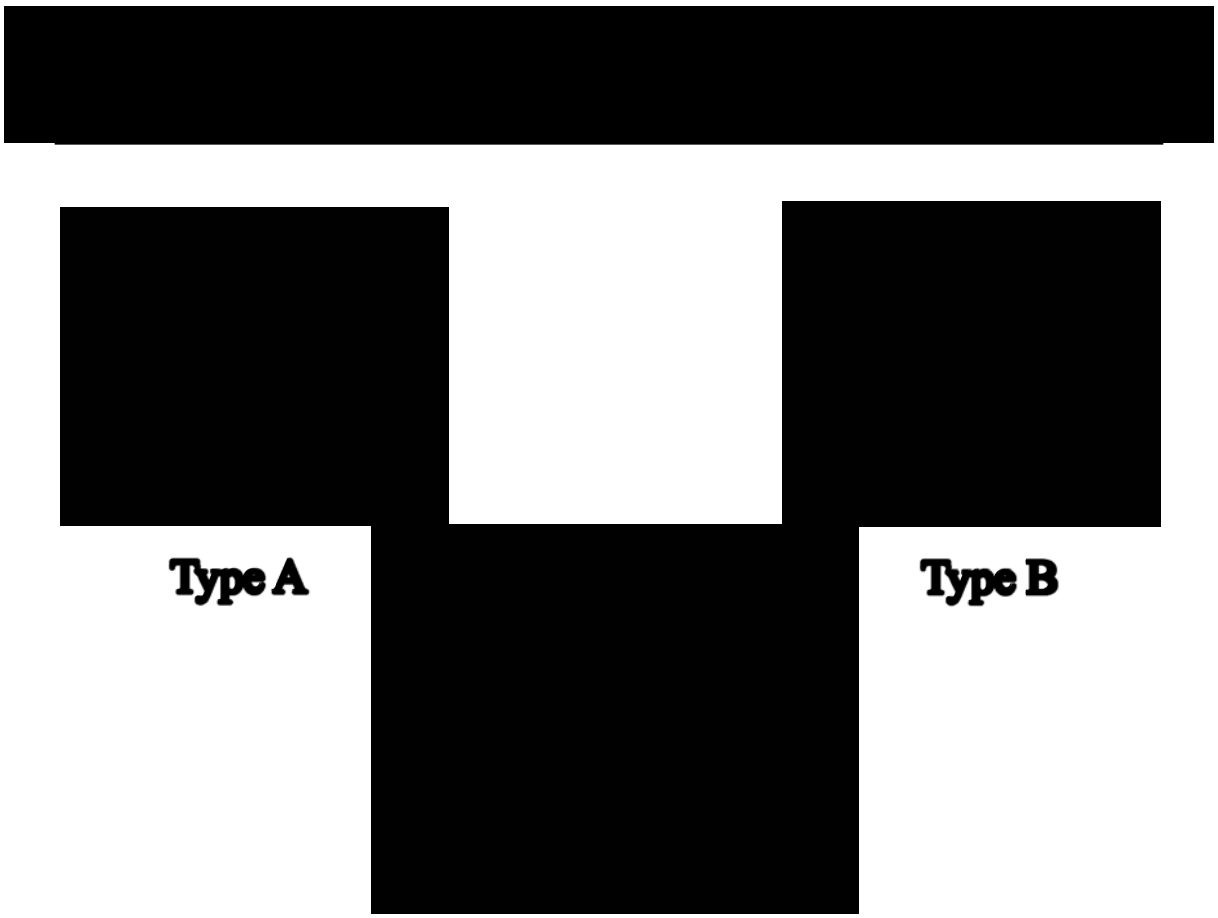
COOH

Nicking —— Activation Efficacy

Jankovic and Schwartz *Neurology*. 1995; 45:1743-1746; Borodic et al *Neurology*. 1996; 46:26-29

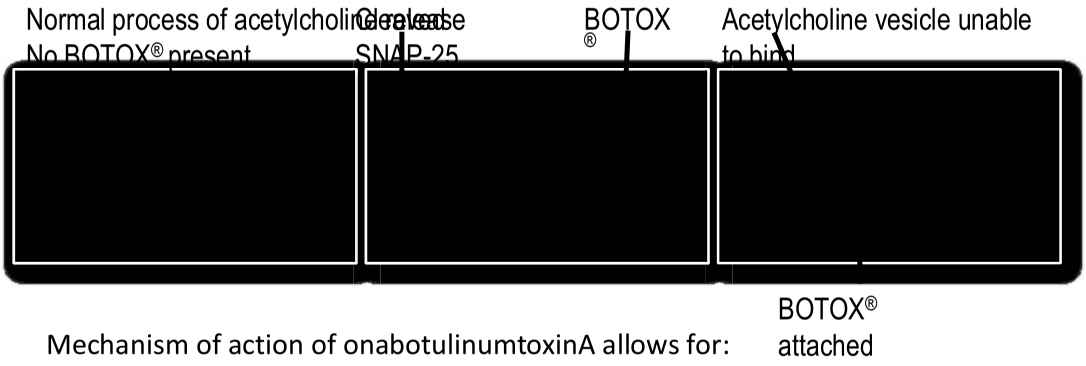


- **Heavy Chain (100 kD)**
- **Light Chain (50 kD)**
- **BoNT-A inhibits calcium- dependent vesicle exocytosis**


Type A
Type B

BOTULINUM TOXIN A

- BOTOX® neurotoxin directly acts on motor neurons to reduce muscle activity[1]
- BOTOX® cleaves SNAP-25 in motor neurons, which inhibits acetylcholine release at the motor end plate[2]



Mechanism of action of onabotulinumtoxinA allows for:

- Targeted reduction of hypertonicity[3]
- Transient and reversible effect[1,4,5]

1. O'Brien CF. *Clin J Pain*. 2002;18(6 suppl):S182-S190. 2. Cui M et al. *Pain*. 2004;107:125-133. 3. Simpson DM et al. *Neurology*. 1996;46:1306-1310. 4. Rowland LP. *N Engl J Med*. 2002;347:382-383. 5. Bergfeldt U et al. *J Rehabil Med*. 2006;38:166-171.
Image adapted from Arnon SS et al. *JAMA*. 2001;285:1059-1070.

Comparisons

Similarities & Differences Among Serotypes

Similarities:

- Clostridial neurotoxin
- Bi-chain structure
- Inhibition of acetylcholine release
- Production of flaccid paralysis which is reversible

Differences:

- Antigenically distinct
- Distinct binding sites
- Distinct enzymatic actions
- Pharmacologic differences
- Different species specificity

Simpson LL, et al. J Pharmacol Exp Ther. 2004;308:857-864.

Characteristics of Approved BoNT Preparations and NT 201(IncobotulinumtoxinA)

	Onabotulinum-toxinA	Abobotulinum-toxinA	Rimabotulinum-toxinB	NT 201
Preparation	Powder	Powder	Ready-to-use solution	Powder
Storage conditions	Below 8°C	Below 8°C	Below 8°C	Below 25°C
Shelf-life	24 months	15 months	24 months	36 months
***Clostridium botulinum* strain**	Hall A	Ipsen strain	Bean B	Hall A
SNARE target	SNAP25	SNAP25	VAMP	SNAP25
Purification process	Precipitation and chromatog.	Precipitation and chromatog.	Precipitation and chromatog.	Precipitation and chromatog.

Adapted from: Dressler D, Benecke R. Disabil and Rehab 2007;29(3):1761-1768.

Characteristics of Approved BoNT Preparations and NT 201

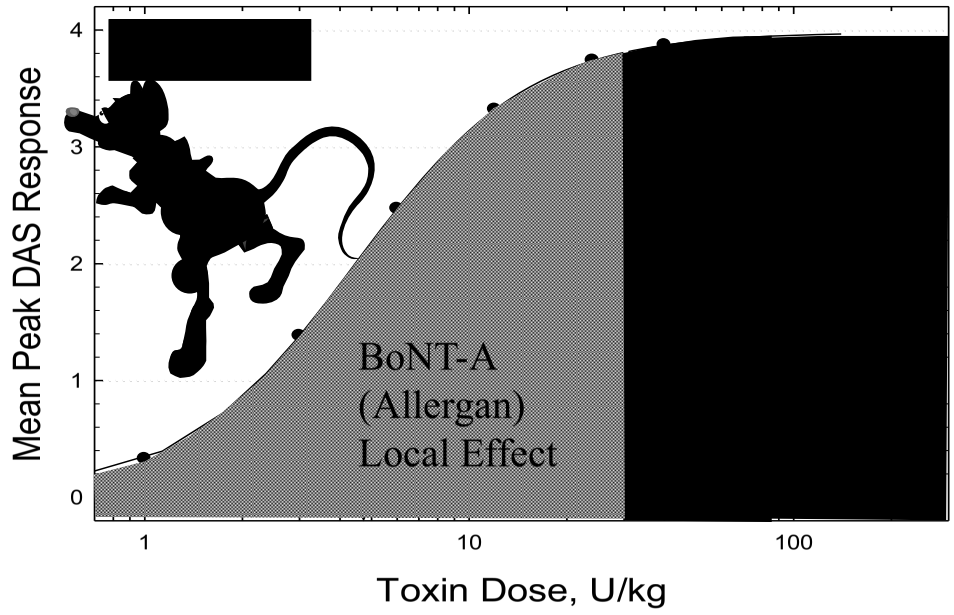
	Onabotulinum-toxinA	Abobotulinum-toxinA	Rimabotulinum-toxinB	NT 201
pH after reconstitution	7.4	7.4	5.6	7.4
Stabilization	Vacuum drying	Freeze-drying (lyophilisate)	pH-reduction	Vacuum drying
Excipients	Human serum albumin 500 ug/vial NaCl 900 ug/vial	Human serum albumin 125 ug/vial Lactose 2500 ug/vial	Not reported	Human serum albumin 1 mg/vial Sucrose 5 mg/vial
Biological activity	100MU-A/vial	500MU-I/vial	1.0/2.5/10.0kMU-E/vial	100MU-M/vial
Specific biological activity	60MU-EV/ngBNT	100MU-EV/ngBNT	5MU-EV/ngBNT	167MU-EV/ngBNT

MU-A=mouse unit in the Allergan mouse lethality assay; MU-E=mouse unit in the Solstice mouse lethality assay; MU-I=mouse until in the Ipsen lethality assay; MU-EV=equivalence mouse unit, 1 MU-EV=1 MU-A=1 MU-I=40 MU-E

Adapted from: Dressler D, Benecke R. Disabil and Rehab 2007;29(3):1761-1768.

Botulinum toxin type	[redacted]	[redacted]	[redacted]
Target intracellular protein (SNAP)	[redacted]	[redacted]	[redacted]
Reconstitution pH	[redacted]	[redacted]	[redacted]
Formulation	[redacted]	[redacted]	[redacted]
Cervical dystonia (CD) dosage	[redacted]	[redacted]	[redacted]

[redacted]



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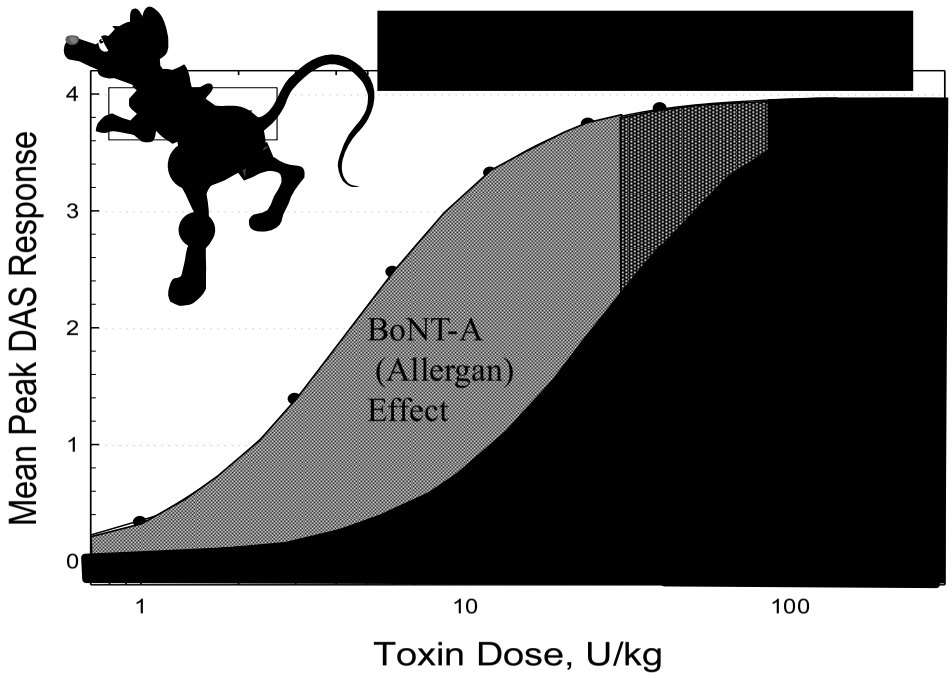
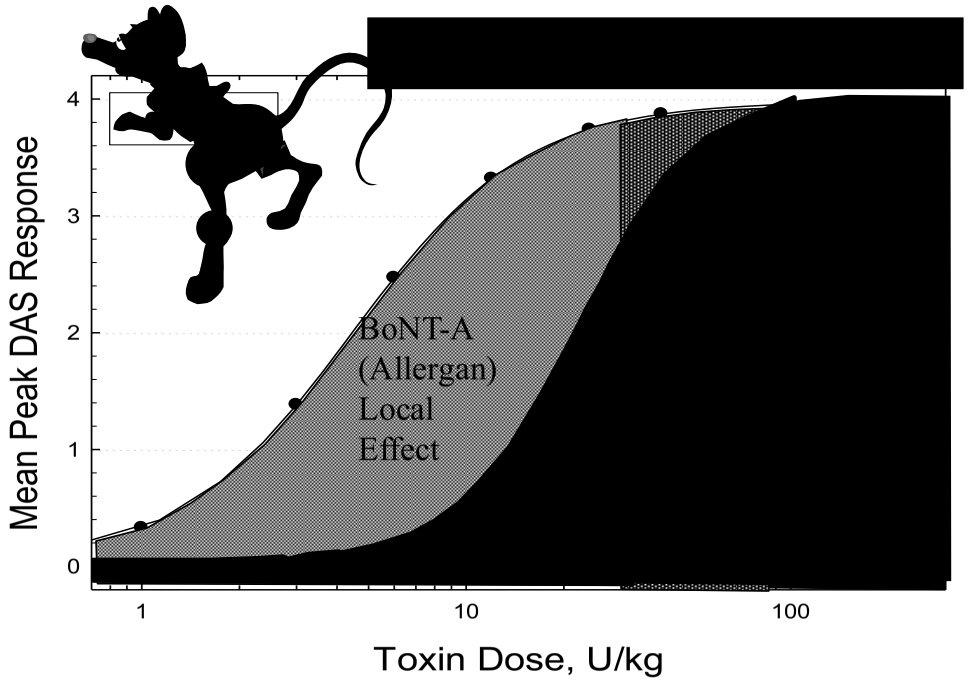


[redacted]

[redacted]



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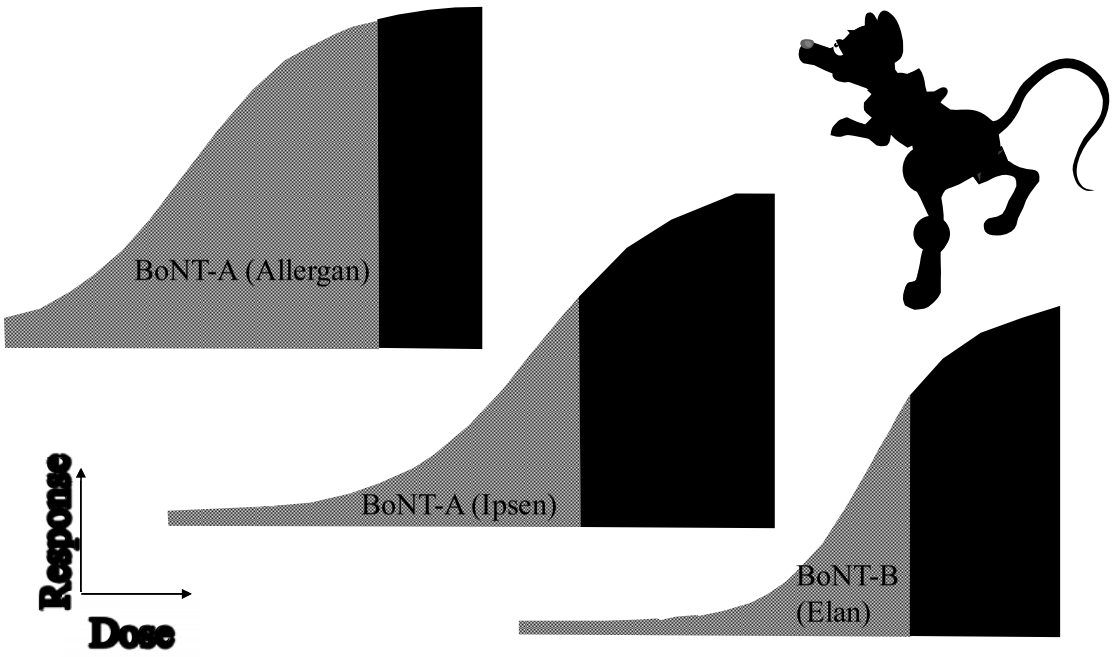
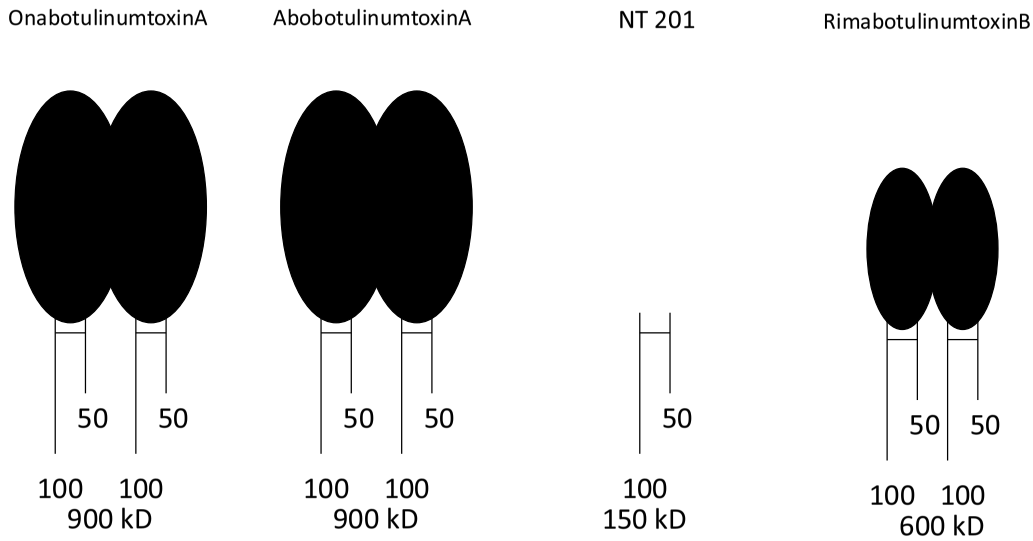


Composition of Botulinum Toxin Components



Adapted from Dressler D. Der Nervenarzt. 2006;77(8):912-921

FDA BLACK BOX WARNING

FDA ALERT [08/2009]: As announced on April 30, 2009, based on a safety evaluation of the botulinum toxin products, FDA has concluded that the prescribing information for OnabotulinumtoxinA (marketed as Botox/Botox Cosmetic) and RimabotulinumtoxinB (marketed as Myobloc) must be updated to ensure their continued safe use. On July 31, 2009, FDA, under the authorities granted by the Food and Drug Administration Amendments Act (FDAAA) of 2007, approved the following revisions to the prescribing information of Botox/Botox Cosmetic and Myobloc:

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm174949.htm

FDA ALERT

- Boxed warning
- Highlight the possibility of life threatening consequences from distant spread of BTX after local injection
- Risk assessment and mitigation strategy (REMS)
- Change to the established drug names
- Reinforce individual potencies
- Prevent medication errors

Considerations for Health Care Professionals

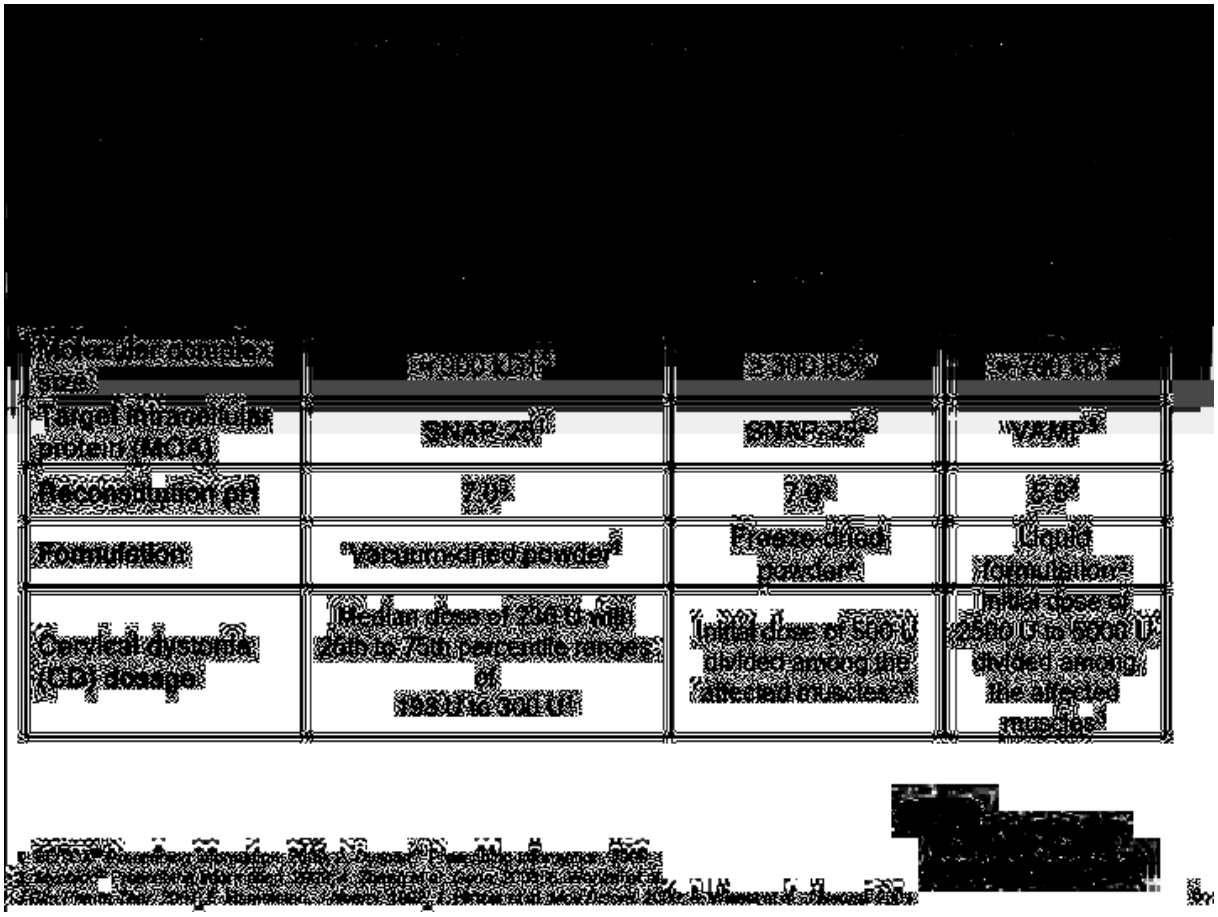
- Unexpected loss of strength/ development of weakness
- Hoarseness or trouble talking (dysphonia)
- Dysarthria
- Loss of bladder control
- Difficulty breathing
- Difficulty swallowing
- Double vision, blurred vision, droopy lids

General Dosing Information

Indication specific dosage and administration recommendations should be followed.

In treating adult patients for one or more indications, the maximum cumulative dose should generally not exceed 360 Units, in a 3 month interval.

The safe and effective use of BOTOX® depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques. Physicians administering BOTOX® must understand the relevant neuromuscular and/or orbital anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures. An understanding of standard



Botulinum toxin type	[illegible]	[illegible]	[illegible]
Target intracellular protein (SNAP-25 or VAMP)	SNAP-25[illegible]	SNAP-25[illegible]	VAMP[illegible]
Reconstitution pH	7.0[illegible]	7.0[illegible]	5.6[illegible]
Formulation	Vacuum-dried powder[illegible]	Freeze-dried powder[illegible]	Liquid formulation[illegible]
Cervical dystonia (CD) dosage	Median dose of 236 U with 25th to 75th percentile ranges of 193 U to 300 U[illegible]	Initial dose of 5000 U divided among the affected muscles[illegible]	Initial dose of 2500 U to 5000 U divided among the affected muscles[illegible]

[illegible]

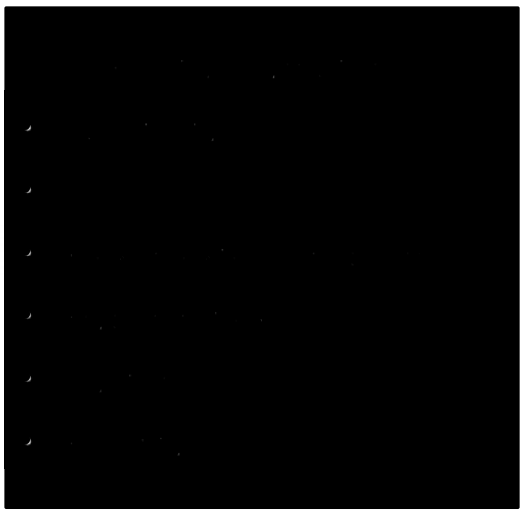
Spasticity

Definition of Spasticity

"Spasticity is a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome."

— Lance, 1980

Upper Motor Neuron Syndrome

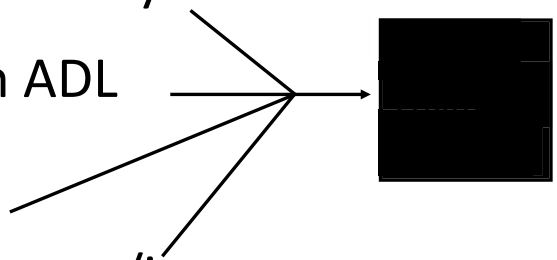


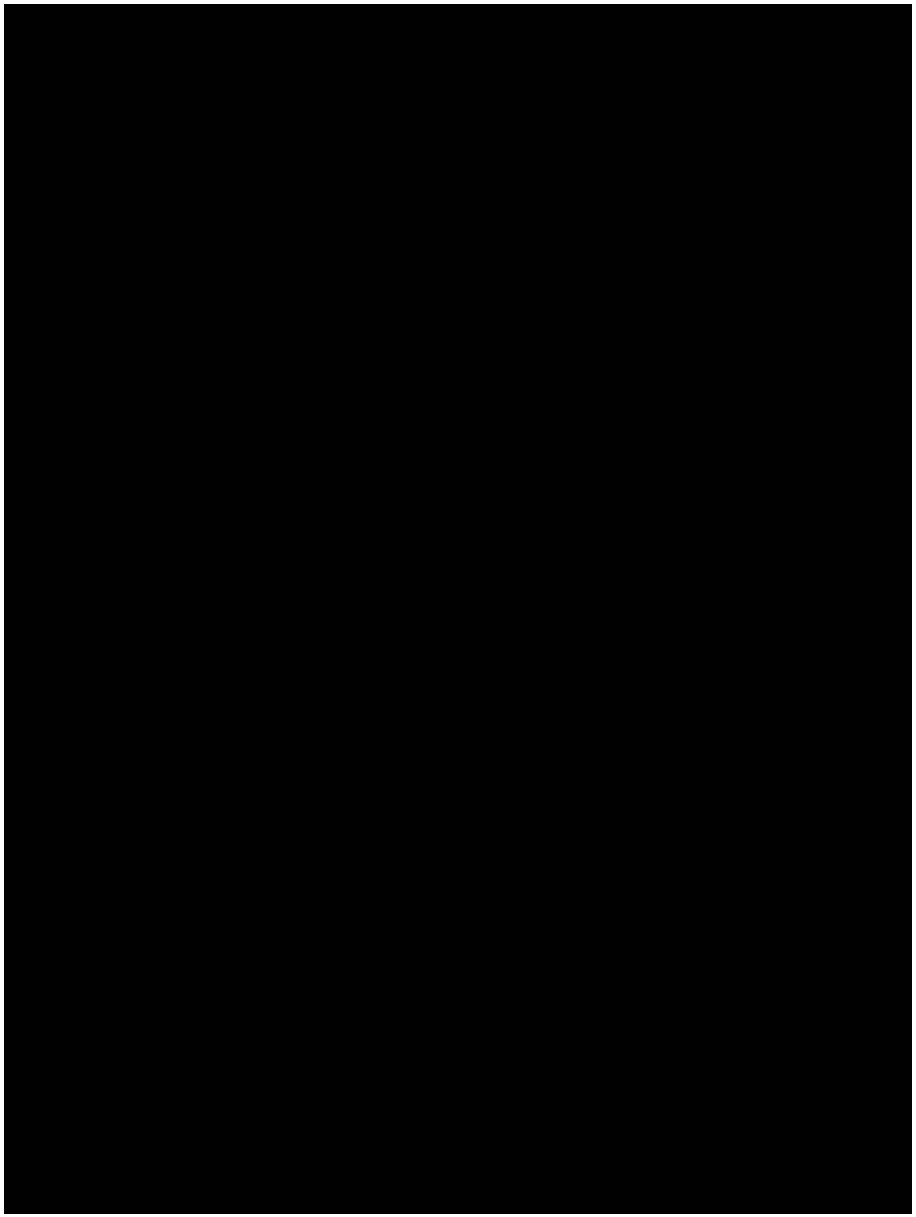
Etiologies

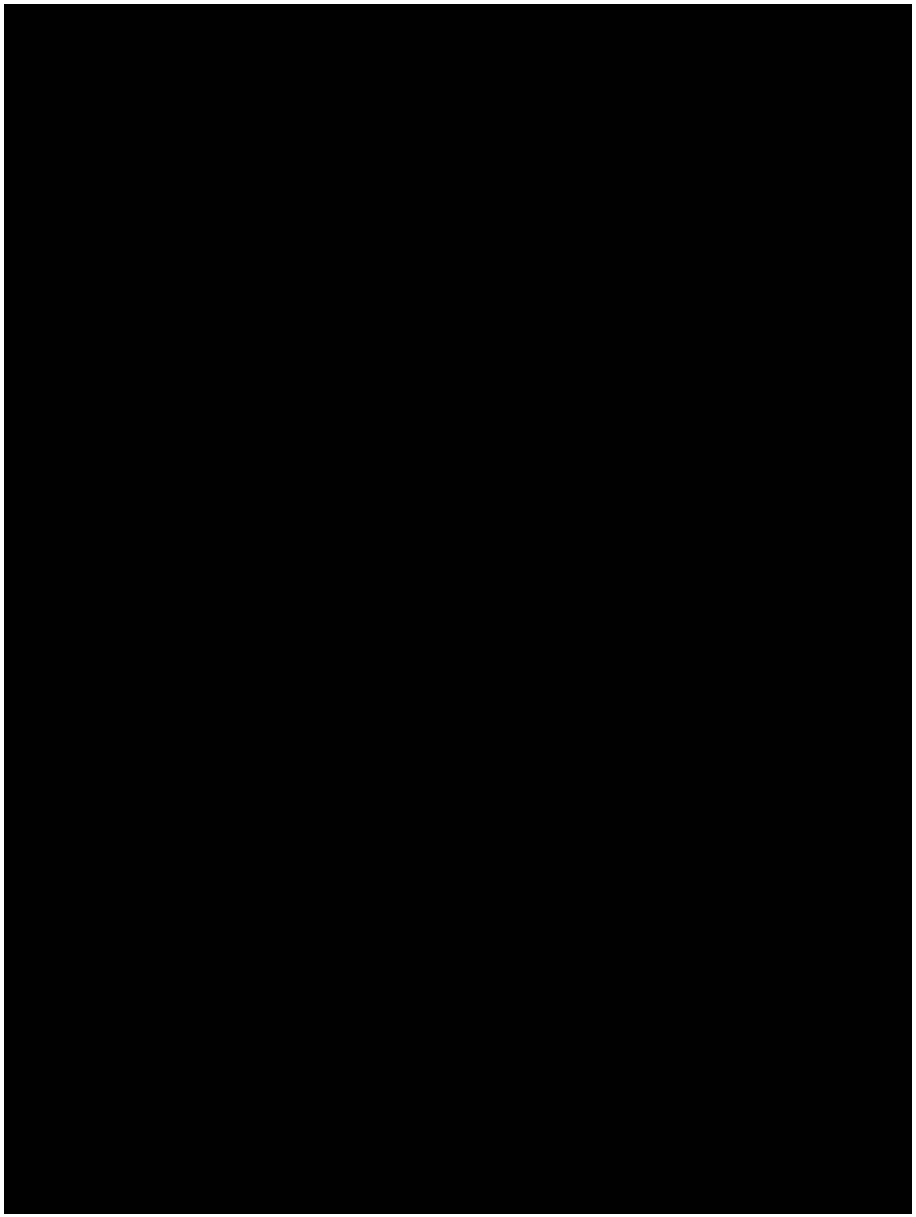
- Stroke
- Traumatic brain injury
- Multiple sclerosis
- Spinal cord injury
- Cerebral palsy
- Anoxia
- Neurodegenerative disease

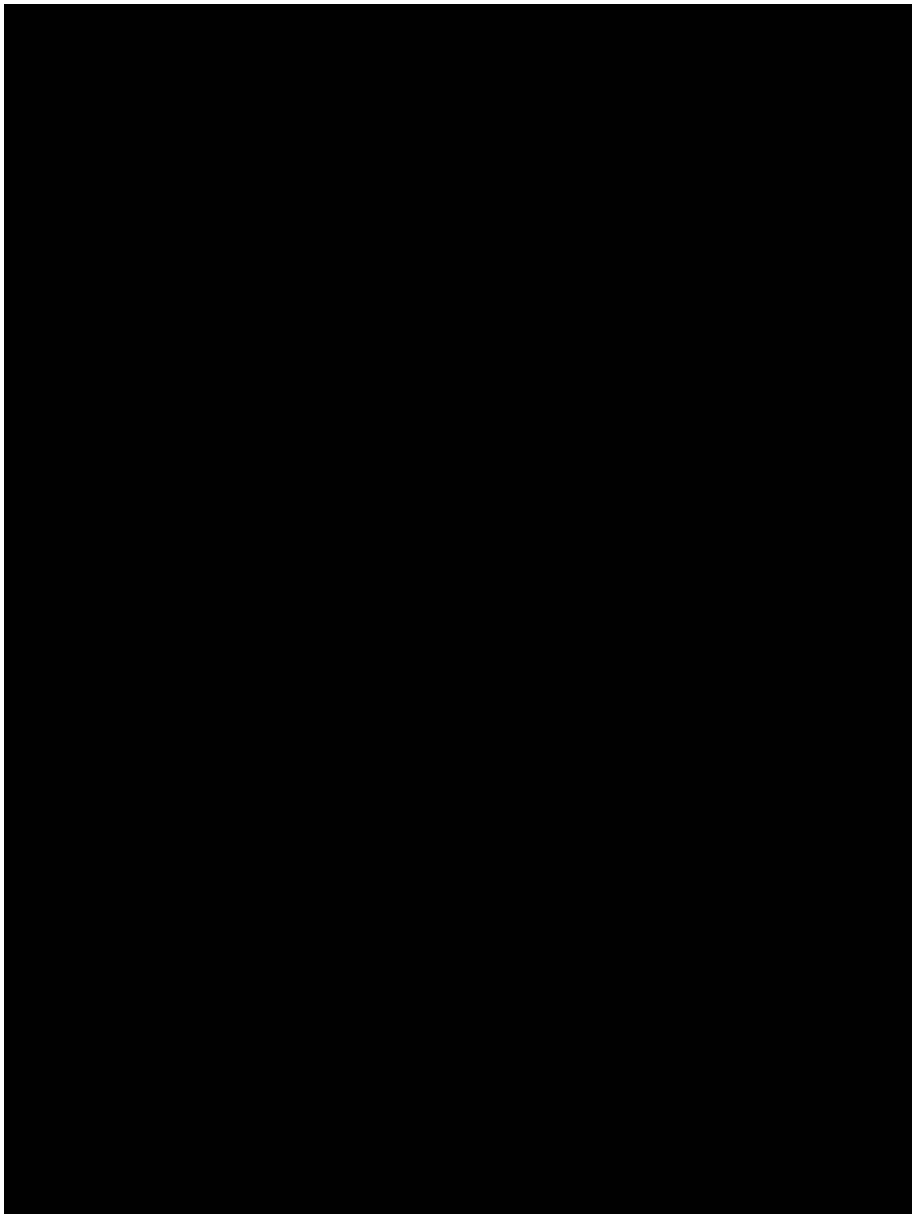
Evaluation of the Spastic Patient

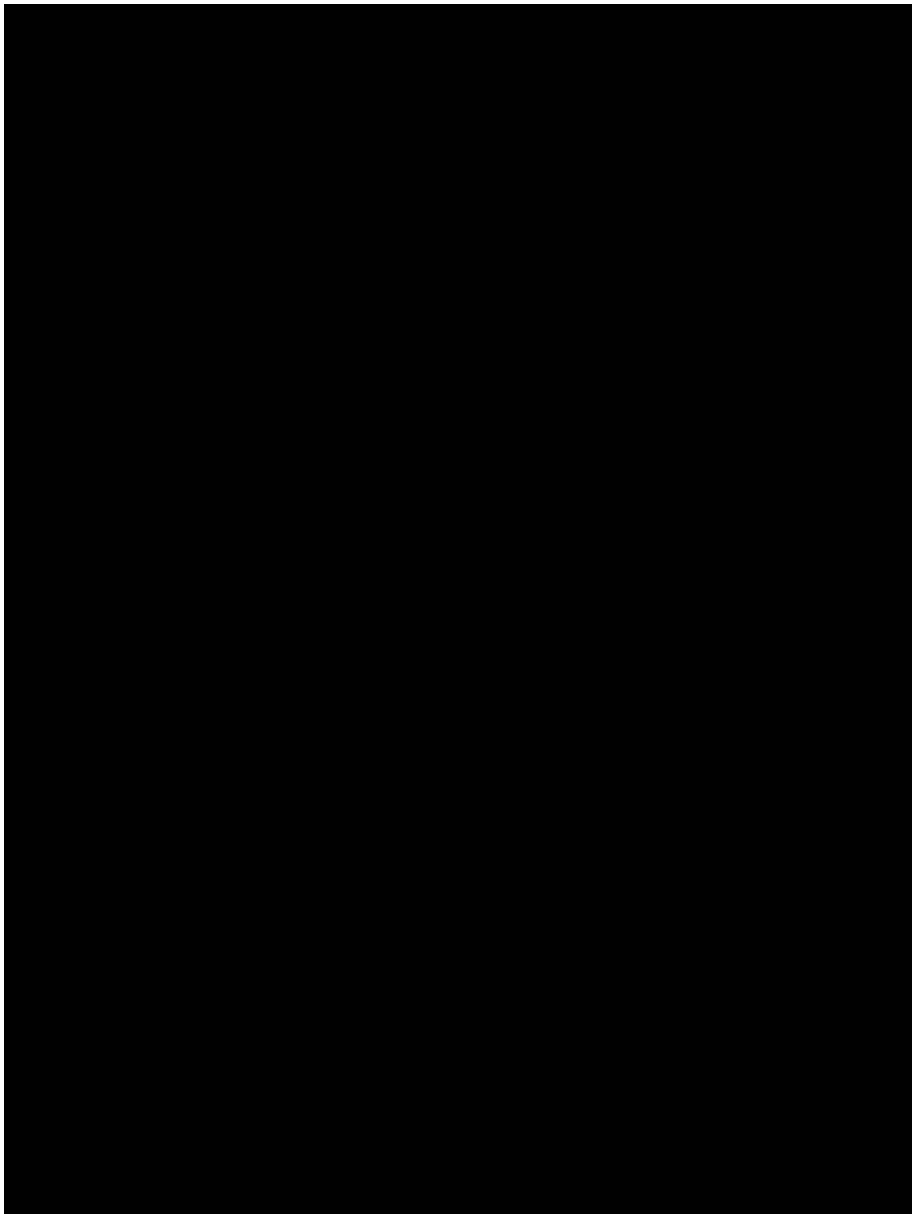
- Participation of patient/caregiver in
  - Assessment of spasticity
  - Performance with ADL
  - Level of support
  - Life-style maintenance/improvement












ADDUCTED THIGHS & FLEXED KNEES

Common Clinical Patterns: Lower Limbs

Equinovarus

Striatal Toe

Extended Knee

Flexed Knee

Adducted Thighs

Patient Evaluation (cont'd)

- Physical Examination
  - Standard and consistent technique is important to obtain unbiased results
  - Use a fixed evaluation sequence
    - Provide consistency in outcome measurements
    - Valid assessment measure
- Therapist Feedback

MAKING DECISIONS: BOTULINUM TOXIN OR OTHER MODALITY?

NERVE BLOCK

EVALUATION

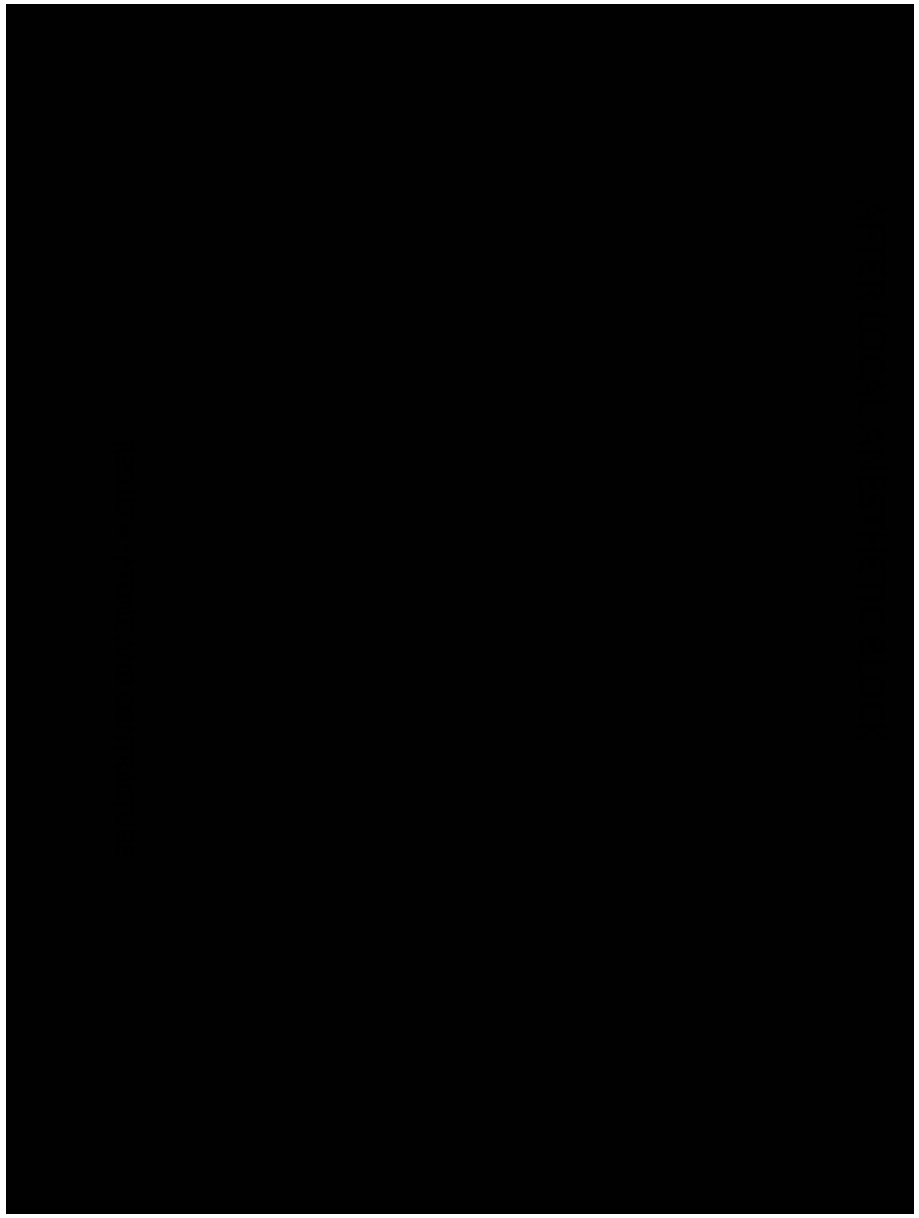
EVALUATION

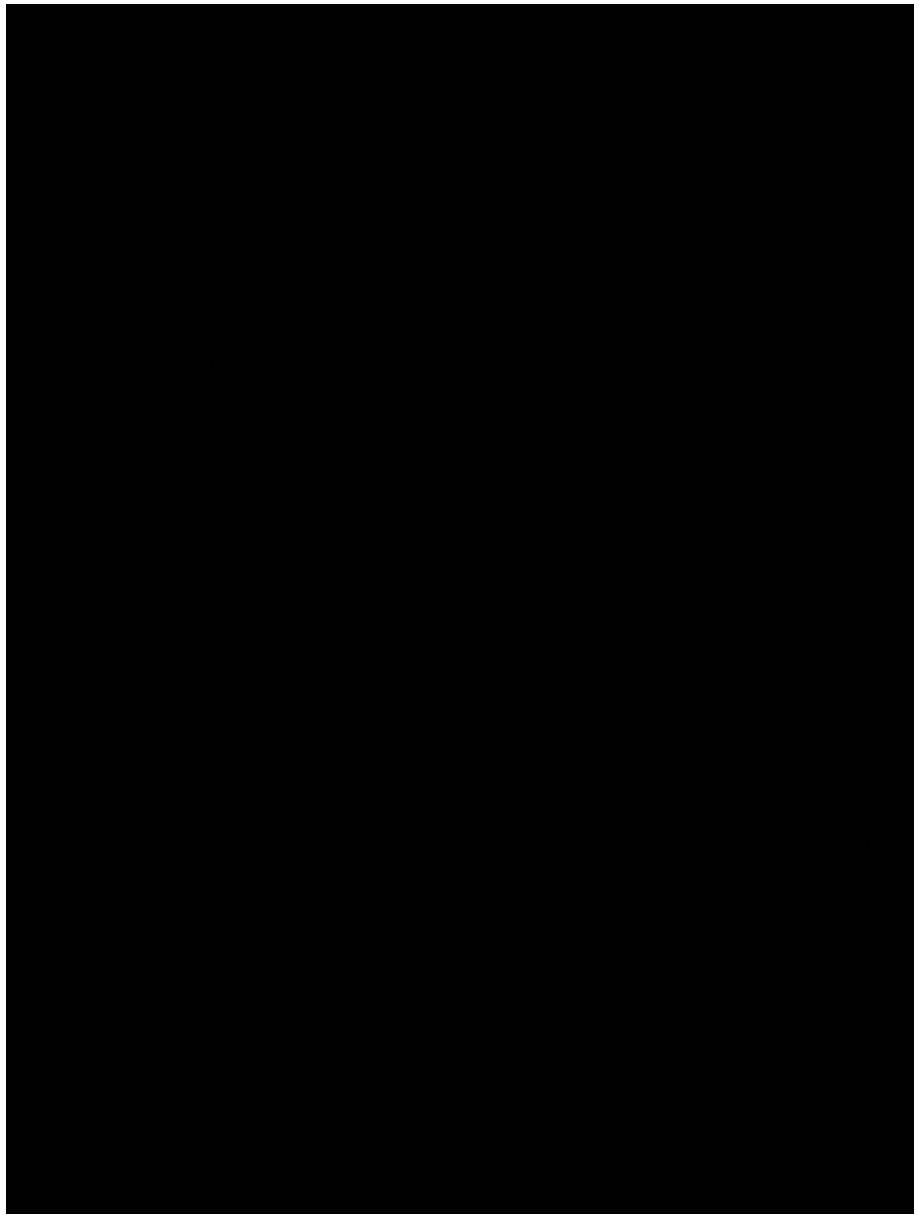
TIBIAL NERVE BLOCK

EVALUATION

S.R.

TRAUMATIC BRAIN INJURY

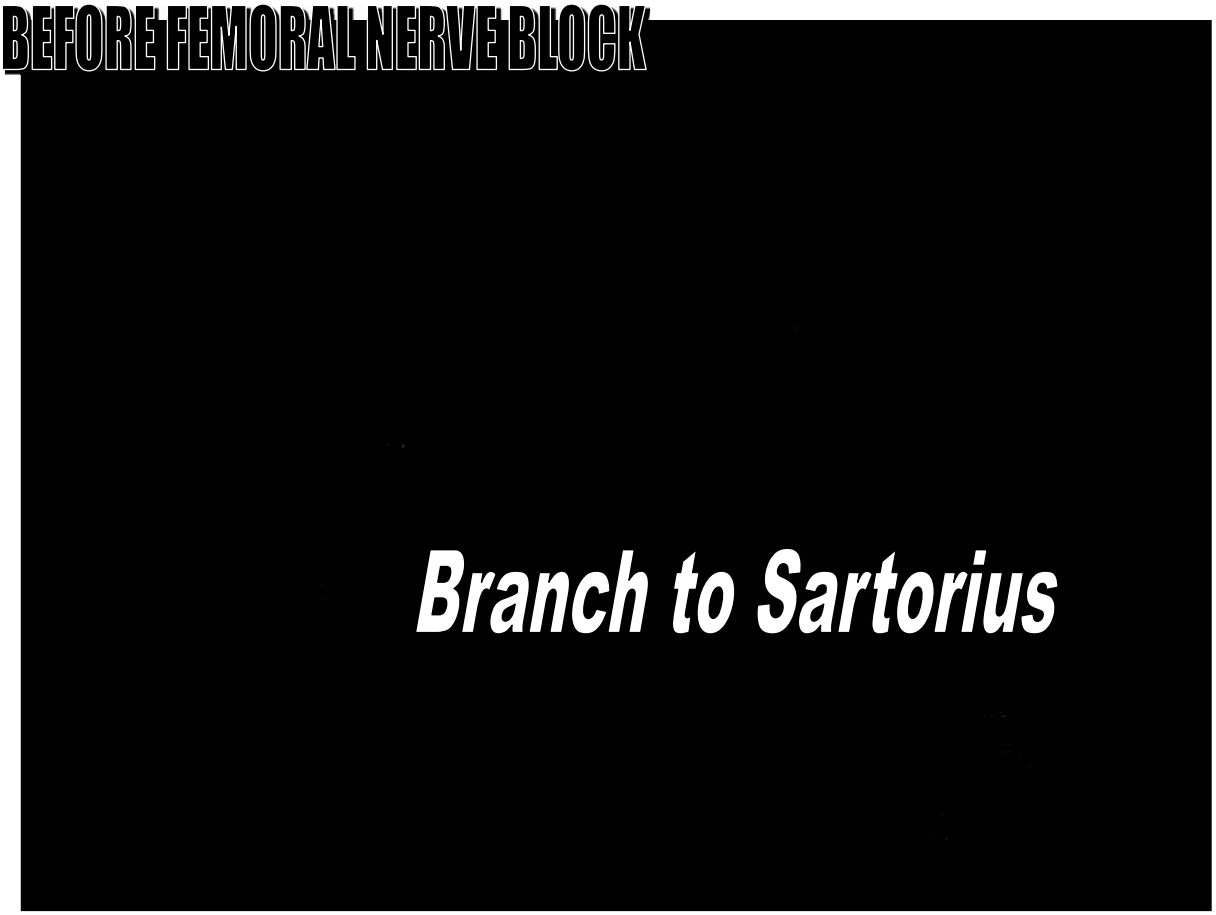




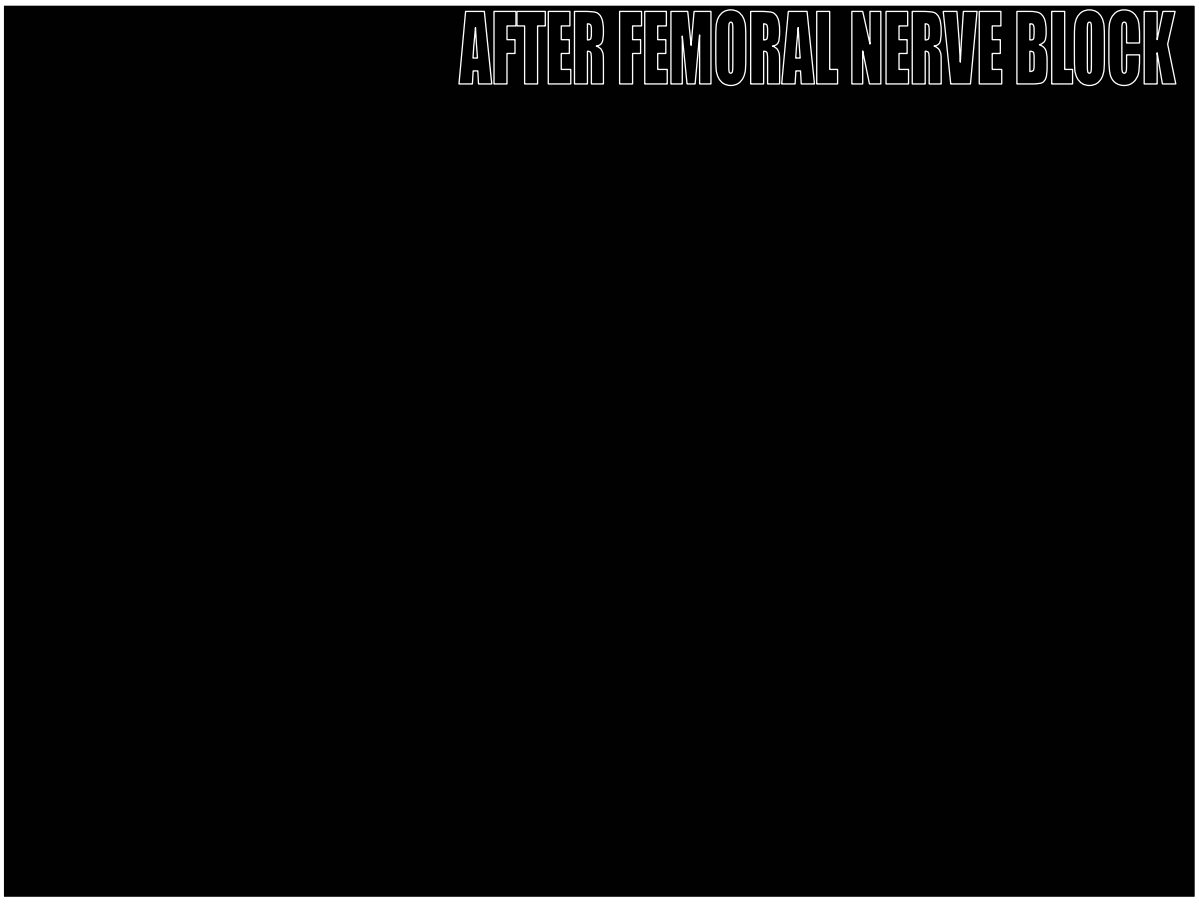
SPINAL CORD INJURY

- Twenty-plus year old ♀
- Spastic paraparesis
- Knee flexion contractures and spastic dystonia
- Hip flexion contractures and spastic dystonia
- Evaluate to determine management

BEFORE FEMORAL NERVE BLOCK



AFTER FEMORAL NERVE BLOCK



NERVE BLOCK

EVALUATION

EVALUATION

EVALUATION

MEDIAN NERVE BLOCK:
1% LIDOCAINE

Bulf

SPASTIC TETRAPARESIS

SIX % PHENOL

DIPLEGIC CP

TIBIAL NERVE NEUROLYSIS

S. T.

SPASTIC PARAPARESIS

SCIATIC NERVE BLOCK

SCIATIC NERVE

AFTER BLOCK

T. L.

TOE HYPERFLEXION

STROKE

R. C.

TOE HYPERFLEXION

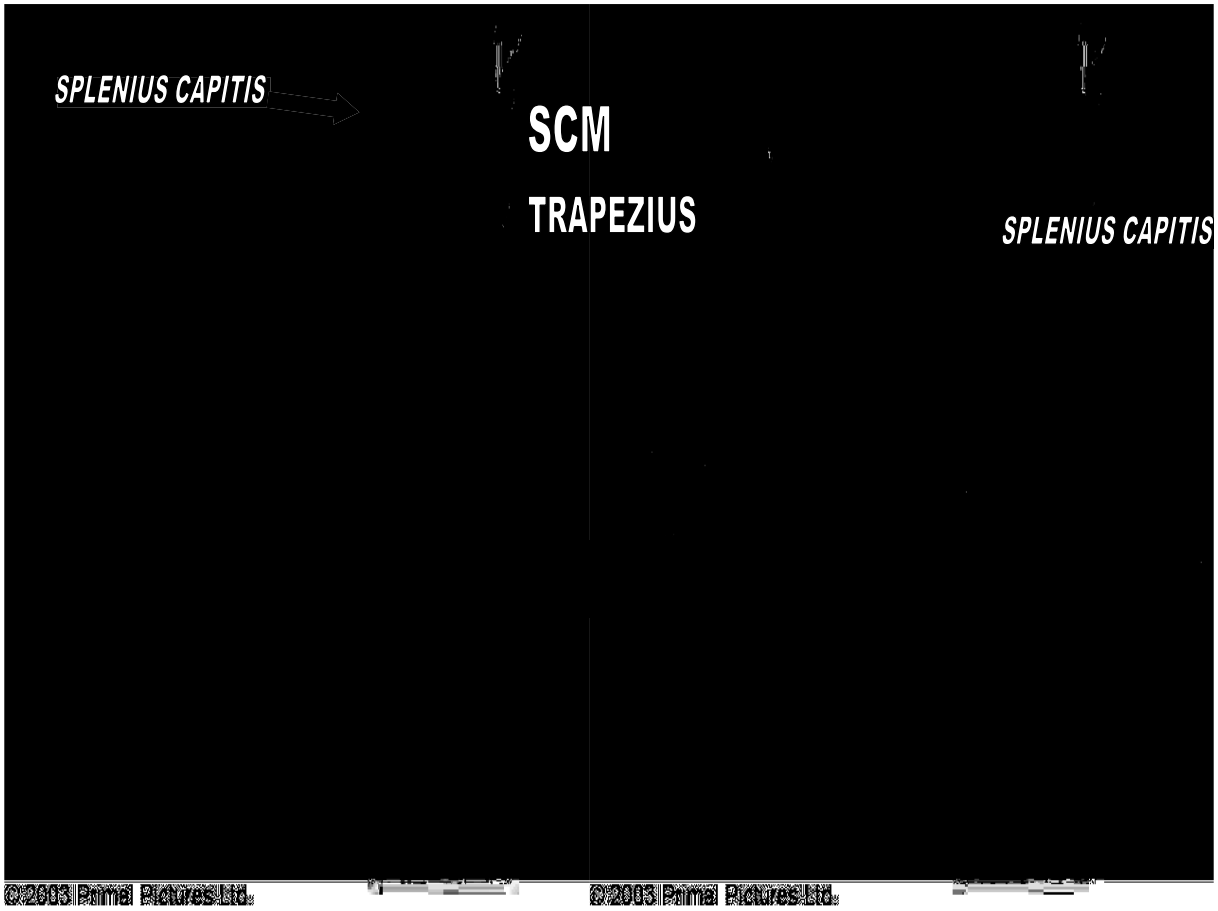
EMG NEEDLE PLACEMENT

R. C.

OROMANDIBULAR & LINGUAL DYSFUNCTION

EMG of the TONGUE

E. S.



SAMPLE EMG NEEDLE PLACEMENT

CERVICAL DYSTONIA

SPLENIUS CAPITIS

R. H.

SUMMARY

- Botulinum toxins inhibit release of acetylcholine at the neuromuscular junction
- Botulinum toxin: Useful tool for Rx of focal spasticity
- Cases must be well selected
- EDX skills helpful in choosing appropriate procedures and muscles for injection
- Set clear, attainable treatment goals