# Spasticity: Diagnosis and Management with Focus on Botulinum Toxin

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## Disclosures

- ***Research/Grants:*** Allergan; Ipsen; Merz
- ***Speakers Bureau***: Allergan; Ipsen; Merz
- ***Consultant***: Allergan; Ipsen; Merz

# Learning Objective 1

Recognize the varied presentations of spasticity

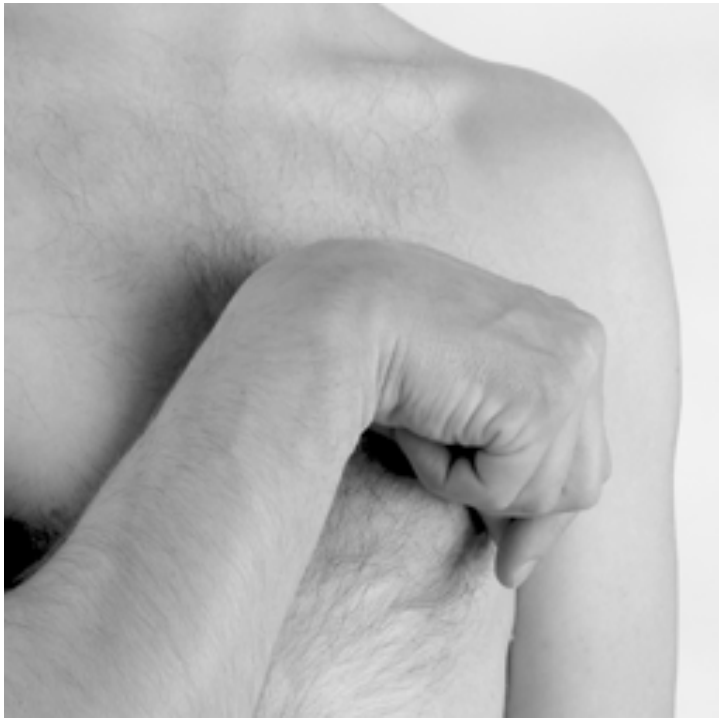
# Learning Objective 2

Develop individualized treatment strategies based on shared goals and available treatment options

# Spasticity: Diagnosis and Treatment Agenda

- Spasticity: Definitions
- Associated features of spasticity
- Forms of spasticity
- Diagnostic assessment of spasticity
- Setting of goals and expectations
- Treatment options for spasticity
- Botulinum toxin therapy

# 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

Ozcakir S, Sivrioglu K. *Clin Med Res*. 2007;5(2):132-138.

# Upper Motor Neuron Syndrome

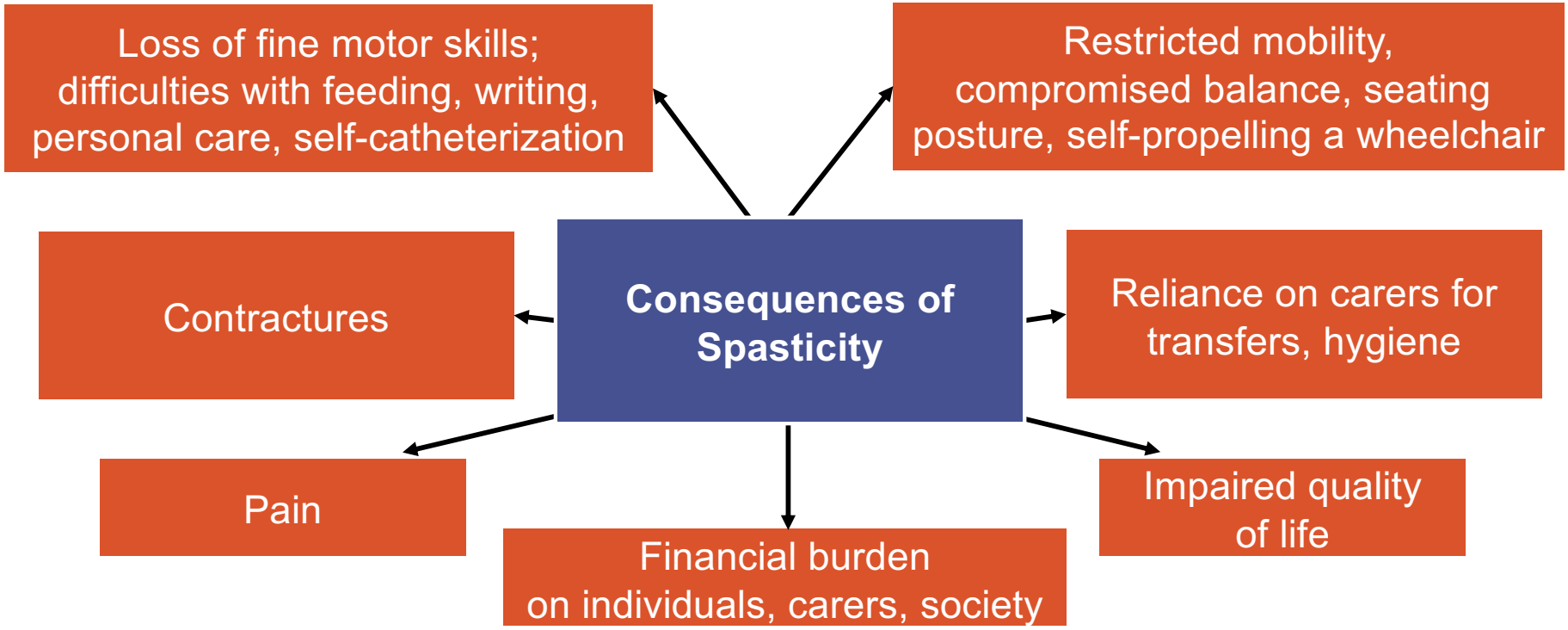
- Group of symptoms caused by damage to 1 (or more) area(s) of the central nervous system (CNS) involved in controlling voluntary movement

**Damage to CNS**

| Loss of connections to lower motor neurons | Loss of inhibition of lower motor neurons |
|---|---|
| **Lack of muscle activity** | **Muscle overactivity** |
| **Negative Symptoms**[1-3]<br>• Weakness[1-3]<br>• Fatiguability[1-3]<br>• Loss of dexterity[1-3]<br>• Sensory deficits[3] | **Positive Symptoms**[1-3]<br>• Spasticity[1-3]<br>• Hyper-reflexia[1]<br>• Clonus[1-3]<br>• Co-contraction[1,2]<br>• Extensor and flexor spasms[1-3]<br>• Extensor plantar response (Babinski sign)[2,3] |

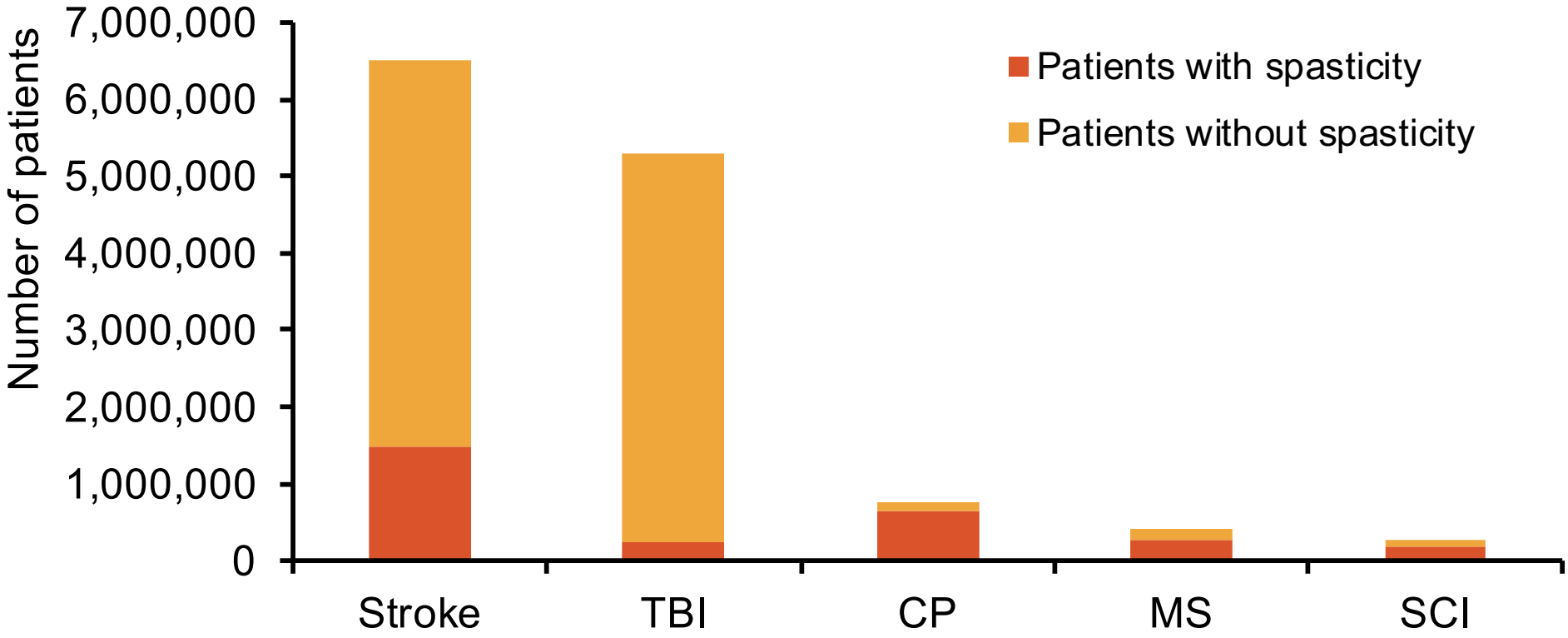
1. Mayer NH, et al. *Phys Med Rehabil Clin N Am*. 2003;14(4):855-83, vii-viii. 2. Ward AB. *J Neural Transm (Vienna)*. 2008;115(4):607-616. 3. Wissel J, et al. *J Rehabil Med*. 2009;41(1):13-25.

# Consequences of Spasticity



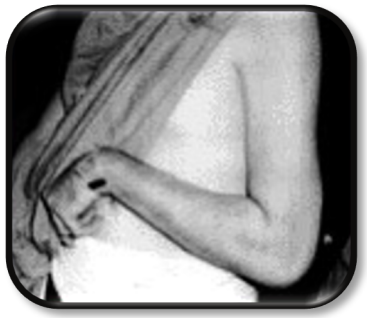

Wissel J, et al. *J Rehabil Med*. 2009;41(1):13-25.

# Prevalence of Spasticity by Etiology




McGuire JR. Epidemiology of spasticity in the adult and child. In: Elovic E and Brashear A, eds. Spasticity Diagnosis and Management. New York, NY: Demos Medical Publishing; 2011:5-15.

# Spasticity: Upper Limbs



The Adducted/Internally Rotated Shoulder

The Flexed Wrist

The Pronated Forearm

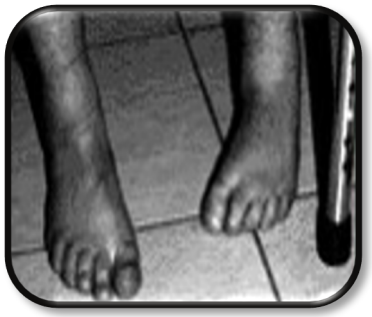
The Clenched Fist

The Flexed Elbow

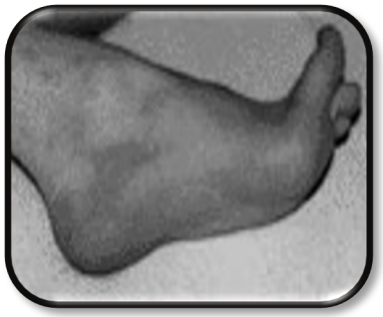
The Thumb-in-Palm Deformity

Photographs courtesy of Dr. David M. Simpson, New York, NY.

# Spasticity: Lower Limbs

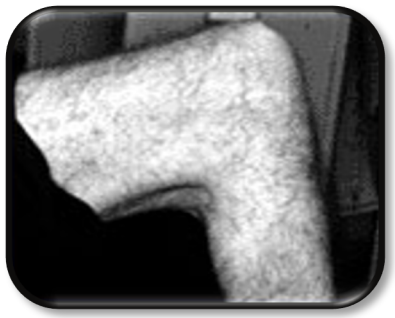


Equinovarus

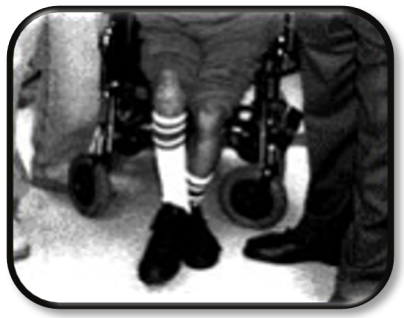


Striatal Toe

Extended Knee



Flexed Knee



Adducted Thighs

Photographs courtesy of Dr. David M. Simpson, New York, NY.

# What Is Meaningful Function?

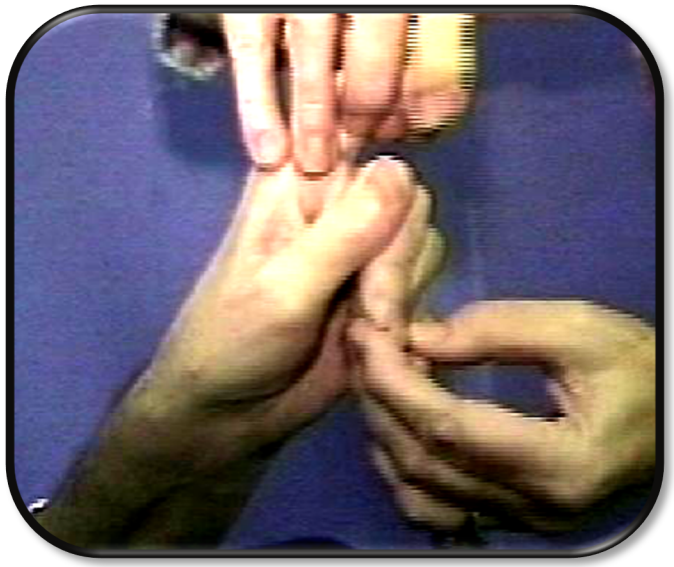
- Active function
- Improved upper limb use: reaching, grasping, releasing
- Improved mobility
- Improved gait
- Decreased energy expenditure
- Passive function
- Increased ROM
- Improved positioning
- Increased ease of hygiene
- Improved cosmesis
- Decreased spasm frequency
- Improved orthotic fit
- Decreased pain

ROM = range of motion.

Brin M. *Muscle Nerve*. 1997;20:S208.

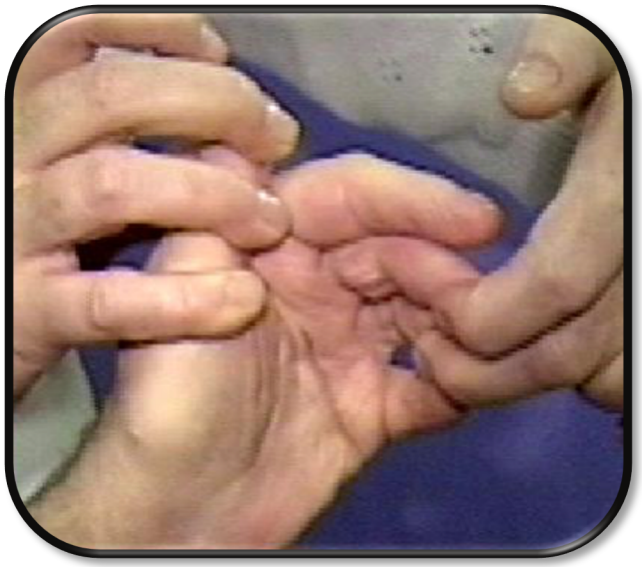
# Passive: Personal Care Problems

## Before treatment



Long and ring fingers are clenched into palm; poor access to malodorous; macerated palm

## After treatment



Greater access after chemodenervation of FDS

FDS = flexor digitorum superficialis.
Photographs courtesy of Dr. David M. Simpson, New York, NY.

# Active: Limb Use Problems

- Upper limb
  - Reach
  - Grasp
  - Transport
  - Release

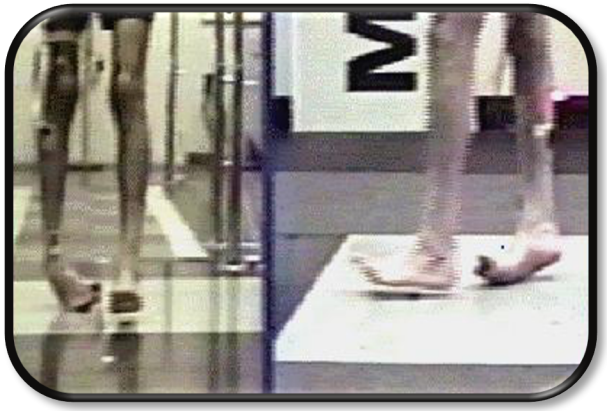
**Before treatment**


**After treatment**


Photographs courtesy of Dr. David M. Simpson, New York, NY.

# Active: Mobility Problems

Weight borne painfully on lateral border of right foot with equinovarus



Weight borne on right plantigrade foot after neurolysis

Photographs courtesy of Dr. David M. Simpson, New York, NY.

# Treatment Goals for Spasticity

| Goals | Examples |
|---|---|
| Provide symptom relief | • Reduce muscle pain<br>• Reduce muscle spasms<br>• Prevent contractures<br>• Better limb position |
| Ease patient care and decrease caregiver burden | • Dressing<br>• Hygiene (palm, elbow crease, axilla, perineum)<br>• Positioning in bed or chair<br>• Transfers |
| Improve patient function | • Upper limb – reaching, grasping, releasing |
| Other | • Facilitate physical therapy – stretching, splinting<br>• Delay or prevent surgery<br>• Prevent need for unnecessary medication or other treatments |

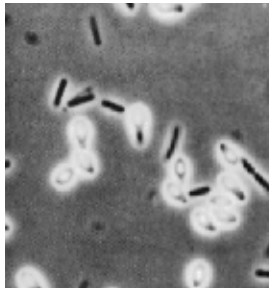
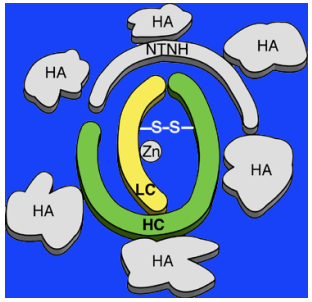
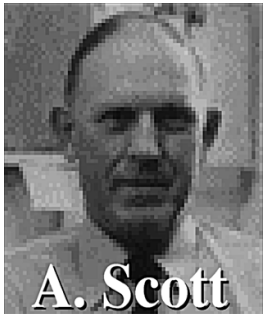
1. Ward AB. *J Neural Transm (Vienna)*. 2008;115(4):607-616. 2. Sheean G. *Drug Saf.* 2006;29(1):31-48.

# Treatment Options for Spasticity

- Only disabling pattern should be treated[1]
- There are several different therapies for spasticity, generally a combination of treatment options are employed:
  - Physiotherapy[1]
  - Occupational therapy[1]
  - Pharmacotherapy (oral medications; intrathecal baclofen therapy)[1,2]
  - Surgical interventions[1,2]
  - Chemodenervation[1,2] (botulinum toxin)

1. Ward AB. *J Neural Transm (Vienna)*. 2008;115(4):607-616. 2. Ozcakir S, Sivrioglu K. *Clin Med Res*. 2007;5(2):132-138.

# Development of the First Commercial Botulinum Neurotoxin Product for Clinical Use

| 1700s-1800s | 1944 | 1950s-1960s | 1968 |
|---|---|---|---|
|  |  |  |  |
| Identified as cause of botulism by *Clostridium botulinum* | E. Schantz, et al began purifying botulinum toxin Type A | Type A 900 kD complex purification optimization | Medical use evaluation |

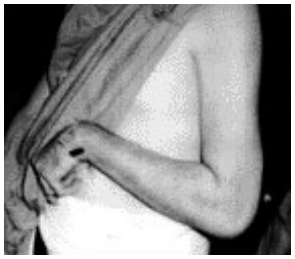
R. Aoki, - March 2000

# Reported Clinical Use of BoNT Is Diverse and Expanding

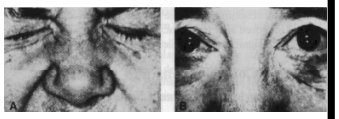
## Neuromuscular

**Strabismus***

**Cerebral Palsy***

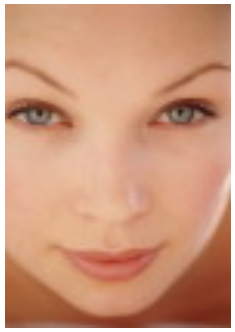


**Adult Spasticity***



**Blepharospasm***

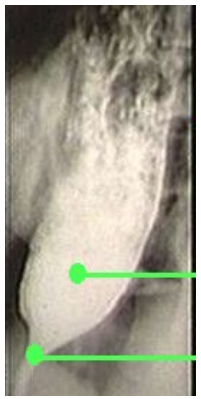
**Cervical Dystonia***



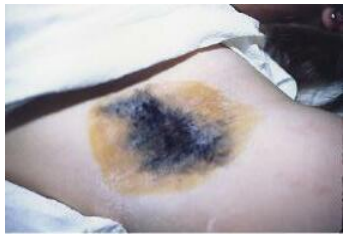
**Wrinkles***

US approved indications for botulinum toxin*

## Autonomic

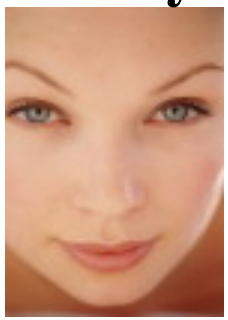


**Achalasia**

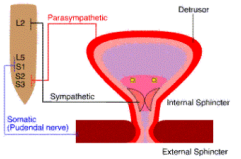


**Hyperhidrosis***

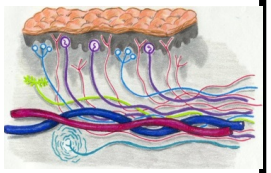
## Sensory



**Chronic Migraine***




**Neurogenic Bladder***



**Painful Neuropathy**


JANUARY 16, 2017
TIME
Depression.
Heart trouble.
Migraines.
Erectile dysfunction.
Back pain.
Sweaty palms.
Drooling.
And 793 other problems.
How Botox Became the Drug That's Treating Everything.
By Alexandra Sifferlin
BOTOX
time.com

# Botulinum Toxin: Commercially Available Toxins

- Type A
  - OnabotulinumtoxinA (BOTOX®)
  - AbobotulinumtoxinA (Dysport®)
  - IncobotulinumtoxinA (Xeomin®)
  - DaxibotulinumtoxinA (under development)
- Type B
  - RimabotulinumtoxinB (Myobloc®/NeuroBloc®)
- BoNT types are not interchangeable—no conversion ratios (FDA)

# BoNT Formulations: US FDA-approved Indications

| | AboBoNT-A[1] | IncoBoNT-A[2] | OnaBoNT-A[3] | RimaBoNT-B[4] |
|---|---|---|---|---|
| Cervical dystonia in adults | ✓ | ✓ | ✓ | ✓ |
| ULS in adults | ✓ | ✓ | ✓ | -- |
| Lower limb spasticity (LLS) | ✓ (pts ≥2 y) | -- | ✓ (adults) | |
| Severe primary axillary hyperhidrosis | -- | -- | ✓ | -- |
| Strabismus | -- | -- | ✓ | -- |
| Neurogenic detrusor overactivity | -- | -- | ✓ | -- |
| Migraine in adults | -- | -- | ✓ | -- |
| Blepharospasm | -- | ✓ (adults previously treated with onaBoNT-A) | ✓ (patients ≥12 y) | -- |

1. DYSPORT [Prescribing information]. Basking Ridge, NJ: Ipsen Biopharmaceuticals, Inc.; 12/2016. 2. XEOMIN. [Prescribing information]. Raleigh, NC: Merz Pharmaceuticals, LLC; 12/2015. 3. BOTOX [Prescribing information]. Irvine, CA: Allergan; 1/2016.

# Therapeutic Considerations: Setting Priorities

- Efficacy
- Safety/tolerability
- Ease of use
- Cost/access

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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;86:1-9

Simpson DM, et al. *Neurology*. 2016;86:1818-1826.

# AAN 2016 Guidelines: Levels of Evidence

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 | | |

Simpson DM, et al. *Neurology*. 2016;86:1818-1826

# Clinical Trials of BoNT in Adult Spasticity: Upper Limb Conclusions and Recommendations

- Demonstrated as safe and effective and should be offered (Level A):
  - AboBoNTA (Dysport)
  - OnaBoNTA (Botox)
  - IncoBoNTA (Xeomin)
- Probably safe and effective and should be considered (Level B):
  - RimaBoNTB (Myobloc/NeuroBloc)
- Active functional gains: data inconsistent from Class 1 studies

Simpson DM, et al. *Neurology*. 2016;86:1818-1826

# Clinical Trials of BoNT in Adult Spasticity: Upper Limb Conclusions and Recommendations

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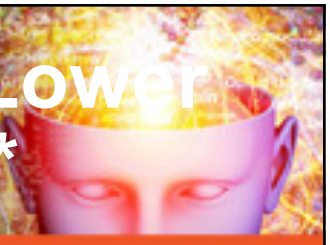
Simpson DM, et al. *Neurology*. 2016;86:1818-1826

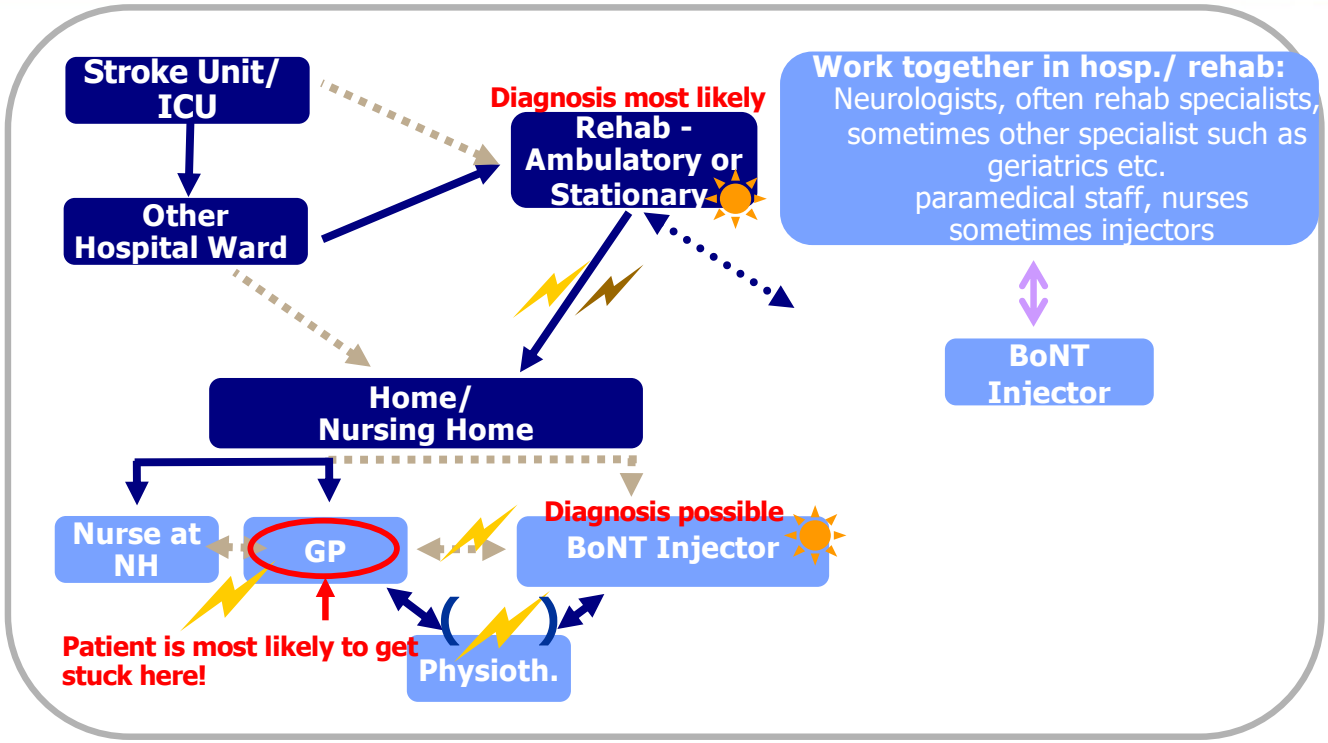
# Clinical Trials of BoNT in Adult Spasticity: Lower Limb—Conclusions and Recommendations*



- Demonstrated as safe and effective and should be offered (Level A):
  - AboBoNTA (Dysport)
  - OnaBoNTA (Botox)
- Insufficient evidence — no Class 1 studies available:
  - IncoBoNTA
  - RimaBoNTB (Myobloc/NeuroBloc)
- Active functional gains: data inconsistent or inadequate

*Those available as of September 2015.

# Post-Stroke Spasticity Patient Flow



# BoNT vs Oral Tizanidine (TIZ) in Upper Limb Spasticity: Study Design

- Multicenter, randomized, parallel, double-blind; N=60; 9 sites
- Treatment groups:
  - BoNT injection + oral placebo
  - Placebo injection + oral TIZ
  - Placebo injection + oral placebo
- 18-week follow-up; maintain physical therapy/occupational therapy
- Outcome measures:
  - Primary: wrist flexors' Ashworth score
  - Secondary: Ashworth score in finger, elbow flexors; DAS; function: Frenchay Activities Index; successful study completion
  - Safety: adverse events

DAS = Disability Assessment Scale.

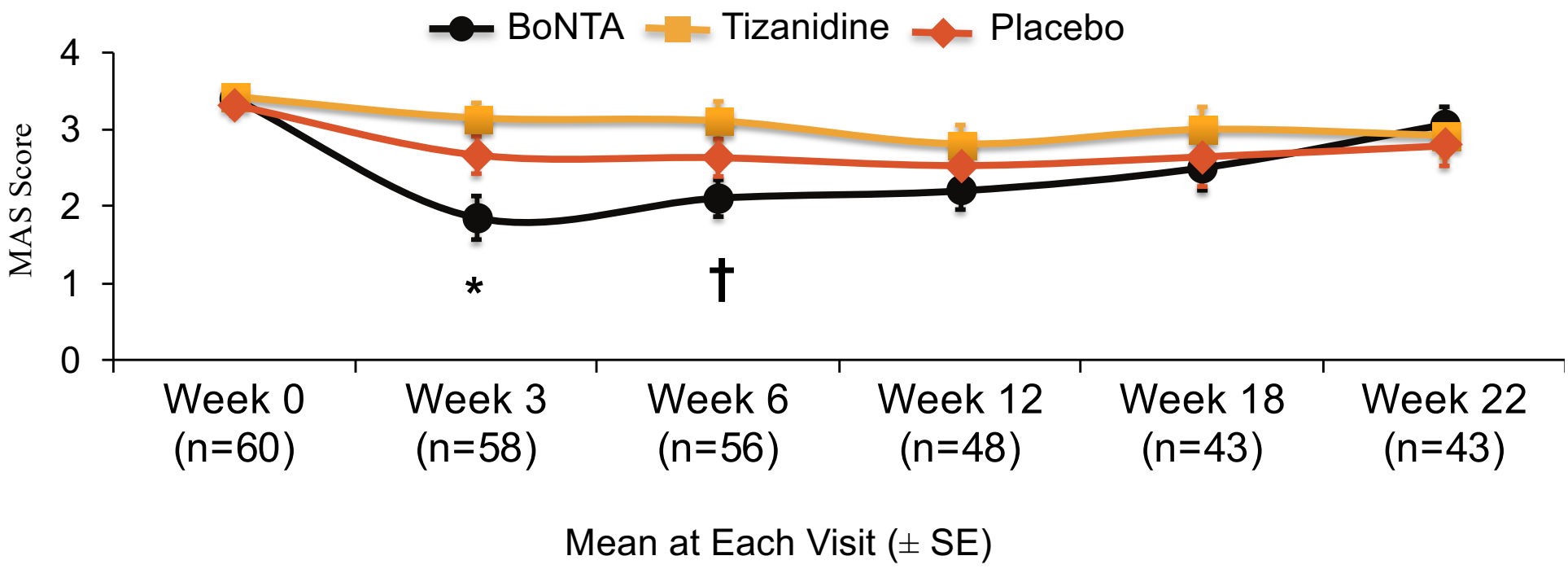
Simpson D, et al. *J Neurol Neurosurg Psych*. 2009;80(4):380-385.

# BoNT vs Oral Tizanidine in Upper Limb Spasticity: Dose of Study Drugs

| Week | BoNTA, Units (mean +/- SD) | Tizanidine, mg (mean +/- SD) |
|---|---|---|
| Baseline | 393 +/- 128 U | |
| 6 | | 20.0 +/- 12.1 mg |
| 12 | | 20.3 +/- 14.2 mg |
| 18 | | 14.7 +/- 13.5 mg |
| Maximum dose | 500 U | 36 mg |

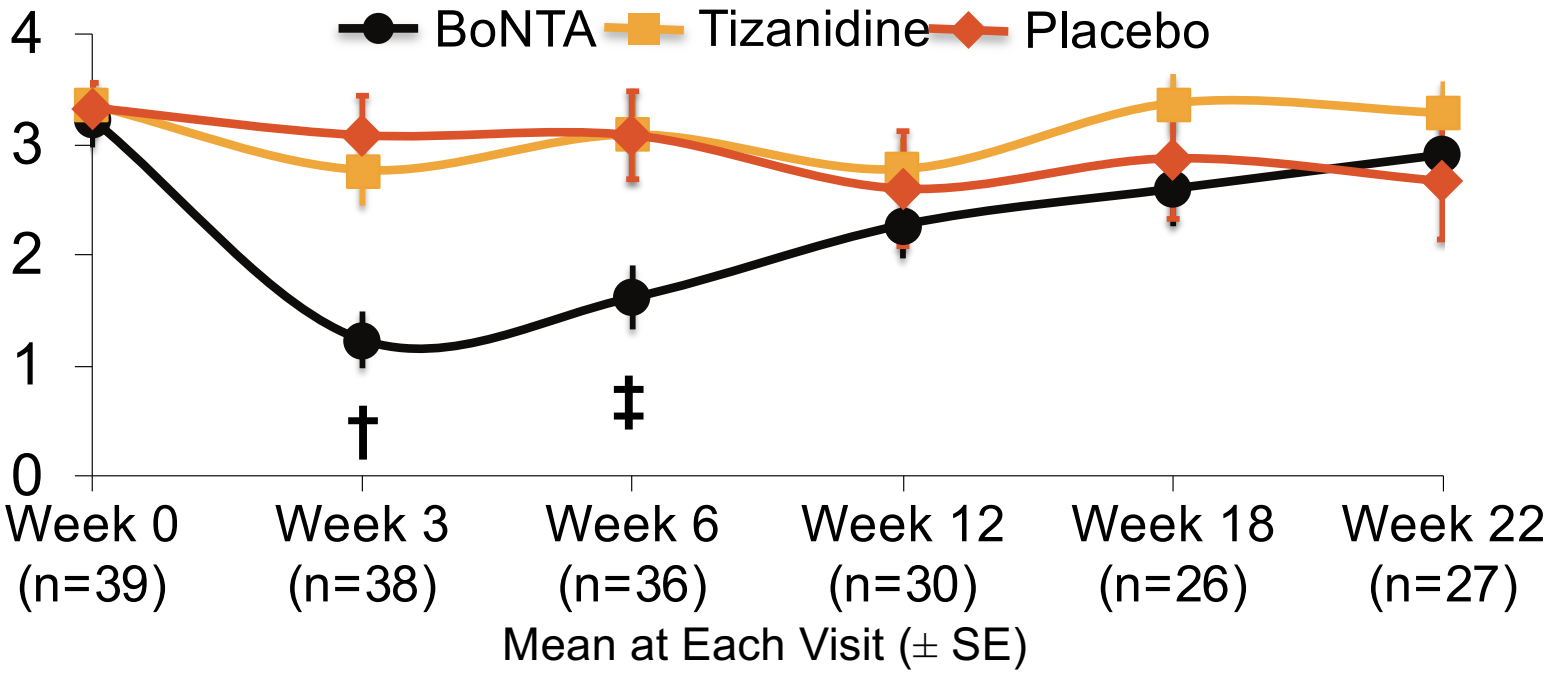
Simpson D, et al. *J Neurol Neurosurg Psych*. 2009;80(4):380-385.

# BoNT vs Oral Tizanidine in Upper Limb Spasticity: Modified Ashworth Scale (MAS) Wrist Flexors




*$P \leq .0221$ vs tizanidine and placebo.
†$P \leq .001$ vs tizanidine.
Simpson D, et al. *J Neurol Neurosurg Psych*. 2009;80(4):380-385.

# BoNT vs Oral Tizanidine in Upper Limb Spasticity: Modified Ashworth Scale (MAS)—Finger Flexors*




*Subjects with dose ≥100 Units.
†*P* ≤.0013 vs tizanidine and placebo.
‡*P* ≤.0107 vs tizanidine and placebo.
Simpson D, et al. *J Neurol Neurosurg Psych*. 2009;80(4):380-385

# BoNT vs Oral Tizanidine (TIZ) in Upper Limb Spasticity: Adverse Events—Treatment-Related

| | BoNT (n = 20) | | TIZ (n = 21) | | Placebo (n = 19) | |
|---|---|---|---|---|---|---|
| | Subjects | Events | Subjects | Events | Subjects | Events |
| n (%) | 8 (40.0) | 20 (45.5) | 19 (90.5) | 39 (70.9) | 10 (52.6) | 19 (55.9) |
| *p* value ($Chi^2$) | .0007* (vs. TIZ) | | .0074 (vs. placebo) | | .4290 (vs. BoNT) | |
| Most Common | Sedation | | Sedation; Dizziness | | Sedation | |

Simpson D, et al. *J Neurol Neurosurg Psych*. 2009;80(4):380-385.

# BoNT vs Oral Tizanidine in Upper Limb Spasticity: Conclusions

- BoNT results in greater reduction in muscle tone than tizanidine or placebo
- BoNT has a lower AE profile than tizanidine
- Tizanidine dosing was limited by adverse effects in most patients
- BoNT resulted in improved cosmesis
- Analysis of active functional scales is under way (ie, Frenchay Activities Index)
- Reconsider first-line treatment in adult cerebral spasticity

AE = adverse event;
Simpson D, et al. *J Neurol Neurosurg Psych*. 2009;80(4):380-385.

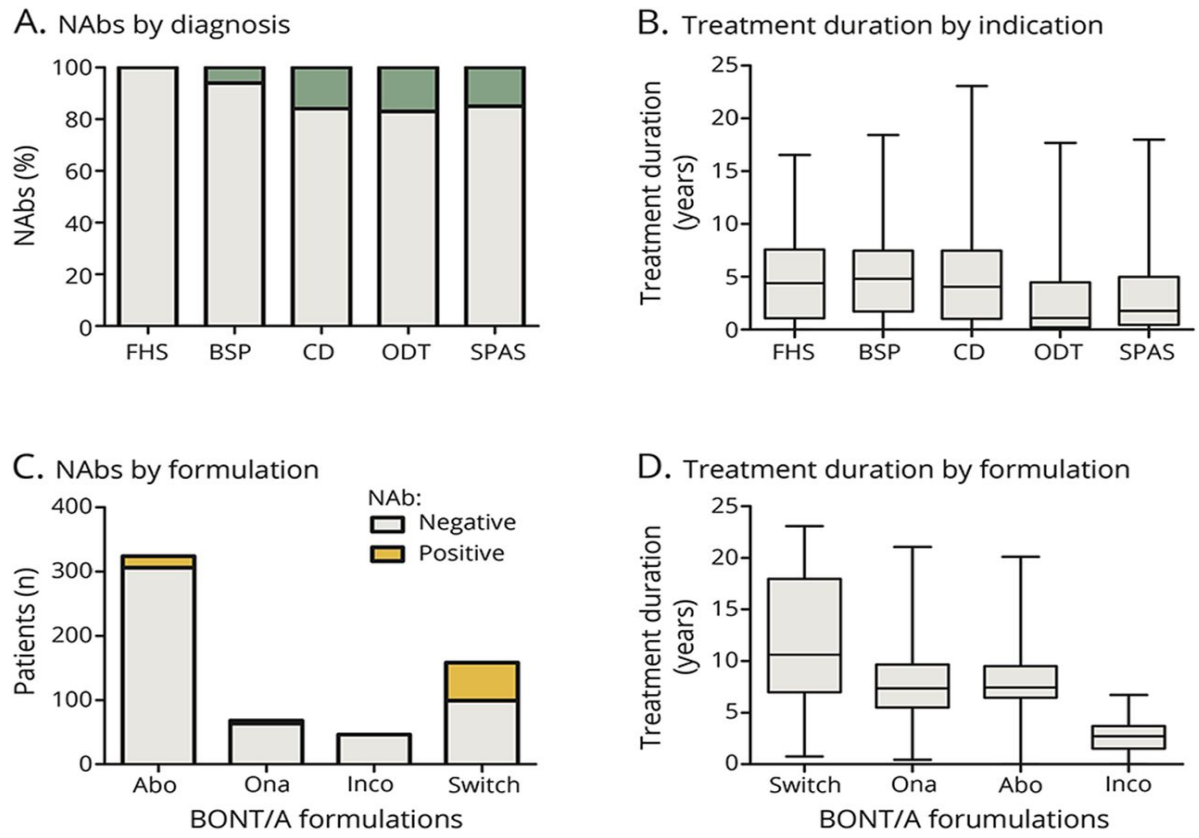
# BoNTA in Biceps Overactivity: Endplate Targeting/Volume Study—Results

- Double-blind study of BoNTA:
  - Treatment of biceps overactivity following stroke or TBI
  - Endplate targeting vs nontargeting injection techniques
  - 2 BoNTA dilutions used
- Factors improving efficacy of BoNTA injection:
  - Endplate targeting
  - Nontargeted; high volume; low potency
  - MRV: High volume > endplate > low volume
  - Spasticity angle: High volume = endplate > low volume
  - MVC: High volume = endplate = low volume

TBI = traumatic brain injury; MRV = mean rectified voltage; MVC = maximal voluntary contraction.

Gracies J-M, et al. *Arch Phys Med Rehab.* 2009;90:9-16.

# High Prevalence of Neutralizing Antibodies After Long-term Botulinum Neurotoxin Therapy



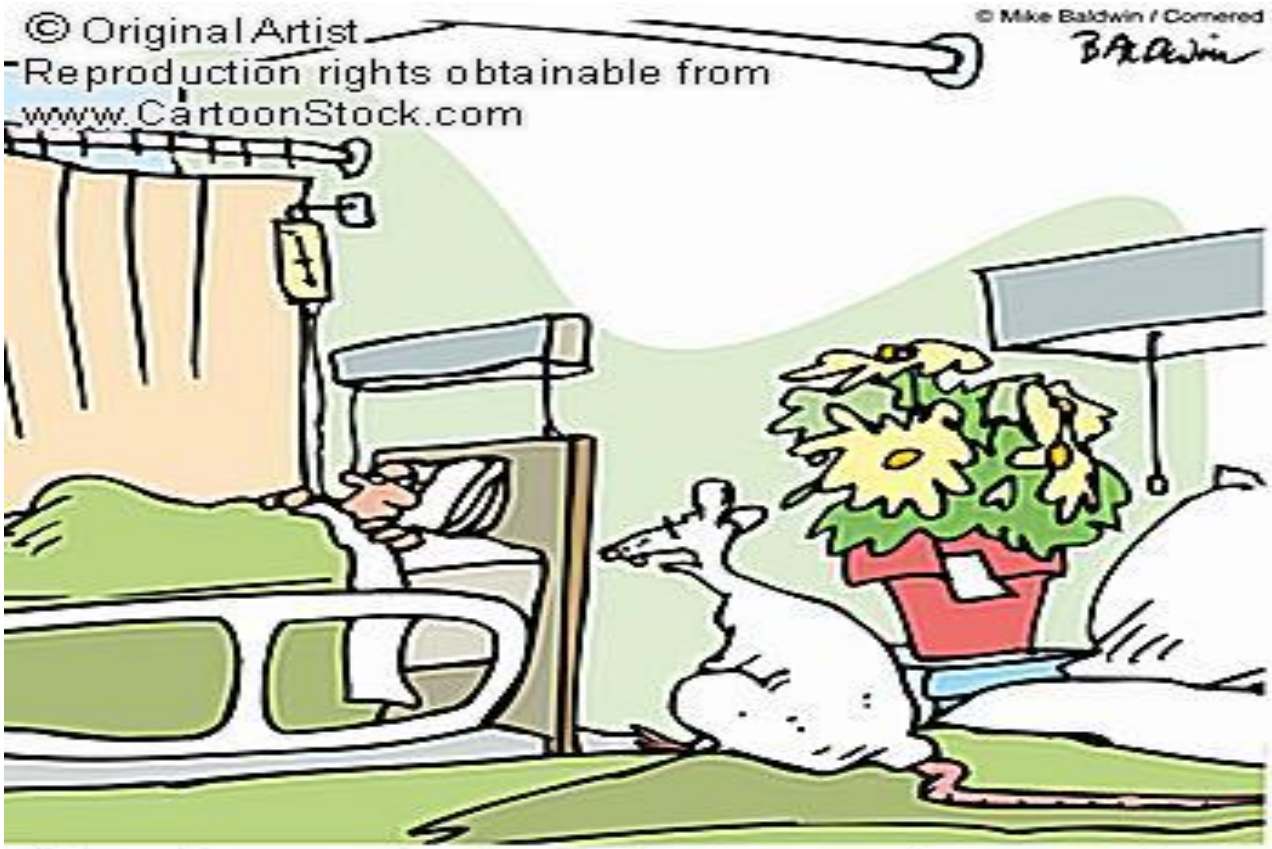

Albrecht P, et al. Neurology 2019;92:e48-e54.

# Botulinum Toxin (BoNT) Therapy: Open Questions

- Injection technique
  - Surface anatomy; EMG; electrical stimulation; ultrasound
- Optimal dose; volume; dilution
- Number and location of injection sites
- Serotype/brand differences
- Booster injections
- Immunogenicity and clinical relevance
- Patient access (cost; regulatory approval)

EMG = electromyography

# Setting Expectations in Therapy



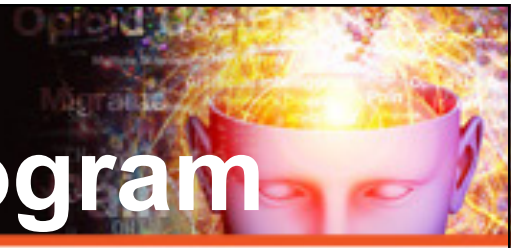

"I go home today. They cured me using this new miracle drug. I'm afraid it'll be years before it's approved for humans."

# SMART Goals

## Specific, Measurable, Attainable, Relevant, Timely

- Recognize the varied causes and presentations of spasticity in your patients and the impact on their quality of life
- Partner with patients to develop an individualized treatment plan that focuses on shared goals and improvements in quality of life

# Mount Sinai Botulinum Toxin Research Program



## Research Team

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- Migueal Escalon, MD

Mount Sinai

# Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.