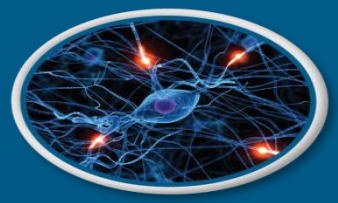
Spasticity and Botulinum Toxin :
Challenges and Opportunities

David M Simpson, MD
Professor of Neurology
Director, Clinical Neurophysiology Labs
Director, Neuromuscular Disorders
Icahn School of Medicine at Mount Sinai
New York, NY
President, International Neurotoxin Association



Disclosures

I have the following potential conflicts of interest to report:

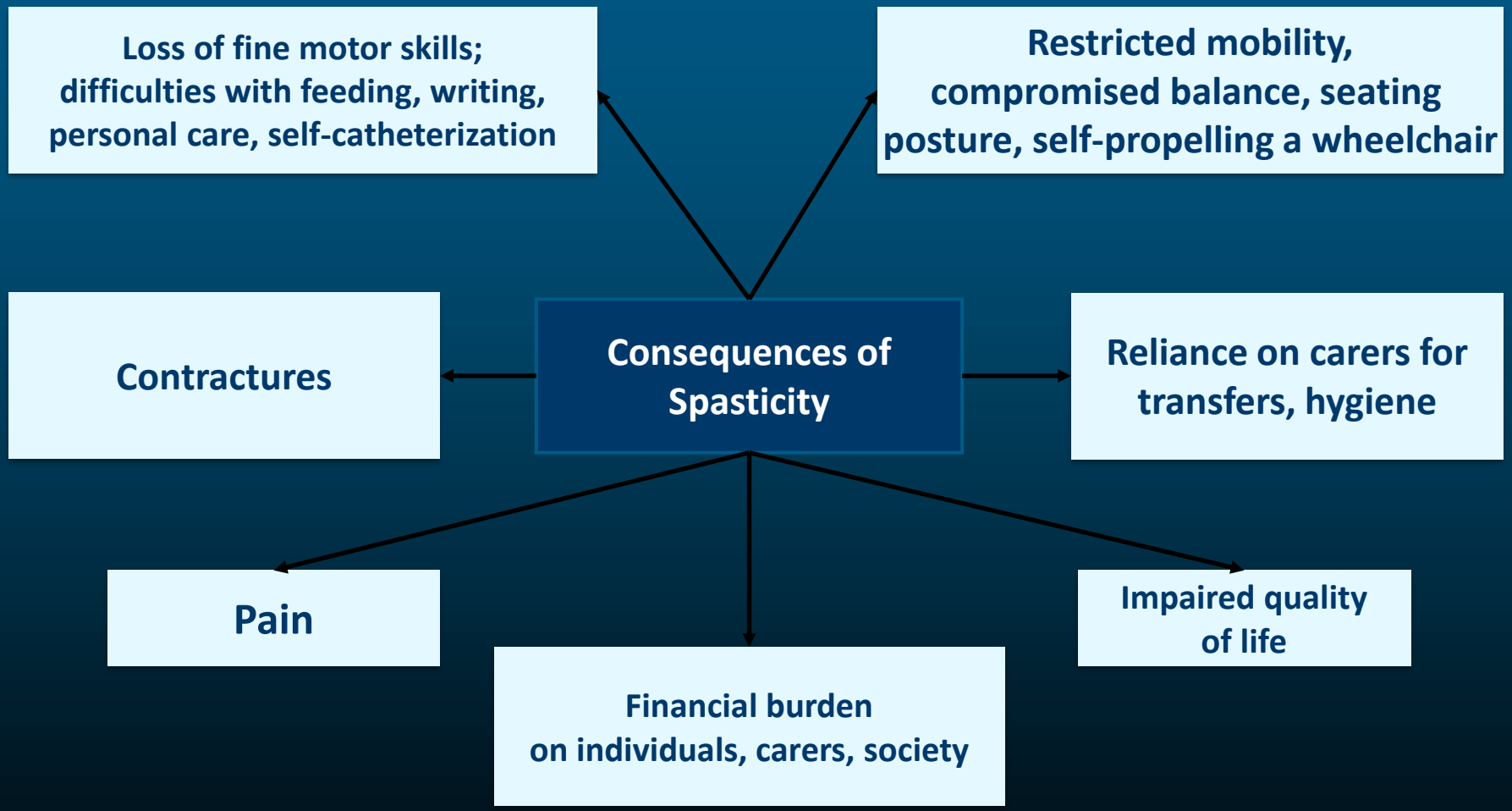
- Receipt of research support/consultant's fees:
  Merz, Ipsen, Abbvie

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

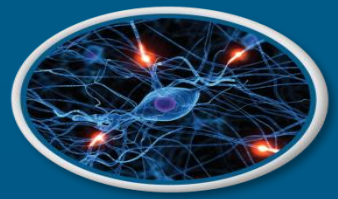
Lance J. Spasticity: Disordered Motor Control; 1980

Consequences of Spasticity



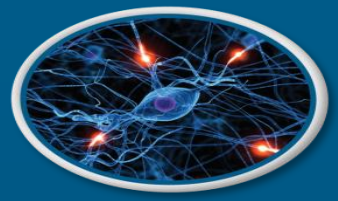
Mount Sinai

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



Definitions of Abnormal Tone

Tone	Passive contraction of muscle in resting state
Spasticity	Velocity-dependent increase in tone and/or stretch reflexes
Dystonia	Involuntarily sustained or intermittent contractions
Athetosis	Abnormal, involuntary writhing muscle movement
Rigidity	Resistance with joint movement that is not fixed
Contracture	Permanent shortening of a muscle; not related to tone but consequence of abnormal tone



Modified Ashworth Scale: Strengths and Limitations

Strengths

- Fast
- Inexpensive
- Inter-rater reliability 86.7%[1]

Limitations

- Lack of sensitivity to subtle changes in spasticity
- Difficult to distinguish contractures from spasticity
- Some muscles may be more difficult to test than others[1]

Modified Ashworth Scale	
0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end ROM when the affected part(s) is moved in flexion or extension
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
2	More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

1. Bohannon RW, Smith MB. *Phys Ther*. 1987;67:206-207.

BoNT for Spasticity: Initial Placebo-Controlled Trials

Botulinum toxin type A in the treatment of upper extremity spasticity:

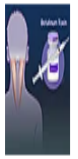
A randomized, double-blind, placebo-controlled trial

D.M. Simpson, MD; D.N. Alexander, MD; C.F. O'Brien, MD; M. Tagliati, MD; A.S. Aswad, MS; J.M. Leon, PhD; J. Gibson, MD; J.M. Mordaunt, MS; and E.P. Monaghan, PhD

Article abstract—Spasticity is a disorder of excess muscle tone associated with CNS disease. We hypothesized that botulinum toxin, a neuromuscular blocking agent, would reduce tone in spastic muscles after stroke. This randomized, double-blind, placebo-controlled, multicenter clinical trial evaluated the safety and efficacy of botulinum toxin type A (BTXA) in the treatment of chronic upper limb spasticity after stroke. Thirty-nine patients received IM injections of a total dose of either 75, 150, or 300 units of BTXA or placebo into the biceps, flexor carpi radialis, and flexor carpi ulnaris muscles. At baseline, patients demonstrated a mean wrist flexor tone of 2.9 and elbow flexor tone of 2.6 on the Ashworth Scale (0 to 4). Treatment with the 300-unit BTXA dose resulted in a statistically and clinically significant mean decrease in wrist flexor tone of 1.2 ($p = 0.028$), 1.1 ($p = 0.044$), and 1.2 ($p = 0.026$) points and elbow flexor tone of 1.2 ($p = 0.024$), 1.2 ($p = 0.028$), and 1.1 ($p = 0.199$) at weeks 2, 4, and 6 postinjection. In the placebo group, tone reduction at the wrist was 0.3, 0.2, and 0.0 and at the elbow was 0.3, 0.3, and 0.6 at weeks 2, 4, and 6 postinjection. BTXA groups reported significant improvement on the physician and patient Global Assessment of Response to Treatment at weeks 4 and 6 postinjection. There were no serious adverse effects. In this 3-month study, BTXA safely reduced upper extremity muscle tone in patients with chronic spasticity after stroke.

NEUROLOGY 1996;46:1306–1310

The NEW ENGLAND JOURNAL of MEDICINE



A correction has been published 1

ORIGINAL ARTICLE

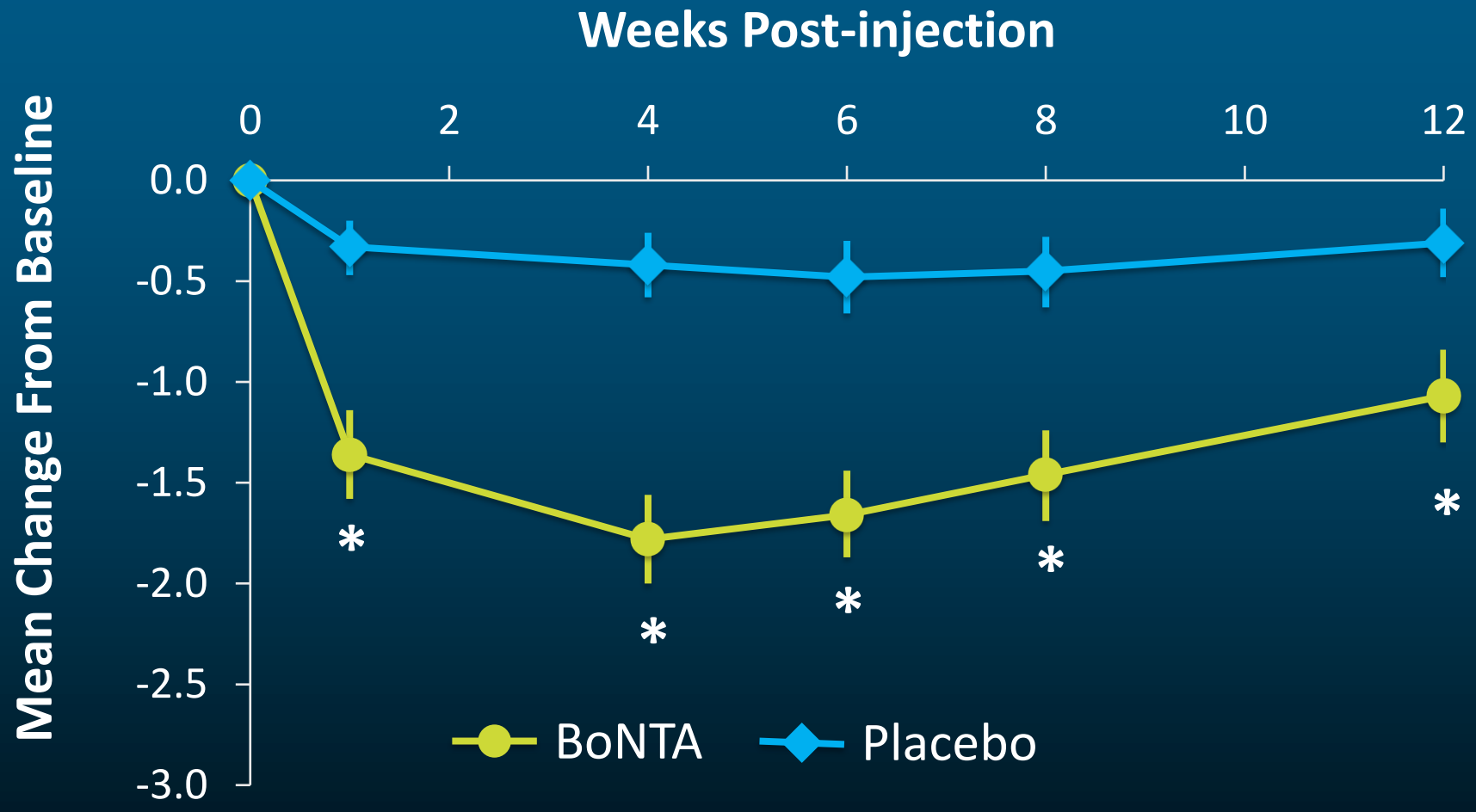
Intramuscular Injection of Botulinum Toxin for the Treatment of Wrist and Finger Spasticity after a Stroke

Allison Brashear, M.D., Mark F. Gordon, M.D., Elie Elovic, M.D., V. Daniel Kassicieh, D.O., Christina Marciniak, M.D., Mai Do, B.S., Chia-Ho Lee, M.S., Stephen Jenkins, M.D., and Catherine Turkel, Pharm.D. for the Botox Post-Stroke Spasticity Study Group*

Article Figures/Media

August 8, 2002

BoNT Injection for Wrist and Finger Spasticity: Ashworth Wrist Flexor Scores



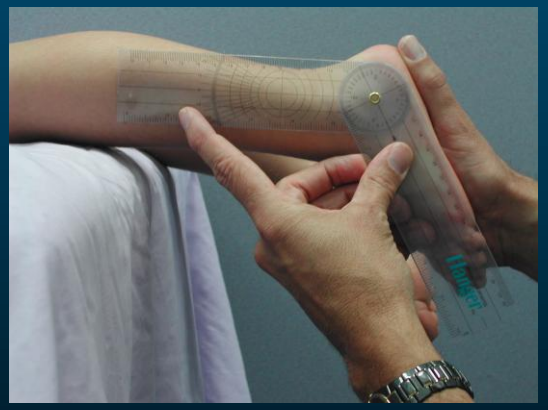
*P<.001 vs placebo

Brashear A, et al. *N Engl J Med*. 2002;347(6):395-400.

Modified Tardieu Scale or “R1/R2”

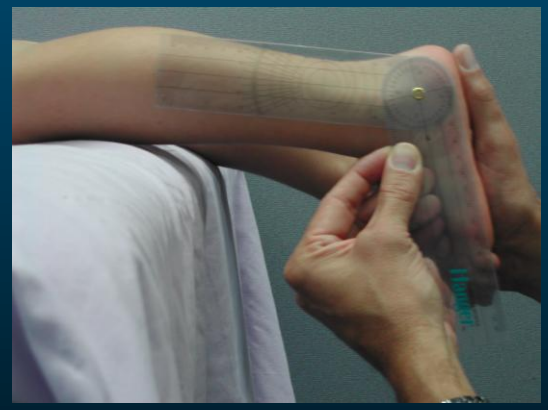
R1

May also be referred to as „initial end range” or “first catch”

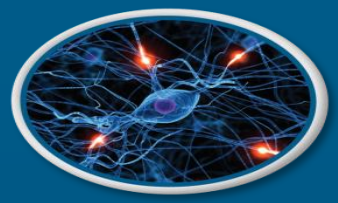


R2

Refers to maximum end range with torque applied



Cusick BD. *Serial Casting for the Restoration of Soft-Tissue Extensibility in the Ankle and Foot*. 3rd ed. Progressive GaitWays, LLC; 2007.



What Is Meaningful Function

Passive function

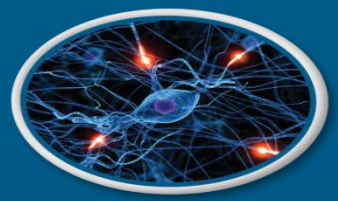
- Increased ROM
- Improved positioning
- Increased ease of hygiene
- Improved cosmesis
- Decreased spasm frequency
- Improved orthotic fit
- Decreased pain

Active function

- Improved upper limb use: reaching, grasping, releasing
- Improved mobility
- Improved gait
- Decreased energy expenditure

Adapted from Esqenazi and Mayer

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

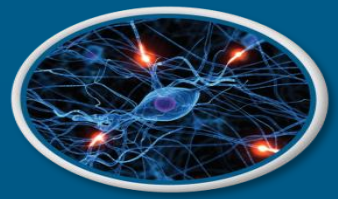


Disability Assessment Scale (DAS)

Domain	Description
Hygiene	Extent of palm maceration, ulceration, and/or infection; palm cleanliness; ease of cleaning and nail trimming; effect of hygiene-related disability on patient's life
Dressing	Ability to put on clothing; effect of dressing-related disability on patient's life due to upper limb spasticity
Limb posture	Psychological and/or social interference that the limb's posture has in the patient's life
Pain	Intensity of pain; discomfort and interference of upper limb pain in patient's life

DAS Scores: 0 = no functional disability; 1 = mild; 2 = moderate; 3 = severe.

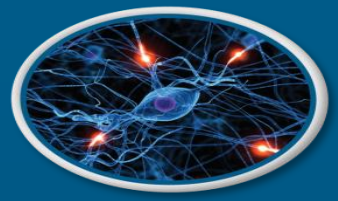
Brashear A, et al. *N Engl J Med*. 2002;347(6):395-400.



Treatment Goals for Spasticity

Goals	Examples
Provide symptom relief	• Reduce muscle pain • Reduce muscle spasms • Prevent contractures • Better limb position
Improve passive function Ease patient care and decrease caregiver burden	• Dressing • Hygiene (palm, elbow crease, axilla, perineum) • Positioning in bed or chair • Transfers
Improve active function	• Upper limb – reaching, grasping, releasing • Lower limb-gait
Other	• Facilitate physical therapy – stretching, splinting • Delay or prevent surgery • 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]
- Usually a combination of treatment options are employed:
  - Physiotherapy/Occupational therapy[1]
  - Pharmacotherapy (oral medications; intrathecal baclofen therapy)[1,2]
  - Surgical interventions[1,2]
  - Chemodenervation[1,2] (phenol/alcohol; botulinum toxin)
- What treatment to use first?

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.

Botulinum neurotoxin versus tizanidine in upper limb spasticity: a placebo-controlled study

D M Simpson,[1] J M Gracies,[1,2] S A Yablon,[3] R Barbano,[4] A Brashear,[5] the BoNT/TZD Study Team

ABSTRACT

Background: While spasticity is commonly treated with oral agents or botulinum neurotoxin (BoNT) injection, these treatments have not been systematically compared.

Methods: This study performed a randomised, double-blind, placebo-controlled trial to compare injection of BoNT-Type A into spastic upper limb muscles versus oral tizanidine (TZD), or placebo, in 60 subjects with upper-limb spasticity due to stroke or traumatic brain injury (TBI). Wrist flexors were systematically injected, while other upper limb muscles were injected as per investigator judgement. Participants were randomised into three groups: (1) intramuscular BoNT plus oral placebo; (2) oral TZD plus intramuscular placebo; (3) intramuscular placebo plus oral placebo. The primary outcome was the difference in change in wrist flexor modified Ashworth score (MAS) between groups. Other outcome measures included MAS at elbow and finger joints, Disability Assessment Scale (DAS) and adverse events (AE).

Results: BoNT produced greater tone reduction than TZD or placebo in finger and wrist flexors at week 3 ($p<0.001$ vs TZD; $p<0.02$ vs placebo) and 6 ($p = 0.001$ vs TZD; $p = 0.08$ vs placebo), and greater improvement in the cosmesis domain of the DAS at week 6 ($p<0.01$). TZD was not superior to placebo in tone reduction at either time point ($p \geq 0.09$). The incidence of AE related to study treatment was higher with TZD than in the BoNT ($p<0.01$) or placebo groups ($p = 0.001$).

Conclusions: BoNT is safer and more effective than TZD in reducing tone and disfigurement in upper-extremity spasticity, and may be considered as first-line therapy for this disorder.

METHODS

This study was a randomised, controlled, parallel group, double blind, multicentre study of the efficacy, safety and tolerability of BoNT-A (Botox, Allergan, Irvine, California) injection into upper-limb muscles versus oral TZD (Zanaflex, Acorda Therapeutics, Hawthorne, New York) in subjects with upper-limb spasticity due to stroke or TBI.

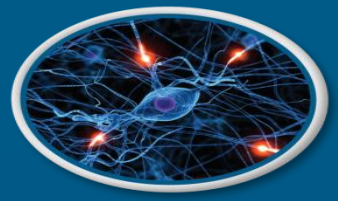
Eligibility and enrolment

Study population

Eligible participants were 18–85 years of age, with prior stroke (cerebrovascular accident with a neurological deficit persisting at least 24 h) or traumatic brain injury (TBI) ⩾ 3 months earlier, and spasticity of the wrist, as demonstrated by a score of ⩾3 for wrist flexor tone on the modified Ashworth Scale (MAS),[14] with 0 indicating normal tone and 5 rigid flexion. An additional criterion for enrolment was difficulty with hygiene or dressing, pain or malposition of the wrist, as evidenced by a score of ⩾2 on the Disability Assessment Scale (DAS).[2] One domain was chosen by the investigator and the participant or care giver as the Principal Therapeutic Target (PTT) as assessed at the time of initial screening. A score of 0 on the DAS indicates no disability, and 3 is severe disability.

Exclusion criteria included severe contracture at the wrist (inability to passively move the joint by >10°); prior tendon transfer; prior phenol/alcohol nerve block in the study limb; BoNT injection into the target limb within 4 months; prior casting of the

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



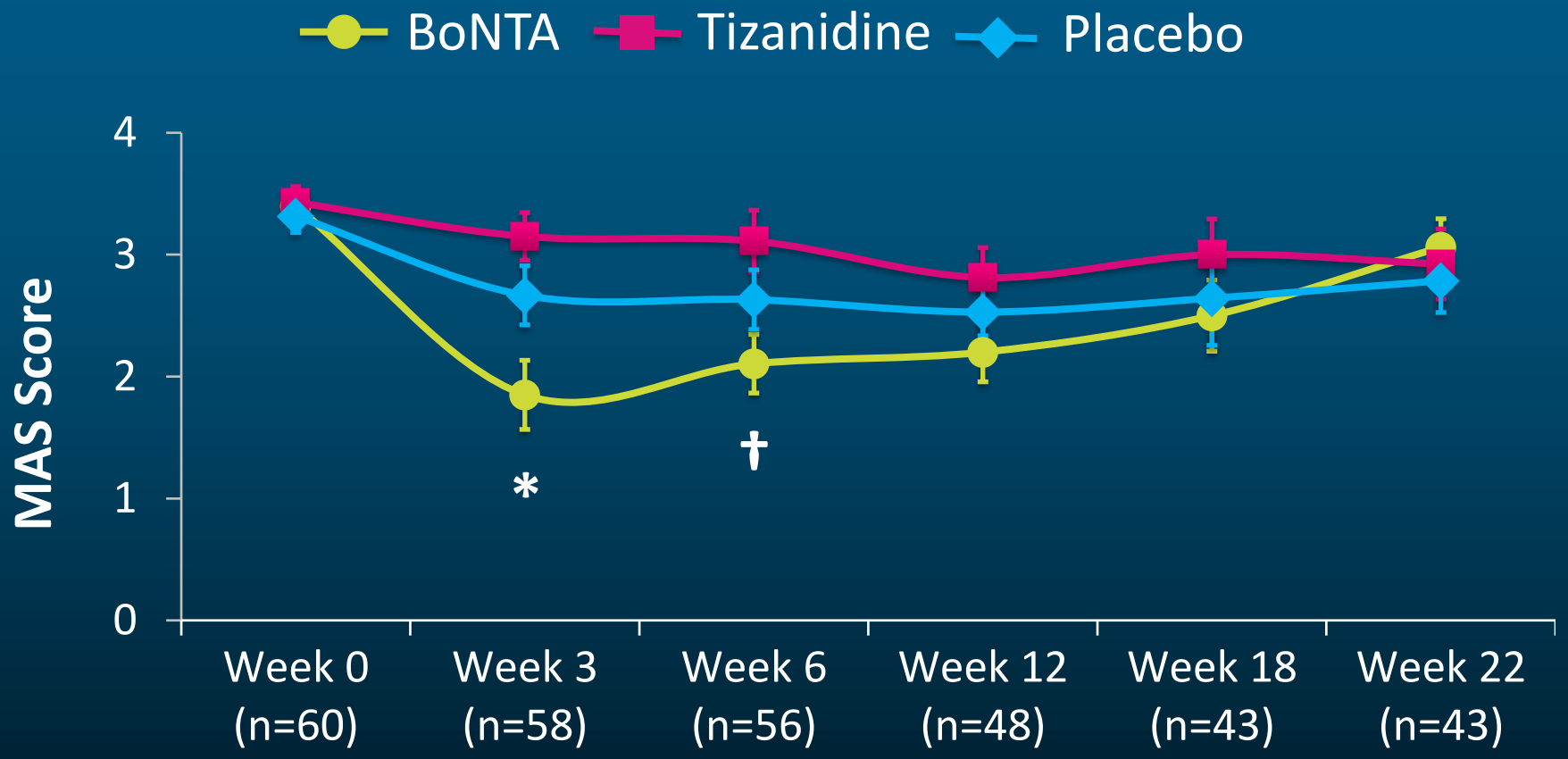
BoNT vs Oral Tizanidine in Upper Limb Spasticity: Study Design

- 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.

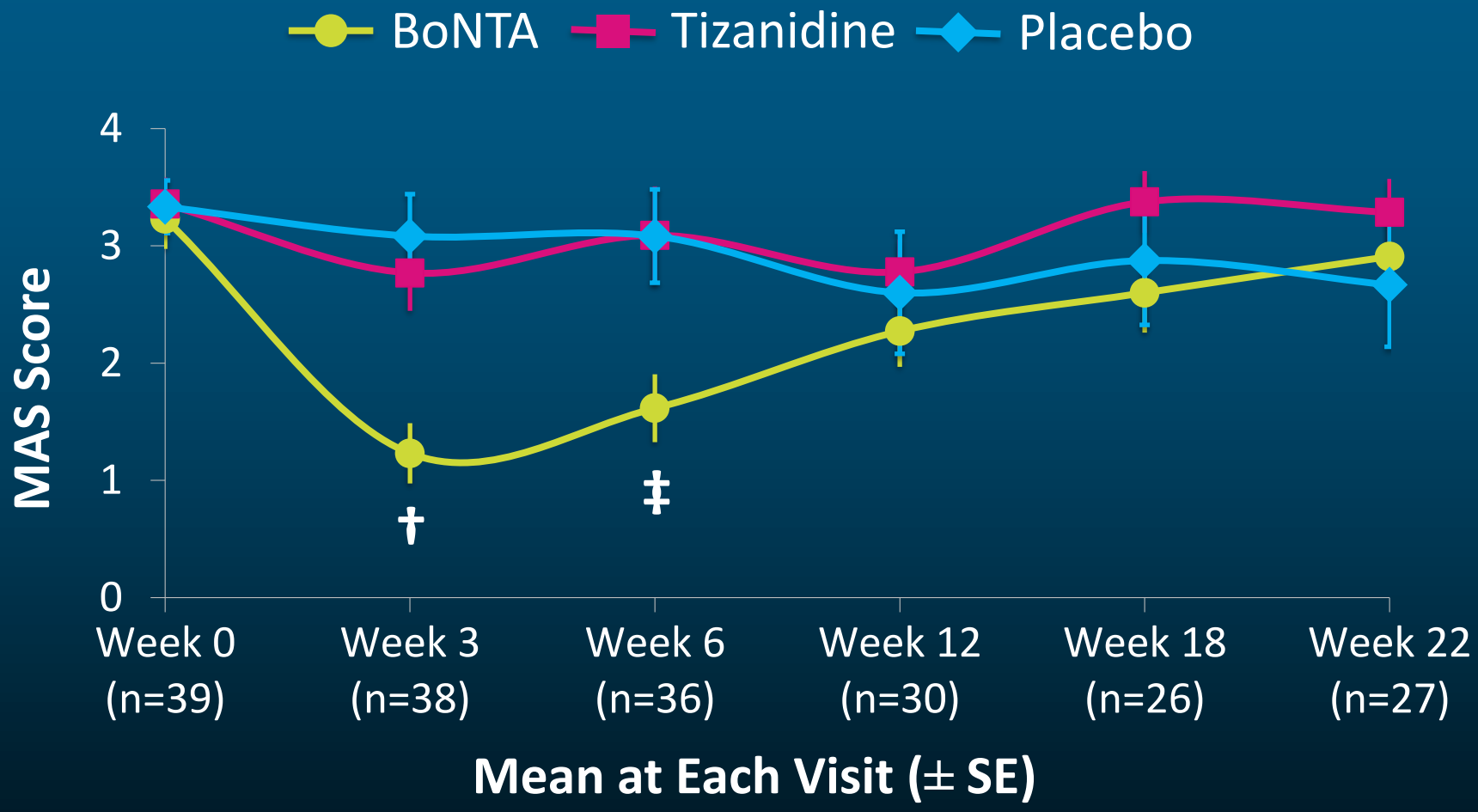
BoNT vs Oral Tizanidine in Upper Limb Spasticity:
Modified Ashworth Scale (MAS)—Wrist Flexors



*$P \leq .0221$ vs tizanidine and placebo.
†$P \leq .001$ vs tizanidine.

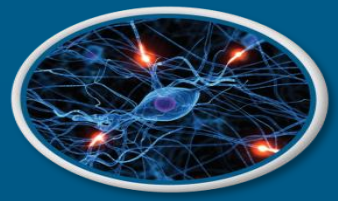
Simpson D, et al. *J Neurol Neurosurg Psych*. 2009;80(4):380-385.

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



*Subjects with dose ≥100 Units.
†$P \leq .0013$ vs tizanidine and placebo.
‡$P \leq .0107$ vs tizanidine and placebo.

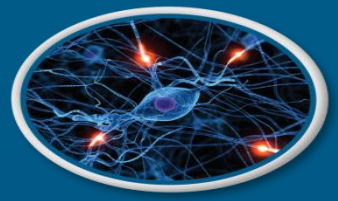
Simpson D, et al. *J Neurol Neurosurg Psych*. 2009;80(4):380-385.



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.



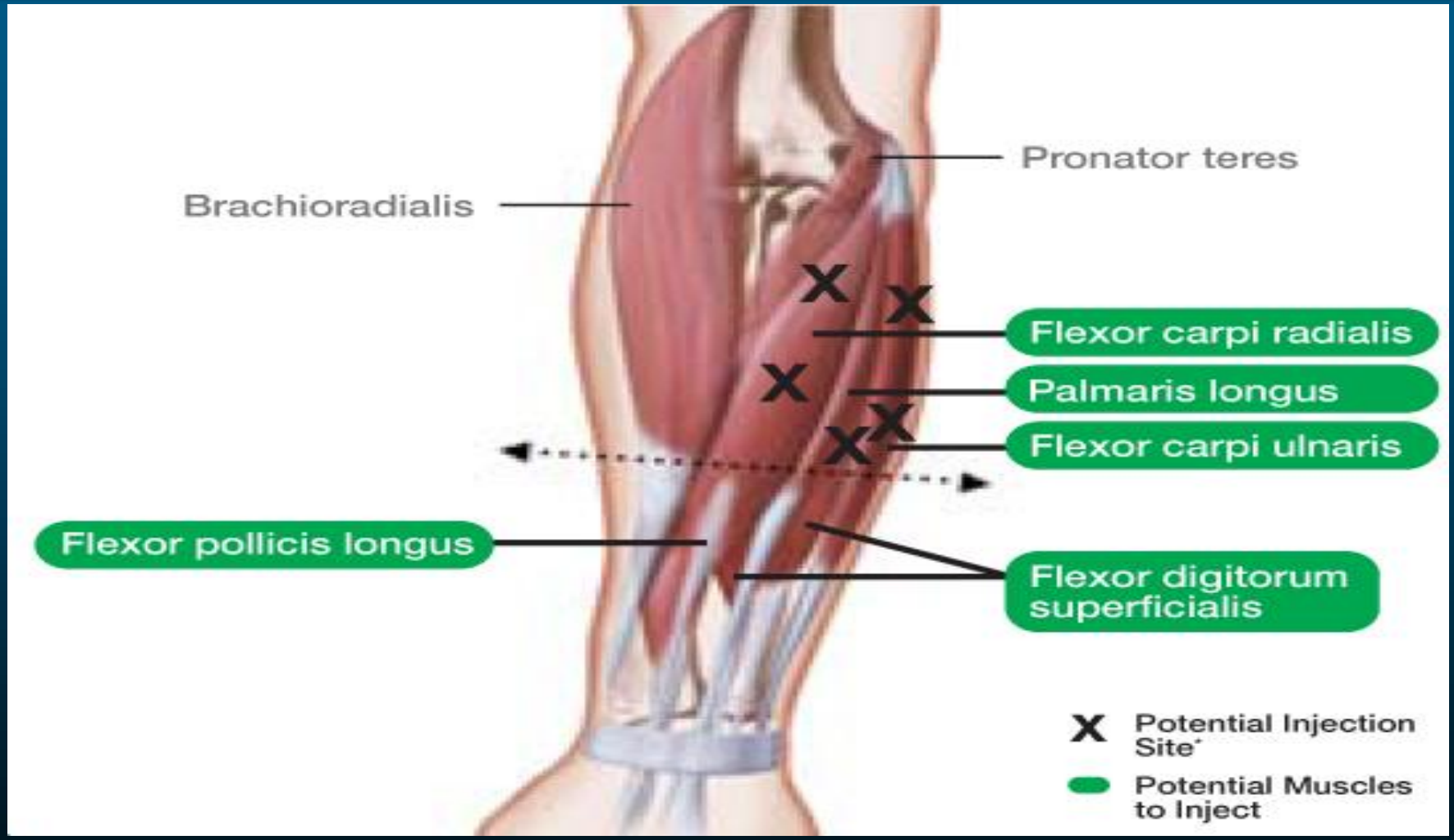
BoNT vs Oral Tizanidine (TIZ) in Upper Limb Spasticity: Adverse Events—Treatment-Related

	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.

Common Injection Sites and Potential Target Muscles

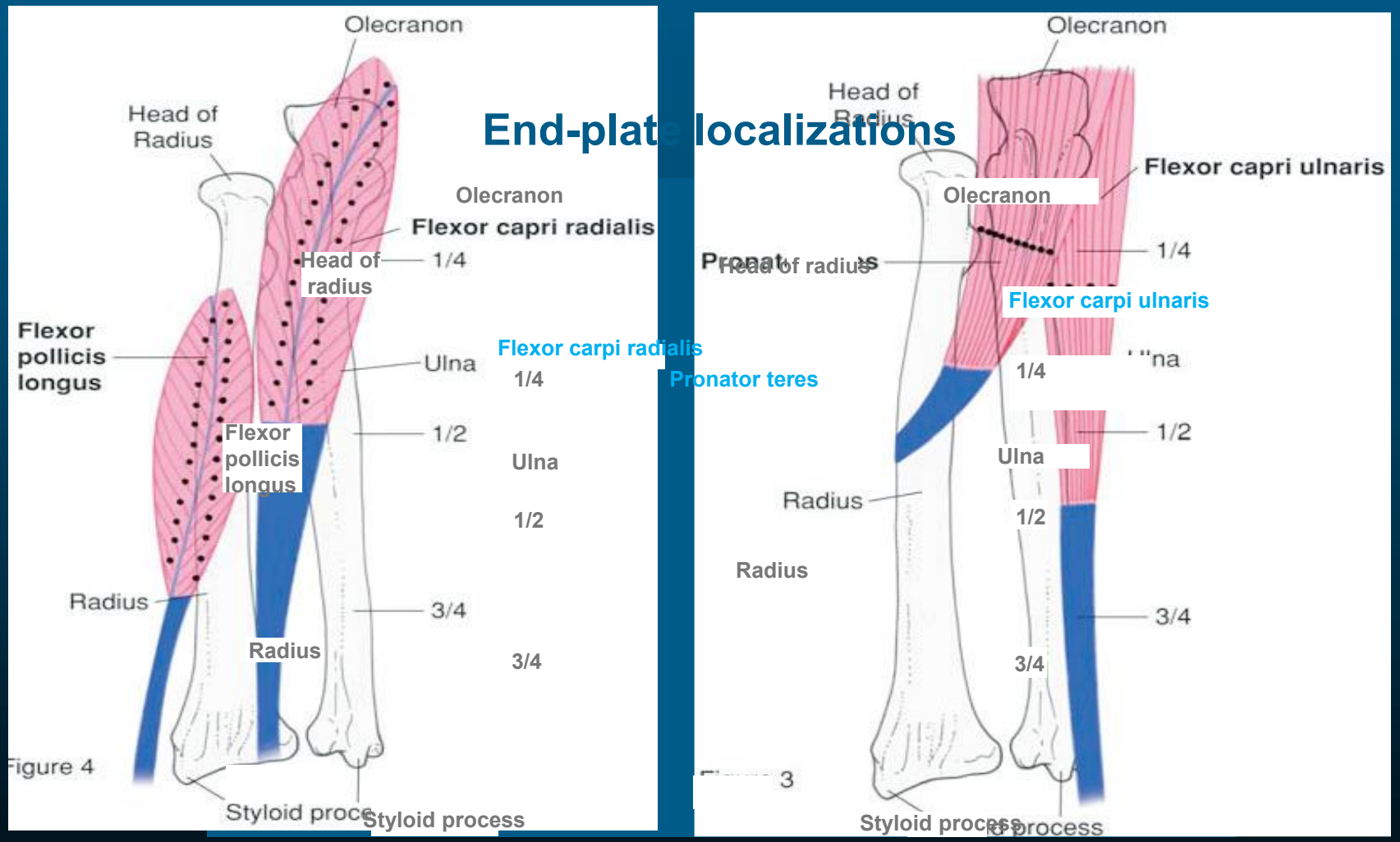
- Flexed wrist and fingers



Reproduced with permission from the Neurotoxin Institute. Gracies JM, McGuire J. Potential muscles of the upper limb involved in common limb positions associated with upper motor neuron syndrome. Wall chart.

Common Injection Sites and Potential Target Muscles

- Wrist flexors

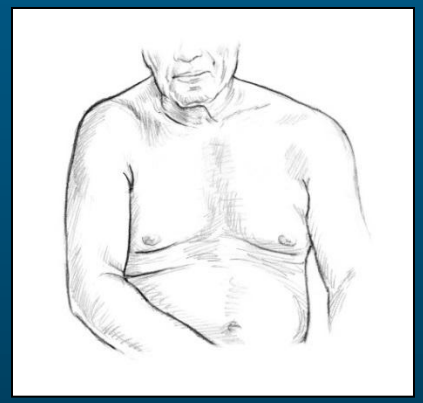


Using a Delphi Panel to Identify a Treatment Paradigm for Injecting Botulinum Toxin to Treat Common Postures in Post-Stroke Upper Limb Spasticity

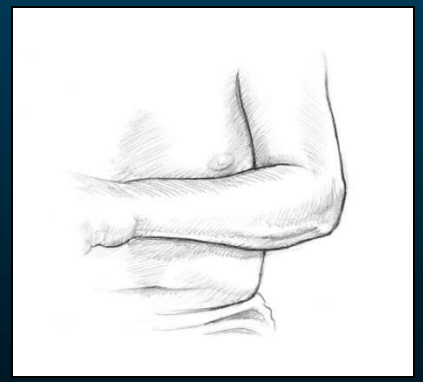
David M. Simpson
Atul T. Patel
Abraham Alfaro
Ziyad Ayyoub
David Charles
Khashayar Dashtipour
Alberto Esquenazi
Glenn D. Graham
John R. McGuire
Ib Odderson

Simpson D, et al. Phys Med and Rehab. 2016 Published online before print doi:10.1016/j.pmrj.2016.06.016

Adducted Shoulder with Internal Rotation & Flexed Elbow



Delphi Results for Adducted Shoulder with Internal Rotation			
	Pectoralis complex	**Latissimus dorsi**	**Total dose**
Muscle frequency	87.5%	75.0%	
Dose (mode)	75	75	150
Dose (range)	75-100	75	100-200
Injection sites/muscle	4	4	



Delphi Results for Flexed Elbow				
	Brachioradialis	**Biceps brachii**	**Brachialis**	**Total dose**
Muscle frequency	100%	87.5%	75.0%	
Dose (mode)	25	50	75	150
Dose (range)	25-50	0-50	50-100	100-150
Injection sites/muscle	2	4	2	

Simpson D, et al. Phys Med and Rehab. 2016 Published online before print doi:10.1016/j.pmrj.2016.06.016

Disability and Rehabilitation, 2005; 27(4): 176–184

Taylor & Francis
Taylor & Francis Group

RESEARCH PAPER

The lowest effective dose of botulinum A toxin in adult patients with upper limb spasticity

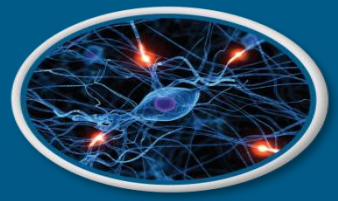
A. SUPUTTITADA[1], & N.C. SUWANWELA[2]

[1]*Department of Rehabilitation Medicine, and* [2]*Division of Neurology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*

Conclusion: Optimal dose of Abo-BoNT (Dysport) in upper limb spasticity: 500U

Escalating Doses of IncobotulinumtoxinA (400U–800U) Lead to Increasing Improvements in Disability Due to Multifocal Upper- and Lower-Limb Spasticity

Wissel et al. Neurology 2017;88:1321-1328.

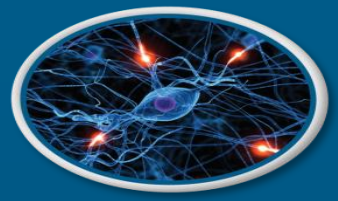


Doses Administered by Injection Cycle

IncobotulinumtoxinA Dose	Subjects, n (%)
Cycle 1 (N=155) 300–400 U **400 U**	14 (9) **141 (91.0)**
Cycle 2 (N=152) 500–600 U **600 U** 600–700 U	13 (8.6) **138 (90.8)** 1 (0.7)
Cycle 3 (N=140) 500–600 U 600–700 U 700–800 U **800 U**	1 (0.7) 8 (5.7) 15 (10.7) **116 (82.9)**

- The mean number of patterns treated
  - Cycle 1: 3.9 per subject
  - Cycle 2: 4.9 per subject
  - Cycle 3: 5.8 per subject

Wissel et al. Neurology 2017;88:1321-1328.



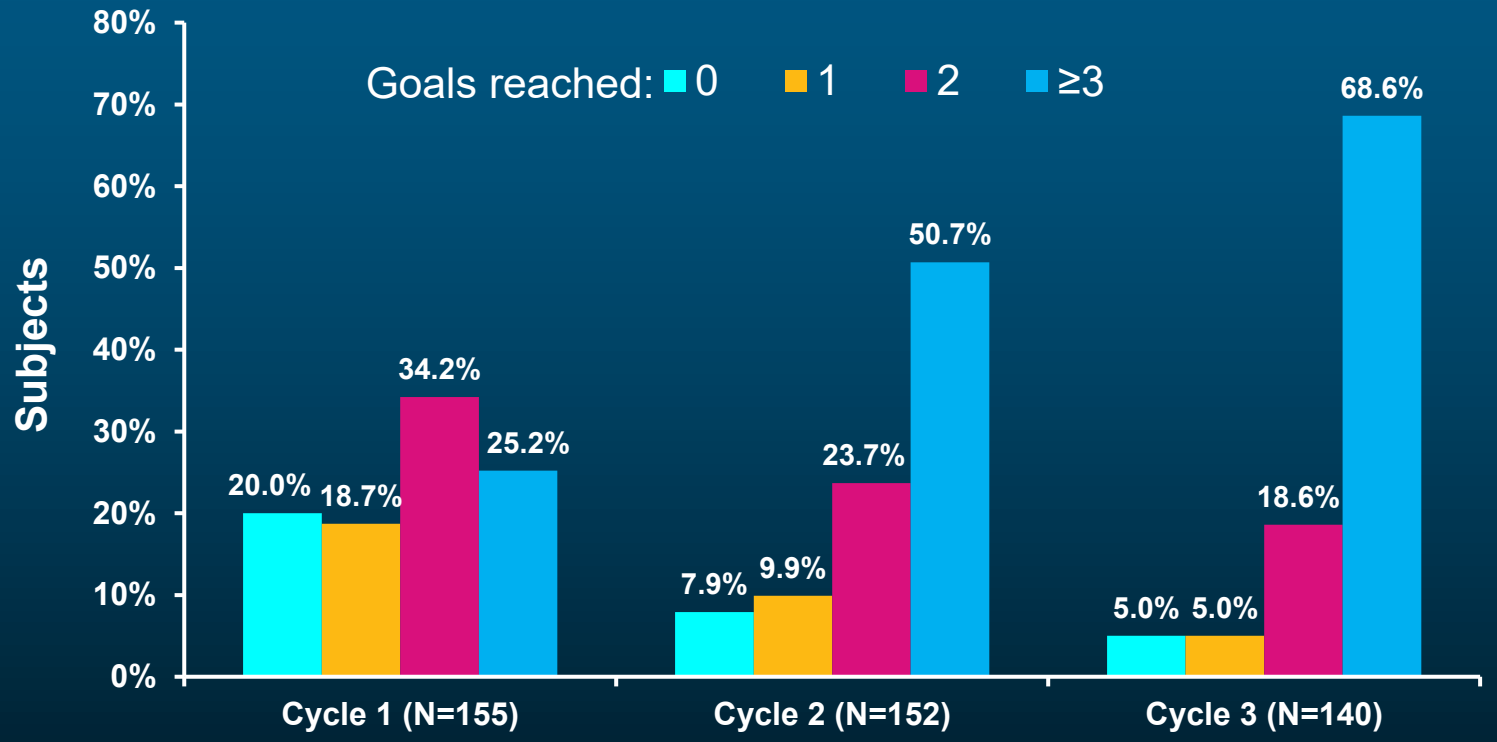
Summary of Adverse Events by Injection Cycle

Subjects, n (%)	Overall (N=155)	Cycle 1 (N=155)	Cycle 2 (N=152)	Cycle 3 All Doses (N=140)	Cycle 3 800 U Dose (N=116)
Any AE	97 (62.6)	57 (37.5)	36 (25.7)	36 (25.7)	33 (28.4)
Any treatment-related AE	17 (11.0)	7 (4.5)	8 (5.3)	4 (2.9)	3 (2.6)
Any AESI	19 (12.3)	6 (3.9)	8 (5.3)	7 (5.0)	6 (5.2)
Any treatment-related AESI*	**8 (5.2)**	**2 (1.3)**	**4 (2.6)**	**3 (2.1)**	**3 (2.6)**
Any serious AE	17 (11.0)	4 (2.6)	11 (7.2)	3 (2.1)	3 (2.6)
Any treatment-related serious AE	0	0	0	0	0
Any AE leading to discontinuation	5 (3.2)	1 (0.6)	4 (2.6)	0	0
Any treatment-related AE leading to discontinuation	4 (2.6)	1 (0.6)	3 (2.0)	0	0

AE, adverse event, AESI, adverse event of special interest
*AEs were classified as AESIs on the basis of a predefined list of AEs that could potentially indicate toxin spread, regardless of whether an AE was regarded as treatment-related by the investigator.

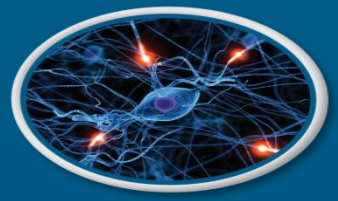
Wissel et al. Neurology 2017;88:1321-1328.

Goal Attainment by Injection Cycle



- **Increased doses enabled achievement of a greater number of goals**

Wissel et al. Neurology 2017;88:1321-1328.



Mount Sinai/NYU/NIH/International Spasticity and Botulinum Toxin Research Program

Mt Sinai

David M. Simpson, MD

Susan Shin, MD

NYU

Steven Frucht, MD

NIH

Mark Hallett, MD

Katharine Alter, MD

Barbara Karp, MD

Codrin Lungu, MD

Mt Sinai Research Staff

Mary Catherine George, PhD

Alexandra Nmashie, MD

Adisa Gruda

International Collaborators

Jorg Wissel, Germany

Michele Vecchio, Italy

Jean-Michel Gracies, France

Anthony Ward, England

Raymond Rosales, Philipines

Mount Sinai