

### La spasticità dell'arto superiore: la diagnosi e il trattamento con BoNTA

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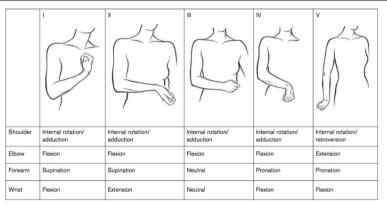




### Disclosures

- ☐ Honoraria/Expenses from Allergan, Ipsen
- □ Consulting/Advisory Board from Allergan, Ipsen
- ☐ Funded Research from Allergan, Ipsen, Merz

## **UL** spasticity



Upper limb spasticity patte flexed, intrinsic lumbrical). Note: All five upper limb patterns could be combined with any spastic hand and finger position (e.g. claw, spastic

Hefter et al, 2012

### OnabotulinumtoxinA Injection for Upper Limb PSS

Adducted shoulder with internal rotation



Flexed elbow



Pronated forearm



Flexed wrist



Flexed fingers



Thumb-in-palm



Clenched fist



Figure 3. Post-Delphi revisions: final redrawn images for Common Postures of Spasticity Picture Guide: Upper Limb.

D.M. Simpson et al. / PM R 9 (2017) 136-148

Journal of Neurology
https://doi.org/10.1007/s00415-018-8759-1

ORIGINAL COMMUNICATION

Defining spasticity: a new approach considering current movement
disorders terminology and botulinum toxin therapy

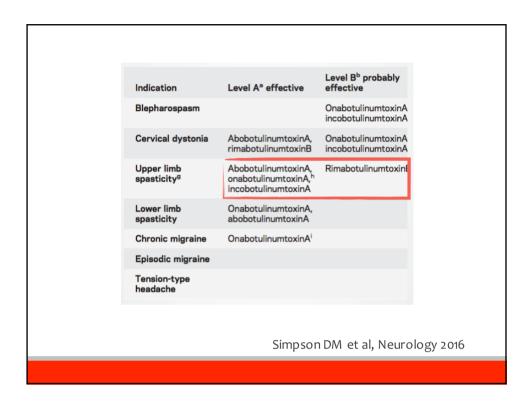
Dirk Dressler¹ · Roongroj Bhidayasir¹² · Saeed Bohlega³ · Pedro Chana⁴ · Hsin Fen Chien⁵ · Tae Mo Chung⁶ ·
Carlo Colosimo⁵ · Markus Ebke⁶ · Klemens Fedoroff॰ · Bernd Frank¹⁰ · Ryuji Kaji¹¹ · Petr Kanovsky¹² · Serdar Koçer¹³ ·
Federico Micheli¹⁴ · Olga Orlova¹⁵ · Sebastian Paus¹⁶ · Zvezdan Pirtosek¹७ · Maja Relja¹⁶ · Raymond L. Rosales¹⁰ ·
José Alberto Sagástegui-Rodríguez²⁰ · Paul W. Schoenle²¹ · Gholam Ali Shahidi²² · Sofia Timerbaeva²³ ·
Uwe Walter²⁴ · Fereshte Adib Saberi²⁵

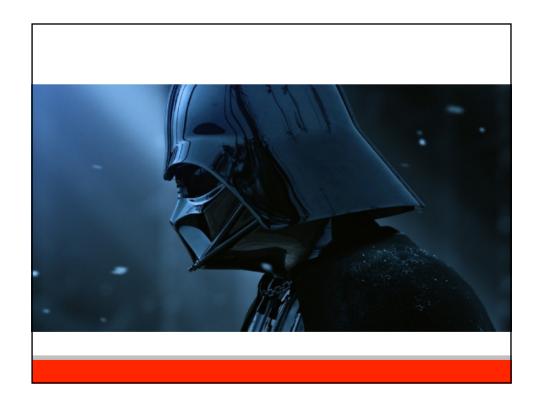
### Spasticity: definition

The involuntary muscle hyperactivity can consist of various forms of muscle hyperactivity:

- □ <u>spasticity sensu strictu</u>: involuntary muscle hyperactivity triggered by rapid passive joint movements
- □ <u>rigidity</u>: involuntary muscle hyperactivity triggered by slow passive joint movements
- □ dystonia: spontaneous involuntary muscle hyperactivity
- □ <u>spasms</u>: complex involuntary movements usually triggered by sensory or acoustic stimuli.
- □ complications: contractures, pain

Dressler et al, J Neurol 2018







### Botulinum Toxin for the Upper Limb After Stroke (BoTULS) Trial

Effect on Impairment, Activity Limitation, and Pain

Lisa C. Shaw, MRCP; Christopher I.M. Price, MD; Frederike M.J. van Wijck, PhD; Phil Shackley, PhD; Nick Steen, PhD; Michael P. Barnes, MD; Gary A. Ford, FRCP; Laura A. Graham, MD; Helen Rodgers, FRCP; on behalf of the BoTULS Investigators

- □ No significant difference in achievement of improved arm function (Action Research Arm Test) at 1 month (intervention group: 42 of 167 [25.1%], control group 30 of 154 [19.5%]; P 0.232).
- □ Significant differences in favor of the intervention group were seen in muscle tone at 1 month; upper limb strength at 3 months; basic arm functional tasks (hand hygiene, facilitation of dressing) at 1, 3, and 12 months; and pain at 12 months.

(Stroke. 2011;42:1371-1379.)

# Safety and efficacy of abobotulinumtoxinA for hemiparesis in adults with upper limb spasticity after stroke or traumatic brain injury: a double-blind randomised controlled trial

Jean-Michel Gracies, Allison Brashear, Robert Jech, Peter McAllister, Marta Banach, Peter Valkovic, Heather Walker, Christina Marciniak, Thierry Deltombe, Alexander Skoromets, Svetlana Khatkova, Steven Edgley, Fatma Gul, France Catus, Beatrice Bois De Fer, Claire Vilain, Philippe Picaut, for the International AbobotulinumtoxinA Adult Upper Limb Spasticity Study Group\*

#### Added value of this study

The current study shows improvements in tone 4 weeks after a single injection session of 500 U or 1000 U of abobotulinumtoxinA; these improvements were noted as early as week 1 and persisted for at least 12 weeks. Tertiary endpoints showed an improvement in active range of motion in all movements assessed in the upper limb (elbow, wrist, or finger extension) in the abobotulinumtoxinA 1000 U group, and a reduction of spasticity and spastic dystonia (Tardieu Scale). The data obtained with the two doses we studied and their effects might provide relevant information for future recommendations on dosing of abobotulinumtoxinA in adults with spastic paresis.

Lancet Neurol 2015; 14: 992-1001

### Botulinum toxin A for upper limb spasticity



Overall, the study by Gracies and colleagues shows that an injection of abotulinumtoxinA is safe to apply and results in significantly reduced muscle tone for up to 3 months after stroke or traumatic brain injury.

However, whether Botulinum toxin A injections are useful for improving upper limb capacity remains unsolved.

\*Gert Kwakkel, Carel G M Meskers

Published Online August 27, 2015 http://dx.doi.org/10.1016/ S1474-4422(15)00222-7

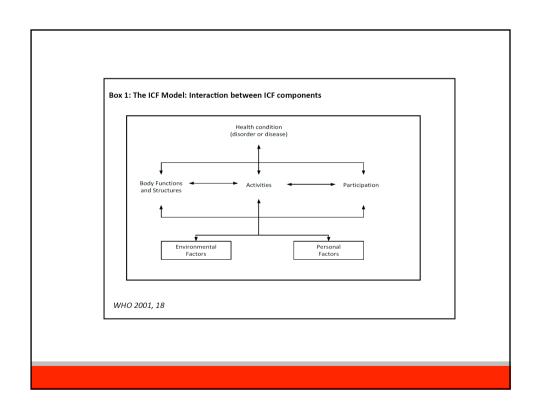
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www.thelancet.com/neurology Vol 14 October 2015



## Il problema della misura



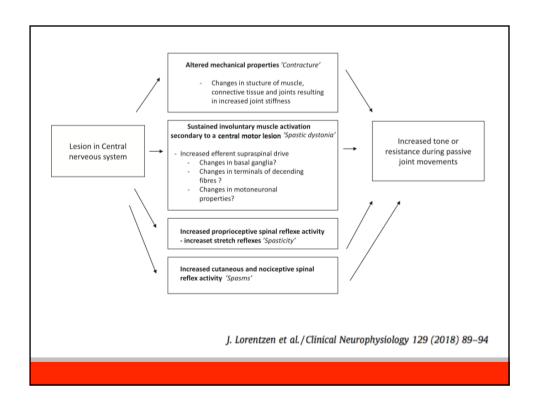


#### RESEARCH ARTICLE

### Systematic Review of Upper-limb Function Measurement Methods in Botulinum Toxin Intervention for Focal Spasticity

Stephen Ashford<sup>1,2†</sup> & Lynne Turner-Stokes<sup>1,2‡</sup>

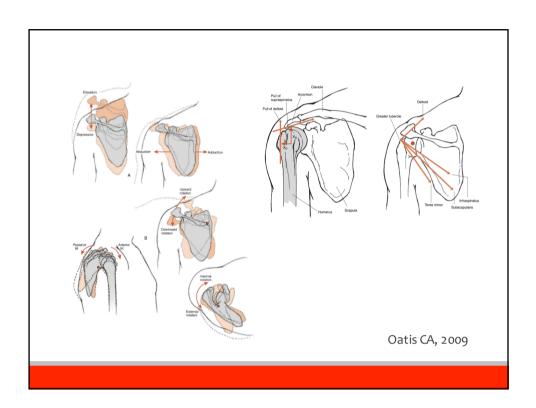
Physiother. Res. Int. 18 (2013) 178-189

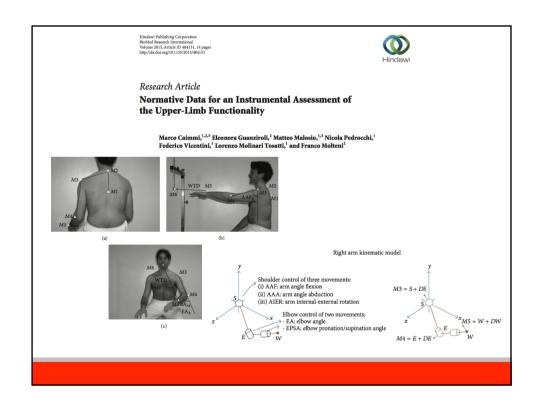


## Cos'è la "funzione attiva"?









## Il "problema" spasticità



### Neurologica

Acta Neurol Scand 2013: 128: 305-310 DOI: 10.1111/ane.12128

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ACTA NEUROLOGICA
SCANDINAVICA

### **Review Article**

Enhancing patient-provider communication for long-term post-stroke spasticity management

Sunnerhagen KS, Francisco GE. Enhancing patient—provider communication for long-term post-stroke spasticity management.

Acta Neurol Scand 2013: 128: 305–310.

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K. S. Sunnerhagen¹,
G. E. Francisco¹

The Institute of Neuroscience and Physiology—Section for Clinical Neuroscience and Rehabilitation.

letter to the editor

## Post-stroke spasticity as a condition: a new perspective on patient evaluation

Alessio Baricich, MD<sup>a</sup>, Alessandro Picelli, MD, PhD<sup>a</sup>, Franco Molteni, MD<sup>a</sup>, Eleonora Guanziroli, MS Biomed Eng, PhD<sup>a</sup>, Andrea Santamato, MD<sup>a</sup> on behalf of the Philosophical Botulinum Toxin Club

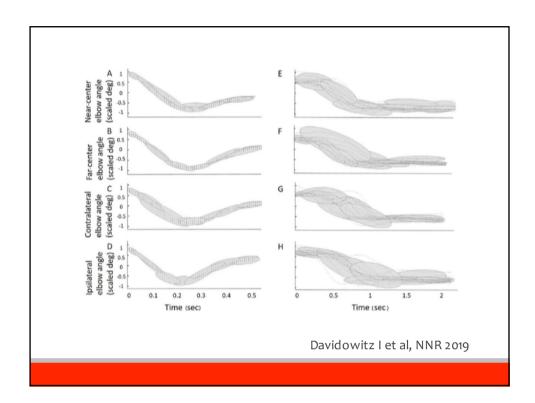
Functional Neurology 2016; 31(3): 179-180

### Relationship Between Spasticity and Upper-Limb Movement Disorders in Individuals With Subacute Stroke Using Stochastic Spatiotemporal Modeling

Neurorehabilitation and Neural Repair 2019, Vol. 33(2) 141–152 © The Author(s) 2019 Article reuse guidelines: agepub.com/journals-permissions DOI: 10.1177/1545968319824050 journals.agepub.com/home/nnr

Isgav Davidowitz, MSc<sup>1</sup>, Yisrael Parmet, MSc, PhD<sup>1</sup>, Silvi Frenkel-Toledo, MSc, PhD<sup>2,3</sup>, Melanie C. Baniña, CAT(C), MSc, PhD<sup>4,5</sup>, Nachum Soroker, MD, PhD<sup>3,6</sup>, John M. Solomon, MPT, PhD<sup>7</sup>, Dario G. Liebermann, MSc, PhD<sup>6</sup>, Mindy F. Levin, PT, MSc, PhD<sup>2,3</sup>, and Sigal Berman, MSc, PhD<sup>1</sup>

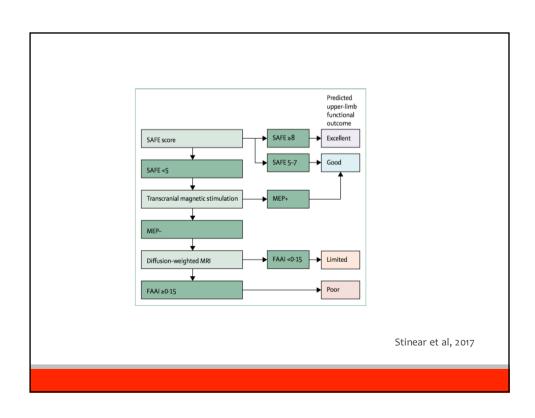


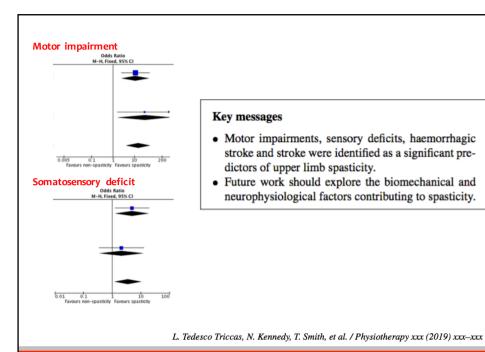


J Rehabil Med 2019; 51: Epub ahead of print Check for updates **SHORT COMMUNICATION** SPASTIC CO-CONTRACTION, RATHER THAN SPASTICITY, IS ASSOCIATED WITH IMPAIRED ACTIVE FUNCTION IN ADULTS WITH ACQUIRED BRAIN INJURY: A PILOT STUDY Alexandre CHALARD, PT,  $MS^{1,2}$ , David AMARANTINI,  $PhD^1$ , Joseph TISSEYRE,  $MS^1$ , Philippe MARQUE, MD,  $PhD^{1,3}$ , Jessica TALLET,  $PhD^1$  and David GASQ, MD,  $PhD^{1,4}$ ☐ Greater co-contraction occurred in patients with brain injury compared with controls. ☐ In contrast to spasticity, strong associations were found between the co-contraction index, the limitation of active elbow extension, the Fugl-Meyer Assessment, and the Action Research Arm Test. Fig. 1. Illustration of the arm and forearm positions used to perform torque and electromyographic recordings during isometric elbow extension on the calibrated dynamometer.

## La prognosi funzionale







Letter by Munin et al Regarding Article, "Botulinum Toxin for the Upper Limb After Stroke (BoTULS) Trial: Effect on Impairment, Activity Limitation, and Pain" Michael C. Munin, Douglas J. Weber and Elizabeth R. Skidmore

Stroke. 2011;42:e412; originally published online June 2, 2011;

With severe baseline weakness in a majority of subjects, it is not surprising that botulinum toxin injections that block neuromuscular transmission and cause selective muscle weakening did not improve active functional movement as measured by the ARAT.

Significantly more abobotulinumtoxinA patients had improvement in subject-reported daily tasks, like opening the palm for cleaning and cutting nails and putting an arm through a coat sleeve.

These findings indicate that different measures give us different information about the effectiveness of interventions on upper limb function and pose the question, which measures are best for measuring changes in upper limb spasticity after stroke?





### Archives of Physical Medicine and Rehabilitation

journal homepage: www.archives-pmr.org Archives of Physical Medicine and Rehabilitation 2013;94:977-89



REVIEW ARTICLE (META-ANALYSIS)

## Treatment With Botulinum Toxin Improves Upper-Extremity Function Post Stroke: A Systematic Review and Meta-Analysis

Norine Foley, MSc,<sup>a</sup> Shelialah Pereira, MSc,<sup>a</sup> Katherine Salter, MSc,<sup>a</sup> Manuel Murie Fernandez, PhD,<sup>b</sup> Mark Speechley, PhD,<sup>c</sup> Keith Sequeira, MD,<sup>d,e</sup> Thomas Miller, MD,<sup>a,d,e</sup> Robert Teasell, MD<sup>a,d,e</sup>

| Table 3 | Treatment | effect | sizes | grouped | by | similarity | of | outcome |
|---------|-----------|--------|-------|---------|----|------------|----|---------|
|         |           |        |       |         |    |            |    |         |

| Measure  | Outcome Type  | Standardized Mean Difference (95% Confidence Interval), <i>P</i> value |
|--|---|--|
| Disability Assessment Scale<br>Disability Scale    | Scales developed specifically to assess response<br>to treatment with BTX-A | 0.688 (0.454-1.012), P<.0001   |
| Action Research Arm Test<br>Motor Assessment Scale | Assessments of motor function   | 0.406 (0.85-0.727), P=.013   |
| Motor Activity Log<br>Barthel Index                | Generalized disability  | 0.372 (-0.002 to 0.746), P=.051  |

J Rehabil Med 2014; 46: 504-513

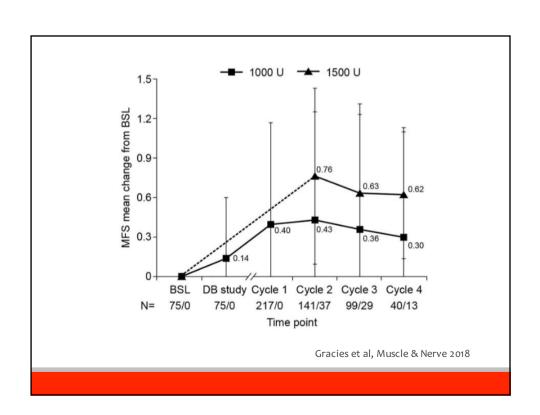
#### ORIGINAL REPORT

### FUNCTIONAL GOAL ACHIEVEMENT IN POST-STROKE SPASTICITY PATIENTS: THE BOTOX® ECONOMIC SPASTICITY TRIAL (BEST)

Anthony B. Ward, MD, FRCP¹, Jörg Wissel, MD, FRCP², Jörgen Borg, MD³, Per Ertzgaard, MD⁴, Christoph Herrmann, MD⁵, Jai Kulkarni, MD, FRCP⁶, Kristina Lindgren, MD⁻, Iris Reuter, MD՞, Mohamed Sakel, FRCP⁶, Patrik Säterö, MD¹ゥ, Satyendra Sharma, MD, FRCPC¹¹, Theodore Wein, MD, FRCPC¹², Nicola Wright, MSc¹³ and Antony Fulford-Smith, MB, BS, MRCGP¹³; on behalf of the BEST study group

Table VI. Level of principal active functional goal attainment, assessed at week 24, or 10 weeks after the second injection

|   | OnabotulinumtoxinA+SC        | Placebo + SC |
|---|------------------------------|--------------|
| Upper limb principal active functional goals <sup>a</sup> , ITT population (assessable patients), n | n=62 (n=54)                  | n=62 (n=52)  |
| +2  | 3 (5.6)                      | 1 (1.9)      |
| +1  | 7 (13.0)                     | 3 (5.8)      |
| 0   | 11 (20.4)                    | 9 (17.3)     |
| -1  | 19 (35.2)                    | 16 (30.8)    |
| -2  | 12 (22.2)                    | 20 (38.5)    |
| -3  | 2 (3.7)                      | 3 (5.8)      |
| Median  | -1                           | -1           |
| Median difference (95% CI); p-value   | 0.0 (0.0  to  1.0); p=0.034  |              |
| Lower timb principal active functional goals*, 111 population (assessable patients), n              | n=//(n=69)                   | n=72 (n=66)  |
| +2  | 3 (4.3)                      | 11 (16.7)    |
| +1  | 9 (13.0)                     | 5 (7.6)      |
| 0   | 18 (26.1)                    | 14 (21.2)    |
| -1  | 17 (24.6)                    | 12 (18.2)    |
| -2  | 19 (27.5)                    | 21 (31.8)    |
| -3  | 3 (4.3)                      | 3 (4.5)      |
| Median  | -1                           | -1           |
| Median difference (95% CI); p-value   | 0.0 (-1.0  to  0.0); p=0.724 |              |
| aITT: intention-to-treat; bSC: standard of care.  |                              |              |



### Influence of Botulinum Toxin Type A Treatment of Elbow Flexor Spasticity on Hemiparetic Gait

#### ABSTRACT

Esquenazi A, Mayer N, Garreta R: Influence of botulinum toxin type A treatment of elbow flexor spasticity on hemiparetic gait. Am J Phys Med Rehabil 2008; 87:305-311.

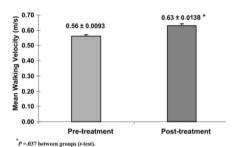


FIGURE 1 Change in self-selected comfortable walking velocity. \*P = 0.037 between groups (t test).

Letter by Munin et al Regarding Article, "Botulinum Toxin for the Upper Limb After Stroke (BoTULS) Trial: Effect on Impairment, Activity Limitation, and Pain" Michael C. Munin, Douglas J. Weber and Elizabeth R. Skidmore

Stroke. 2011;42:e412; originally published online June 2, 2011;

□ Because functional improvement was the primary outcome of this trial, inaccurate placement of toxin combined with suboptimal dosing of limited numbers of muscles may explain why the intervention group did not show improvement in ARAT relative to controls.





PM R 9 (2017) 136-148

#### Original Research

### OnabotulinumtoxinA Injection for Poststroke Upper-Limb Spasticity: Guidance for Early Injectors From a Delphi Panel Process

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

|   | Muscles         |                |               |                          |  |
|---|-----------------|----------------|---------------|--------------------------|--|
| Adducted Shoulder*                                  | Pectoralis Com  | plex Lat       | issimus Dorsi | Technique and Total Dose |  |
| Panelists (%) recommending injection of this muscle | 87.5            | 75             |               | LT: yes†                 |  |
| OnabotulinumtoxinA dose, U (mode)                   | 75              | 75             |               | 150                      |  |
| OnabotulinumtoxinA dose, U (range)                  | 75-100          | 75             |               | 100-200                  |  |
| Number of injection sites per muscle                | 4               | 4              |               |                          |  |
|   | Muscles         |                |               |                          |  |
| Flexed Elbow  | Brachioradialis | Biceps Brachii | Brachialis    | Technique and Total Dose |  |
| Panelists (%) recommending injection of this muscle | 100             | 87.5           | 75            | LT: yes†                 |  |
| OnabotulinumtoxinA dose, U (mode)                   | 25              | 50             | 75            | 150                      |  |
| OnabotulinumtoxinA dose, U (range)                  | 25-50           | 0-50           | 50-100        | 100-150                  |  |
| Number of injection sites per muscle                | 2               | 4              | 2             |                          |  |
|   | Muscles         |                |               |                          |  |
| Pronated Forearm                                    | Pronator Quad   | fratus Pron    | ator Teres    | Technique and Total Dose |  |
| Panelists (%) recommending injection of this muscle | 100             | 100 100        |               | LT: yes†                 |  |
| OnabotulinumtoxinA dose, U (mode)                   | 25 50           |                | 75            |                          |  |
| OnabotulinumtoxinA dose, U (range)                  | 0-25            | 0-25 45-60     |               | 50-100                   |  |
| Number of injection sites per muscle                | 1               | 2              |               |                          |  |
|   | Muscles         |                |               |                          |  |

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|  |                  | Muscles                 |                 |                    |                          |                      |  |
|--|------------------|-------------------------|-----------------|--------------------|--------------------------|----------------------|--|
| Flexed Wrist   |                  | Flexor Carpi Radialis F |                 | exor Carpi Ulnaris | Technique and Total Dose |                      |  |
| Panelists (%) recommending injection of this muscle    |                  | 100                     | 100 100         |                    | LT: yes <sup>†</sup>     |                      |  |
| OnabotulinumtoxinA dose, U (mode)                      |                  | 50                      |                 | i0                 | 100                      |                      |  |
| OnabotulinumtoxinA dose, U (range)                     |                  | 50-75 25-50             |                 |                    | 60-100                   |                      |  |
| Number of injection sites per muscle                   |                  | 2                       |                 | 2                  |                          |                      |  |
|  |                  | Muscles                 |                 |                    |                          |                      |  |
|  |                  | Flexor Digitorum        | n Fl            | exor Digitorum     | -                        |                      |  |
| Flexed Fingers   |                  | Superficialis           | Profundus       |                    | Technique and Total Dose |                      |  |
| Panelists (%) recommending injection of                | this muscle      | 100                     | 100             |                    | LT: yes <sup>†</sup>     |                      |  |
| OnabotulinumtoxinA dose, U (mode)                      |                  | 50                      | 50              |                    | 100                      |                      |  |
| OnabotulinumtoxinA dose, U (range)                     |                  | 20-60                   | 25-75           |                    | 50-100                   |                      |  |
| Number of injection sites per muscle                   |                  | 2 2                     |                 | 2                  |                          |                      |  |
|  |                  | Muscles                 |                 |                    |                          |                      |  |
|  |                  | Flexor Pollicis         | Adductor        | Flexor Pollicis    | s                        |                      |  |
| Thumb-in-palm  |                  | Longus                  | Pollicis        | Brevis             | Technique                | and Total Dose       |  |
| Panelists (%) recommending injection of                | this muscle      | 100                     | 87.5            | 87.5               | LT: yes <sup>†</sup>     |                      |  |
| OnabotulinumtoxinA dose, U (mode)                      |                  | 40                      | 15              | 20                 | 75                       |                      |  |
| OnabotulinumtoxinA dose, U (range)                     |                  | 40-50                   | 10-20           | 12.5-20            | 50-75                    |                      |  |
| Number of injection sites per muscle                   |                  | 2                       | 1               | 1                  |                          |                      |  |
|  | Muscles          |                         |                 |                    |                          |                      |  |
|  | Flexor Digitorum | Flexor Digitorum        | Flexor Pollici: | s Flexor Pollicis  | Adductor Pollicis        | Technique and        |  |
| Clenched Fist  | Superficialis    | Profundus               | Brevis          | Longus             | Longus                   | Total Dose           |  |
| Panelists (%) recommending injection<br>of this muscle | 100              | 100                     | 75              | 100                | 75                       | LT: yes <sup>†</sup> |  |
| OnabotulinumtoxinA dose, U (mode)                      | 50               | 50                      | 15              | 25                 | 10                       | 150                  |  |
| OnabotulinumtoxinA dose, U (range)                     | 40-50            | 25-60                   | 10-15           | 25-30              | 10-12.5                  | 125-175              |  |
| Number of injection sites per muscle                   | 2                | 2                       | 1               | 2                  | 1                        |                      |  |

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### Three most common aggregate postures

|   | Aggregate Postures  | Starting Dose<br>(Typical) | Total Dose<br>(Maximum) |
|---|---|----------------------------|-------------------------|
| 1 | Adducted shoulder<br>Flexed elbow<br>Pronated forearm<br>Flexed wrist | 300 U                      | 400 U                   |
| 2 | Clenched fist<br>Flexed elbow<br>Pronated forearm<br>Flexed wrist     | 300 U                      | 400 U                   |
| 3 | Clenched fist<br>Flexed wrist<br>Clenched fist                        | 200 U                      | 300 U                   |

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J Rehabil Med 2011; 43: 1032-1037

#### ORIGINAL REPORT

INVESTIGATING MUSCLE SELECTION FOR BOTULINUM TOXIN-A INJECTIONS IN ADULTS WITH POST-STROKE UPPER LIMB SPASTICITY

lan J. Baguley, MBBS PhD¹, Melissa T. Nott, PhD¹, Lynne Turner-Stokes, DM FRCP², Stephen De Graaff, MBBS FAFRM³, Pesi Katrak, MD FAFRM⁴, Paul McCrory, MBBS PhD FRACP⁵, Monica de Abadal, MD MBA/HSA⁵ and Andrew Hughes, MD⁻

- ☐ Muscle selection and botulinum toxin-A dosage were not significantly associated with spasticity severity or with patientidentified goals.
- ☐ Between-site differences in injection practices suggested that injector beliefs, rather than patient characteristics, were the dominant feature driving botulinum toxin-A injection strategy for post-stroke upper limb spasticity.
- ☐ This result looks into the "black box" of reha-bilitation, revealing signi cant variation in injector beliefs

#### MANUAL NEEDLE PLACEMENT: ACCURACY OF BOTULINUM TOXIN A **INJECTIONS**

ALEXIS SCHNITZLER, MD,1 NICHOLAS ROCHE, MD,1 PHILIPPE DENORMANDIE, MD,2 CHRISTINE LAUTRIDOU, MD,2 BERNARD PARRATTE, MD, PhD,<sup>3</sup> and FRANÇOIS GENET, MD<sup>1</sup>

<sup>1</sup> Physical Medicine and Rehabilitation Department, Raymond Poincaré Hospital, AP-HP, University of Versailles Saint Quentin, 104 Boulevard Raymond Poincaré, 92380 Garches, France

Orthopaedic Surgery Department, Raymond Poincaré Hospital, AP-HP, University of Versailles Saint Quentin, Garches, France
Physical Medicine and Rehabilitation Department, University of J Minjoz, Besançon, France

Accepted 6 April 2012

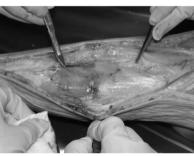


FIGURE 1. Successful injection (ink in the gastrocnemius



FIGURE 2. Unsuccessful injection (superficial, ink in the fat).

Muscle Nerve 46: 531-534, 2012



## Take home messages



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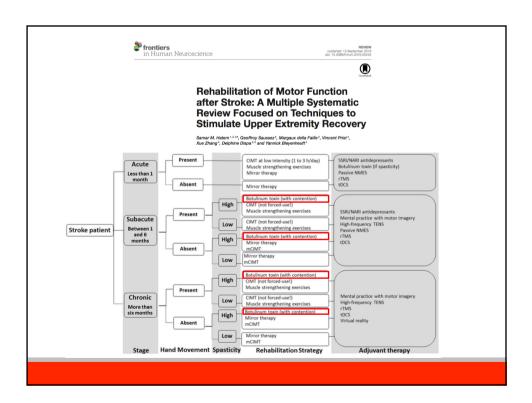
\*Gert Kwakkel, Carel G M Meskers

www.thelancet.com/neurology Vol 14 October 2015

### Take home messages

- ☐ In view of this complexity, it is not surprising that a treatment to counteract the hyperexcitability component of spasticity does not automatically result in improved upper limb function.
- □ There is increasing evidence that the effects of botulinum toxin A injections can be maximised by a team of health professionals such as nurses, physical and occupational therapists, and orthotists, who collectively aim to improve upper limb capacity, improve basic upper limb activities such as hand hygiene and dressing ability, or reduce deformity and pain after stroke or traumatic brain injury.

\*Gert Kwakkel, Carel G M Meskers www.thelancet.com/neurology Vol 14 October 2015





### Take home messages -2

- ☐ Studies are needed to establish how changes in the neuronal component of spasticity interact longitudinally with the progressive biomechanical changes in different phenotypes after stroke or traumatic brain injury.
- Trials are needed in which the accompanying biomechanical changes, including muscle shortening and contractures, are prevented with botulinum toxin A injections at an early stage after brain injury.
- □ Third, the assumed association between reducing muscle tone and meaningful gains in task performance of the upper paretic limb is still poorly understood and seldom adequately investigated. Biomechanical and neurophysiological measurements, preferably done during meaningful tasks, are needed to investigate this association.

\*Gert Kwakkel, Carel G M Meskers www.thelancet.com/neurology Vol 14 October 2015

