Definition: Spasticity

- In every day clinical use, the term spasticity is used as a collective to describe a combination of clinical signs.

- The term spasticity was defined by J.W. Lance in the 1980s as “a motor disorder characterized by a velocity-dependent increase in tonic stretch reflex with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex as one component of the Upper Motor Neuron Syndrome” (UMNS, defined by Young 1994).

- Pandyan et al. (2005) re-defined spasticity as disordered sensorimotor control, resulting from an UMN lesion, presenting as intermittent or sustained involuntary activation of muscles focusing on the positive features of the UMNS, while excluding the negative features of the UMNS and the bio-mechanical alterations in joints and soft tissue.
Mechanisms Leading to Increased Muscle Tone

**A – Lesion of internal capsule**
- corticospinal tract lesion
- corticoreticulare tract lesion

**B: Incomplete spinal Lesion**
- tr. reticulospinalis dorsalis

**C: Complete spinal Lesion**
- tr. reticulospinalis med.
- tr. vestibulospinalis

---

**Sheean G. 1995**

Mechanisms Leading to Increased Muscle Tone
Changes in segmental network and in muscle properties

Burke D, Wissel J, Donnan, GA. Neurology 2013;80:S20-S26
Changes related to Spasticity in the “Final Common Path“

Upper Motor Neuron Syndrome

EARLY: ACUTE / Post-ACUTE

Sub-ACUTE-Phase

Musculoskeletal pathology
- Muscle shortening
- Extrinsic tension
- Joint instability
- Degenerative arthritis

Neuronal pathology
- Loss of inhibition LMN
- Loss of connections to LMN (and other pathways)
- Positive features of UMN syndrome
- Negative features of UMN syndrome
- Weakness
- Fatiguability
- Poor balance
- Sensory deficits

overactivity
shortening
ACUTE/Post-ACUTE PSS is a major factor that hinders early/postacute rehabilitation.

**ICF**
International Classification of Functioning, Disability and Health

- Weakness
- Spasticity
- Sensory loss

Functional restrictions

Discomfort & pain

Care restrictions, altered self image

**Upper Motor Neuron Syndrome**

- Spasticity
- Hyper-reflexia
- Clonus
- Co-contraction

Musculoskeletal pathology
- Muscle shortening
- Bosy position
- Joint instability
- Degenerative arthritis

Sub-ACUTE -Phase

LATE / CHRONIC-Phase
Chronic PSS is a major cause of reduced Health Related – Quality of Life (HR-QoL)

**ICF**
International Classification of Functioning, Disability and Health

**weakness**  **spasticity**  **sensory loss**

- functional restrictions
- muscle shortening
- stiffness / contractures
- discomfort & pain
- care restrictions, altered self image

**Typical upper and lower limb spastic patterns in Post-Stroke Spasticity**

<table>
<thead>
<tr>
<th>Upper Limb Pattern</th>
<th>Lower Limb Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder add-/abduction and internal rotation</td>
<td>Hip flexor / adductor spasticity</td>
</tr>
<tr>
<td>Elbow flexion</td>
<td>Proximal flexor spasms</td>
</tr>
<tr>
<td>Pronation of the forearm</td>
<td>Stiff-knee pattern, extensor spasms</td>
</tr>
<tr>
<td>Flexed wrist and clenched hand</td>
<td>Plantar flexed and inverted foot (pes equino-varus)</td>
</tr>
<tr>
<td>Thumb in palm, intrinsic hand muscle stiffness</td>
<td>Clawed toes &amp; hitchicker’s great toe</td>
</tr>
</tbody>
</table>
Aims of spasticity treatment

- Relief of pain and discomfort
- Improvement of posture
- Facilitation of sitting, standing, and walking
- Reduction in burden of care
- Improvement of hygiene in areas such as palm, axilla, & groin
- Improvement in body image and self esteem
- Prevention of complications such as pressure ulcers

“Medication should rarely be used in isolation but is usually part of a whole treatment strategy”

2. Barnes, 2008

Current Treatment Options
Spasticity Management

- Exercise and physical modalities
- Systemic drugs (e.g. baclofen)
- Chemodenervation (e.g. BoNT A)
- Intrathecal baclofen pump
- Neuro-orthopaedic surgery (fixed contractures and bony destruction)
- Neurosurgical methods (neurotomy)
Management Strategy

Prevention of Provocative Factors

Physical Management & Treatment

Treatment Decision Making & Available Options

Generalised Spasticity

Regional Spasticity

Focal & Multi-Focal Spasticity

Oral Agents

Intrathecal Baclofen

Botulinum Toxin Phenol Blockade

Royal College of Physicians: National Guidelines 2009
**Multidisciplinary Team Approach**

**Education about spasticity** will enhance communication and collaboration between patients, care givers and multidisciplinary team. **Antispastic positioning and "stretching" (pROM)** in the early phase following CNS lesion will help to prevent muscle shortening (complications).

**Management Strategy**

**Prevention of Provocative Factors**

**Physical Management & Treatment**

- Treatment Decision Making & Available Options
  - Generalised Spasticity
  - Regional Spasticity
  - Focal & Multi-Focal Spasticity
  - Oral Agents
  - Intrathecal Baclofen
  - Botulinum Toxin Phenol Blockade

Royal College of Physicians: National Guidelines 2009
Despite years of use, the evidence for oral antispasticity drugs is poor

**2004 systematic review**

“Most trials were of small size, of short duration, & their methodological quality was inadequate...

Only four reports described the magnitude of the antispastic effect... (quantitative data)

The incidence of adverse drug effects (drowsiness, sedation, and muscle weakness) was high...

If any, efficacy is marginal.”


No real improvement in available data since 2004

Management Strategy

**Prevention of Provocative Factors**

**Physical Management & Treatment**

**Treatment Decision Making & Available Options**

- **Generalised Spasticity**
  - Oral Agents
  - Baclofen

- **Regional Spasticity**
  - Intrathecal Baclofen

- **Focal & Multi-Focal Spasticity**
  - Botulinum Toxin
  - Phenol Blockade

Royal College of Physicians: National Guidelines 2009
The efficacy of BoNT A for spasticity & pain in adults

A systematic review and meta-analysis

Objectives: A systematic review and meta-analysis using the Grades of Recommendation, Assessment, Development & Evaluation (GRADE).

All RCTs on adults with spasticity of any origin in the upper or lower limb, treated with a single dose of BoNT A, with outcome measures for pain or spasticity (only: body structure & pain).

Results: A total of 37 studies were reviewed. A meta-analysis was carried out on 21 for spasticity and 10 for associated pain.

Evidence quality was low/very low for pain. No significant effect was found in UL (SMD=0.44, CI -0.02 to 0.90, Z = 1.88, P=0.06), and in LL (RR = 1.01 CI 0.19 to 5.36, Z = 0.02, P=0.99).

Evidence quality for spasticity was moderate. Significant effects were found in the UL (WMD=0.88, CI 0.63 to 1.14, Z = 6.86, P<0.0001), and LL (RR=2.42, CI 1.60 to 3.65, Z=4.18, P<0.0001).

Conclusion: Use of BoNT A is supported for spasticity

Baker JA, Pereira G. Clin Rehabil. 2013

BoNT-A in a comprehensive rehabilitation strategy

- 2013 Cochrane review found only 3 studies of “multidisciplinary rehabilitation” following BoNT A¹
  - 'Low level' evidence for the effectiveness of rehabilitation (CIMT, FES) in improving active function and impairments following BoNT for upper limb spasticity in adults with chronic stroke

- 2014 systematic review found 11 RCT (poor–moderate quality) following BoNT A²
  - ergometer cycling, electrical stimulation, stretch (casting, splinting, taping, or manual or exercise-induced stretch), constraint-induced movement therapy, task-specific motor training, and exercise programs
  - Statistical findings suggested that combined therapy and BoNT-A is slightly more effective than BoNT-A alone (“...as a result we are not able to provide guidance”)

Case Report: Igor
TBI in Moscow
Evaluation 1 year after TBI at home
(in Cheljabinsk, Russia)
Goal of patient/family: „Regain walking ability"

Suggestion: 6 weeks in-patient Neurorehabilitation in Germany
(multi-professional & multi-modal)

Spastic tetraparesis (L>R)
with severe contractures
- elbow and wrist
- ankle and toes

Pseudo-Bulbar-Paralyse with Dysarthria

Neuropsychological Disturbances
- contusions?
- Suspect as side effects of antispastic medication?

Case Report: Igor - Goal Attainment Approach
Baseline

Severe pes equino-varus with - 40° spastic contracture at ankle

Step 1
Goal setting
- Goal selection (goal establishment): “walking domain”
- Expected outcome definition: Agreed goal
  “Walking 20 meters with an aid, e.g. walker”
Case Report: Igor

Baseline

Step 2: Selection and Timing of Interventions
Botulinum Toxin Injektion (pes equinus and toe muscles)

BoNT A: Intervention:
300 units of onabotulinumtoxin (calf muscles and toe flexors and tibial posterior muscle).

Follow Up: 3 weeks later: Mild equinus with - 3° contracture at ankle

Case Report: Igor – BoNT A PLUS: Seriell Casting

Baseline: -40° Injection BoNT A
+10 days: -35°
+14 days: -25°
+18 days: -10°
+ 21 days: -3°
+ 23 days: -3°
Cast and Snikers

**Start:** Oral antispastic treatment
Baclofen 100 mg/d **ADVERSE**
Sirdalut 20 mg/d **EFFECTS**

**REDUCTION OF ORAL DRUGS**
End of NeuroRehabilitation
Baclofen 20 mg/d
Sirdalut 2 mg/d

Adverse effects of oral drugs
Physiotherapy (shaping !!!)
End of Neurorehabilitation (last 3 weeks)

Case report: Assessment - Body Functions & Structures

<table>
<thead>
<tr>
<th></th>
<th>Start of in-patient NeuroRehab</th>
<th>+ 42 days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Functional Ambul.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Category</strong></td>
<td>1/5</td>
<td>3/5</td>
</tr>
<tr>
<td>„aids“</td>
<td>(no ambulation)</td>
<td>(ambulation with aids)</td>
</tr>
<tr>
<td><strong>Muscle tone</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mod. Ashworth Scale)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ankle left</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>ankle right</td>
<td>1+</td>
<td>1+</td>
</tr>
<tr>
<td><strong>pROM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ankle left</td>
<td>0/ 40/ 50°</td>
<td>0/ 5/ 50°</td>
</tr>
<tr>
<td>ankle right</td>
<td>0/ 0/ 50°</td>
<td>0/ 0/ 50°</td>
</tr>
</tbody>
</table>
Re-evaluation +42 days: Ambulation with walker > 250m

Goal attainment: +1 (better than expected) AND Cognitive Improvements
- Agreed goal was 20 m walking with a walker -
- Reduction antispastic drugs -

Original Article

OnabotulinumtoxinA Improves Pain in Patients With Post-Stroke Spasticity: Findings From a Randomized, Double-Blind, Placebo-Controlled Trial

Jörg Wissel, MD, Vaibhavnath Gaurupathy, PhD, MPH, Anthony B. Ward, MD, FRCP, Jörgen Borg, MD, PhD, Per Erazgaard, MD, Christoph Herrmann, MD, Anders Hagstroem, MD, Mohamed Sabet, MD, Julia Ma, PhD, Rosalina Dimitrova, MD, MPH, Antony Fulford-Smith, MB, BS, MRCP, and Patrick Gillard, PharmD, MS

Methods. Patients with PSS (N = 175) were randomized to 2:1 to 34-week double-blind treatment with onabotulinumtoxinA + standard care (SC) or placebo injection + SC, and were eligible to receive open-label onabotulinumtoxinA up to 52 weeks. Assessments included change from baseline on the 11-point pain numeric rating scale, proportion of patients with baseline pain ≥4 achieving ≥50% and ≥50% improvement in pain, and pain interference with walk at Week 12, end of double-blind treatment, and Week 52.

Results. At baseline, most patients (74.3%) experienced pain ≥4 (pain subgroup). Mean pain reduction from baseline at Week 12 was significantly greater with onabotulinumtoxinA + SC (−0.77, 95% CI −1.14 to −0.40) than placebo + SC (−0.13, 95% CI −0.51 to 0.24; P < 0.05). Higher proportions of patients in the pain subgroup achieved ≥50% and ≥50% reductions in pain at Week 12 with onabotulinumtoxinA + SC (53.7% and 57.0%, respectively) compared with placebo (29.8% and 18.6%, respectively; P < 0.05). Reductions in pain were sustained through Week 52. Compared with placebo + SC, onabotulinumtoxinA consistently reduced pain interference with walk.

Conclusions. This is the first randomized, placebo-controlled trial demonstrating statistically significant and clinically meaningful reductions in pain and pain interference with walk with onabotulinumtoxinA in patients with PSS.

OnabotulinumtoxinA Improves Pain in Patients With Post-Stroke Spasticity: Findings From a Randomized, Double-Blind, Placebo-Controlled Trial.
Wissel et al. 2016

Mean change* from baseline in PNRS score during the double-blind and open-label treatment phases. PNRS = Pain Numeric Rating Scale.

273 patients with PSS were randomized double-blind treatment with BoNT (ona-BoNT + standard care ) or placebo + SC and were eligible to receive open-label BoNT (ona-) up to 52 weeks. Assessments included change from baseline on the 11-point pain numeric rating scale,

Proportions of patients who achieved ≥30% and ≥50% reductions in pain score from baseline at Week 12, Week 24/10 weeks after second injection, and at Week 52 in the subgroup of patients with baseline pain scores ≥4. ‘p < 0.05 versus placebo.

Current Treatment Options in Spasticity

- Exercise and physical modalities
- Systemic drugs
- Chemodenervation e.g. BoNT A and Neurolytic injections
- Intrathecal drugs
- Neuro-orthopaedic and Neurosurgical methods
13.6.2016

Disabling spastic elbow flexion two month after stroke in a 62 a old male

BoNT A - injection seven days before casting (onabotulinumtoxinA):
(injection with sonographical guidance)
60 units biceps brachii muscle
40 units bracialis muscle
40 units flexor carpi radialis muscle

Casting: 6 days
4 casts

Physical Treatment Adjunctive to BoNT A

Combining BoNT A injections with taping / splinting & electrical stimulation

N = 32

thermoplastic split, daily stretching, 5 days electrical stimulation
(1 h / d, 50 Hz, 10 s trains)

Carda and Molteni 2005
13.6.2016

Summary I: Spasticity BoNT A - RCTs

Significant improvement in RCTs from focal BoNT A in body function and structure, passive (DAS) and improvement in active function (single pts.): BoNT A is recommended
Summary II: BoNT A +/- rehab-interventions

RCTs (systematic reviews) showed that specific interventions following BoNT A (BoNT A PLUS) can increase efficacy compared to BoNT A alone. Compared with simple stretching, other rehab-interventions (e.g. casting) can be of benefit following BoNT A. Efficacy within 3 months was evident but information on long term effects of BoNT A PLUS is lacking.

+ overactivity
shortening

BoNT A PLUS
(+ intervention)
is recommended

Questions ?

Thank you for your attention and thank you for inviting me!

Prof. Jörg Wissel, MD, FRCP
Neurological Rehabilitation and Physical Therapy
Depts of Neurology, Vivantes Hospitals Spandau & Humboldt Hospital, Berlin, Germany
University of Potsdam
Summary III

early use of BoNT A in spasticity

Spasticity

Systematic Review: Effect of Rehabilitation Interventions following BoTN A Injection in Stroke Patients with Post Stroke Spasticity (PSS)

Identify whether BoNT combined with rehabilitation interventions is more effective than alone in Post-Stroke Spasticity (PSS).

Database Search: Pubmed, Cochrane Central Register of Controlled Trails, EMBASE, CINAHL from 1990 to May 2015.

Study selection criteria: RCTs with BoNT combined with different rehabilitation interventions. Participants received at least one rehabilitation intervention following BoNT injection.

Primary outcome Modified Ashworth Scale (MAS), different Functional Assessments (MAL, ARAT), Range of Motion (ROM), etc.

Total 16 articles: 12 RCTs (with placebo) with 330 participants and 4 with 194 participants for comparative studies (“comparator”) were included.

Jörg Wissel and Song-Jin Ri, Berlin 2015, unpublished data
Review Flow Diagramme

1668 records from the following databases searching: Pubmed-896, Cochrane Central Register of Controlled Trials-267, EMBASE-322, CINAHL-183

1304 records duplicated

187 screened

52 full articles for eligibility

36 full articles excluded with reasons
- 16 Articles: BoTN controlled or dosage compared studies
- 13 Articles: no control
- 4: phenol and others comparative studies
- 3: other diagnosis than stroke (CP, MS, TBI)

16 full articles included

Jörg Wissel and Song-Jin Ri, Berlin 2016, unpublished data

Characteristics of Studies (Post-Stroke Population)

<table>
<thead>
<tr>
<th>Studies</th>
<th>Compared Intervention</th>
<th>Visit</th>
<th>outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roche et al 2015</td>
<td>Exercise</td>
<td>Before, at 1 mo</td>
<td>Maximal gait speed, Timed up and Go, 6MWT, Time to ascend stairs, Time to descend stairs</td>
</tr>
<tr>
<td>Ding et al 2015</td>
<td>AFO</td>
<td>Before, at 1, 3, 6 mos</td>
<td>CSI, FMA, BBS, FIM</td>
</tr>
<tr>
<td>Demetrios et al 2014</td>
<td>Exercise</td>
<td>Before, at 6, 12, 24 weeks</td>
<td>GAS, MAS, Gait speed, ArmA, Global assessment scale, Self-report burden</td>
</tr>
<tr>
<td>Douglas J et al, 2010</td>
<td>FES</td>
<td>Before, at 6, 12 weeks</td>
<td>ARAT, MALO, Motor Activity Log–Self-Report</td>
</tr>
<tr>
<td>Sun et al 2010</td>
<td>CIMT</td>
<td>at Baseline, 1, 3, 6 mos</td>
<td>MAS (0-5), MAL (Motor Activity Log), AOU scale (0-5), QOM scale (0-5), ARAT</td>
</tr>
<tr>
<td>Karadag-Saygi et al 10</td>
<td>Taping</td>
<td>At baseline, 2 weeks, 1.3,6mos</td>
<td>MAS, passive ankle dorsiflexion, gait velocity, and step length</td>
</tr>
<tr>
<td>Lai et al 2009</td>
<td>Splint</td>
<td>Before, at 1, 14 weeks</td>
<td>AROM, MAS</td>
</tr>
</tbody>
</table>

Jörg Wissel and Song-Jin Ri, Berlin 2016, unpublished data
### Studies Compared

<table>
<thead>
<tr>
<th>Studies</th>
<th>Intervention</th>
<th>Visit</th>
<th>outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farina et al 2008</td>
<td>Casting</td>
<td>Before, at 2, 4 mos</td>
<td>static and dynamic baro-podometry, MAS, 10m walking test</td>
</tr>
<tr>
<td>Bayram et al 2006</td>
<td>ES</td>
<td>before and 2, 4, 8, and 12 wks</td>
<td>resting position angle, ankle P-, A-ROM, MAS, 10 m walking 10 m, clonus score, Brace Wear Scale, Global Assessment of Spasticity Scale</td>
</tr>
<tr>
<td>Reiter et al 1998</td>
<td>Taping</td>
<td>Before, at 1, 3 mos</td>
<td>Ankle ROM, MAS, gait velocity, step length</td>
</tr>
<tr>
<td>Hesse et al 1998</td>
<td>ES</td>
<td>Before, at 2, 6 and 12 weeks</td>
<td>MAS, limb position at rest and difficulties encountered during 3 upper limb motor tasks</td>
</tr>
<tr>
<td>Hesse et al 1995</td>
<td>ES</td>
<td>before and 4 weeks</td>
<td>muscle tone, gait velocity, stride length, stance- and swing-symmetry</td>
</tr>
<tr>
<td>Carda et al 2011</td>
<td>Taping, casting,</td>
<td>At baseline, 20, 90 days</td>
<td>MAS, ROM, 6m-, 10m- walking test, Functional Ambulation Categories, ankle dorsiflexor strength</td>
</tr>
<tr>
<td>Baricich et al 2008</td>
<td>ES, Taping,</td>
<td>At baseline, 10, 20, 90 days</td>
<td>MAS, ankle PROM: muscle action potential at the gastrocnemius medialis, max. ankle dorsiflexion angle in stance using gait analysis</td>
</tr>
<tr>
<td>Santamato et al 2015</td>
<td>Stretching,</td>
<td>At baseline, 2 weeks, 1mos</td>
<td>MAS, Disability Assessment Scale, and fingers position at rest</td>
</tr>
<tr>
<td>Santamato et al 2013</td>
<td>ES/T, ES</td>
<td>At baseline, 15, 30, 90 days</td>
<td>MAS, VAS</td>
</tr>
</tbody>
</table>

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### Results: Post-Stroke Population

**Combined BoNT A and Rehabilitation Intervention Strategies**

**Measurement at <1 Month**

#### 1) MAS

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>Experimental SD</th>
<th>Total Mean</th>
<th>Total SD</th>
<th>Control Mean</th>
<th>Control SD</th>
<th>Total Mean</th>
<th>Total SD</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anne M. Lai-10</td>
<td>-1.73 ± 1.34</td>
<td>0.46</td>
<td>0.22</td>
<td>0.15</td>
<td>0.46</td>
<td>0.07</td>
<td>0.22</td>
<td>0.15</td>
<td>-0.37 [-0.47, -0.27]</td>
<td>-0.37 [-0.47, -0.27]</td>
</tr>
<tr>
<td>Martin Dementheo-2014-2</td>
<td>-1.07 ± 0.67</td>
<td>0.46</td>
<td>0.22</td>
<td>0.15</td>
<td>0.46</td>
<td>0.07</td>
<td>0.22</td>
<td>0.15</td>
<td>-0.37 [-0.47, -0.27]</td>
<td>-0.37 [-0.47, -0.27]</td>
</tr>
<tr>
<td>Shifin Enr7</td>
<td>2.5 ± 0.65</td>
<td>0.46</td>
<td>0.22</td>
<td>0.15</td>
<td>0.46</td>
<td>0.07</td>
<td>0.22</td>
<td>0.15</td>
<td>-0.37 [-0.47, -0.27]</td>
<td>-0.37 [-0.47, -0.27]</td>
</tr>
<tr>
<td>Simona Farina-12</td>
<td>-2.41 ± 2.34</td>
<td>0.46</td>
<td>0.22</td>
<td>0.15</td>
<td>0.46</td>
<td>0.07</td>
<td>0.22</td>
<td>0.15</td>
<td>-0.37 [-0.47, -0.27]</td>
<td>-0.37 [-0.47, -0.27]</td>
</tr>
<tr>
<td>Della Hers-17</td>
<td>-0.33 ± 0.26</td>
<td>0.46</td>
<td>0.22</td>
<td>0.15</td>
<td>0.46</td>
<td>0.07</td>
<td>0.22</td>
<td>0.15</td>
<td>-0.37 [-0.47, -0.27]</td>
<td>-0.37 [-0.47, -0.27]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>70</td>
<td></td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.50</td>
<td>0.46</td>
<td>0.07</td>
<td>-0.37 [-0.47, -0.27]</td>
<td>-0.37 [-0.47, -0.27]</td>
</tr>
</tbody>
</table>

**Heterogeneity (Cochran’s CH² = 0.10; df = 4; P = 0.86; I² = 0%)**

**Test for overall effect: Z = 4.13 (P = 0.000)**

**Favours [experimental] Favours [control]**

#### 2) Action Research Arm Test

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Computational Mean</th>
<th>Computational SD</th>
<th>Total Mean</th>
<th>Total SD</th>
<th>Control Mean</th>
<th>Control SD</th>
<th>Total Mean</th>
<th>Total SD</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Douglas J. Weber-6</td>
<td>6.63 ± 2.06</td>
<td>0.46</td>
<td>13</td>
<td>3.04</td>
<td>0.00</td>
<td>[0.77, 2.67]</td>
<td>13</td>
<td>3.04</td>
<td>0.00 [-0.69, 1.00]</td>
<td>0.00 [-0.69, 1.00]</td>
</tr>
<tr>
<td>Shifin Enr7</td>
<td>3.9 ± 0.36</td>
<td>0.46</td>
<td>0.22</td>
<td>0.15</td>
<td>0.46</td>
<td>0.07</td>
<td>0.22</td>
<td>0.15</td>
<td>-0.37 [-0.47, -0.27]</td>
<td>-0.37 [-0.47, -0.27]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>9.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>-0.37 [-0.47, -0.27]</td>
<td>-0.37 [-0.47, -0.27]</td>
</tr>
</tbody>
</table>

**Heterogeneity (Cochran’s CH² = 0.33; df = 1; P = 0.53; I² = 0%)**

**Test for overall effect: Z = 1.78 (P = 0.08)**

---

**Jörg Wissel and Song-Jin Ri, Berlin 2016, unpublished data**
1) MAS

Combined BoNT A and Rehabilitation intervention strategies
Measurement at 3 Months

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Jinny M. Lai 10</td>
<td>-0.43</td>
<td>0.38</td>
<td>15</td>
<td>-0.33</td>
</tr>
<tr>
<td>Minsoo Chemtob-2014-2</td>
<td>-0.8</td>
<td>0.6</td>
<td>20</td>
<td>-0.3</td>
</tr>
<tr>
<td>Shu-Fan Sun-7</td>
<td>-1.8</td>
<td>0.4</td>
<td>15</td>
<td>-1.4</td>
</tr>
<tr>
<td>Simon Fano-12</td>
<td>-0.56</td>
<td>0.34</td>
<td>6</td>
<td>0.43</td>
</tr>
<tr>
<td>Stefan Hesman-17</td>
<td>-1.17</td>
<td>0.31</td>
<td>6</td>
<td>-0.17</td>
</tr>
<tr>
<td><strong>Total (95%) CI</strong></td>
<td>70</td>
<td>74</td>
<td>100.0%</td>
<td>-0.36 [-0.52, -0.00]</td>
</tr>
</tbody>
</table>

Chi² test: $p = 0.08$; df = 4; $p = 0.75$.

2) Action Research Arm Test

Jörg Wissel and Song-Jin Ri, Berlin 2016, unpublished data

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Douglas J. Weber-6</td>
<td>4</td>
<td>2.4</td>
<td>10</td>
<td>5.87</td>
</tr>
<tr>
<td>Shu-Fan Sun-7</td>
<td>1.3</td>
<td>0.5</td>
<td>15</td>
<td>3.1</td>
</tr>
<tr>
<td><strong>Total (95%) CI</strong></td>
<td>25</td>
<td>27</td>
<td>100.0%</td>
<td>0.04 [1.50, 1.50]</td>
</tr>
</tbody>
</table>

Chi² test: $p = 0.08$; df = 1; $p = 0.91$.

3) Motor Activity Log

Jörg Wissel and Song-Jin Ri, Berlin 2016, unpublished data

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Douglas J. Weber-6</td>
<td>0.35</td>
<td>0.14</td>
<td>10</td>
<td>0.24</td>
</tr>
<tr>
<td>Shu-Fan Sun-7</td>
<td>1.1</td>
<td>0.5</td>
<td>15</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Total (95%) CI</strong></td>
<td>25</td>
<td>27</td>
<td>100.0%</td>
<td>0.22 [0.12, 0.32]</td>
</tr>
</tbody>
</table>

Chi² test: $p = 0.08$; df = 1; $p = 0.97$.

Combined BoNT A and Rehabilitation Intervention Strategies
Measurement at 6 Months

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Minsoo Chemtob-2014-2</td>
<td>-0.1</td>
<td>0.7</td>
<td>20</td>
<td>-3.3</td>
</tr>
<tr>
<td>Shu-Fan Sun-7</td>
<td>-1.1</td>
<td>0.9</td>
<td>15</td>
<td>-1.4</td>
</tr>
<tr>
<td><strong>Total (95%) CI</strong></td>
<td>43</td>
<td>45</td>
<td>100.0%</td>
<td>0.00 [0.26, 0.26]</td>
</tr>
</tbody>
</table>

Chi² test: $p = 0.05$; df = 1; $p = 0.37$.

Jörg Wissel and Song-Jin Ri, Berlin 2016, unpublished data.
Stretching compared with other interventions following BoNT A injections

1) Early effect (MAS) at 1 month

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alessio Barlitch et al 2008</td>
<td>-1.25</td>
<td>0.37</td>
<td>8</td>
<td>-0.57</td>
<td>0.39</td>
<td>7</td>
<td>2.0%</td>
<td>-0.68 [-1.07, -0.30]</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Alessio Barlitch et al 2008</td>
<td>-0.75</td>
<td>0.4</td>
<td>8</td>
<td>-0.57</td>
<td>0.39</td>
<td>7</td>
<td>1.8%</td>
<td>-0.18 [-0.60, 0.23]</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Andrea Santamato et al 2015</td>
<td>-1.6</td>
<td>0.14</td>
<td>35</td>
<td>-1.2</td>
<td>0.16</td>
<td>35</td>
<td>59.6%</td>
<td>-0.40 [-0.47, -0.33]</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Stefano Corda et al 2011</td>
<td>-2.5</td>
<td>0.14</td>
<td>27</td>
<td>-1.3</td>
<td>0.17</td>
<td>10</td>
<td>131.3%</td>
<td>-1.04 [-1.35, -0.73]</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Stefano Corda et al 2011</td>
<td>-1.4</td>
<td>0.2</td>
<td>24</td>
<td>-1.3</td>
<td>0.17</td>
<td>10</td>
<td>23.5%</td>
<td>-0.10 [-0.21, 0.01]</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>102</td>
<td>85</td>
<td>100.0%</td>
<td>0.44 [-0.49, 0.38]</td>
<td>---</td>
<td>---</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 137.76, df = 4 (P = 0.00001), I^2 = 97$
Test for overall effect: $Z = 15.70 (P < 0.00001)$

2) Late effect (MAS) at 3 month

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alessio Barlitch et al 2008</td>
<td>-1.38</td>
<td>0.25</td>
<td>8</td>
<td>-0.28</td>
<td>0.35</td>
<td>7</td>
<td>0.0%</td>
<td>-1.10 [-1.41, -0.79]</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Alessio Barlitch et al 2008</td>
<td>-1.22</td>
<td>0.28</td>
<td>8</td>
<td>-0.28</td>
<td>0.26</td>
<td>7</td>
<td>7.0%</td>
<td>-0.94 [-1.16, -0.72]</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Stefano Corda et al 2011</td>
<td>-2.3</td>
<td>0.35</td>
<td>27</td>
<td>-0.3</td>
<td>0.21</td>
<td>18</td>
<td>20.9%</td>
<td>-2.00 [-2.16, -1.84]</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Stefano Corda et al 2011</td>
<td>-0.9</td>
<td>0.17</td>
<td>24</td>
<td>-0.3</td>
<td>0.21</td>
<td>18</td>
<td>55.3%</td>
<td>-0.60 [-0.72, -0.48]</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>67</td>
<td>50</td>
<td>100.0%</td>
<td>-1.06 [-1.15, 0.08]</td>
<td>---</td>
<td>---</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 160.26, df = 3 (P = 0.00001), I^2 = 86$
Test for overall effect: $Z = 23.66 (P < 0.00001)$

Jörg Wissel and Song-Jin Ri, Berlin 2016, unpublished data

"Early versus Late Effects" of Rehabilitation Interventions following BoTN A injection in patients with Post Stroke Spasticity (PSS):
A Systematic Review

1. Rehabilitation interventions such as electrical stimulation, orthosis, various exercises and others following BoNT can increase efficacy of BoNT in reducing PSS (MAS) compared to BoNT alone, but functional assessments were not analysed because of different assessments (only 2 studies with ARAT and MAL).

2. Compared with simple stretching interventions, other rehabilitation interventions (e.g. casting, taping) can be of improvement following BoNT.

3. Efficacy within 3 months after BoNT was evident but only few information is published on long term effects eg. 6 months

Jörg Wissel and Song-Jin Ri, Berlin 2016, unpublished data
## Comparison of effects of Rehabilitation Intervention PLUS „Low dose BoNT“ versus „High dose BoNT“

### 1) Early effects (MAS) at 1 month

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frank Retter-16</td>
<td>-1.2</td>
<td>0.35</td>
<td>9</td>
<td>-1</td>
<td>0.33</td>
<td>9</td>
<td>9</td>
<td>42.7%</td>
<td>-0.20 [0.61, 0.11]</td>
</tr>
<tr>
<td>Suheda Baring-14</td>
<td>-0.5</td>
<td>0.2</td>
<td>6</td>
<td>-0.6</td>
<td>0.25</td>
<td>6</td>
<td>5</td>
<td>57.3%</td>
<td>0.10 [0.17, 0.037]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td>15</td>
<td>100.0%</td>
<td>-0.03 [-0.23, 0.16]</td>
</tr>
</tbody>
</table>

Heterogeneity: C2 = 7.01, df = 1 (P = 0.01), P = 50%
Test for overall effect Z = 0.27 (P = 0.76)

### 2) Late effects (MAS) at 3 month

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frank Retter-16</td>
<td>-1.33</td>
<td>0.2</td>
<td>9</td>
<td>-0.3</td>
<td>0.29</td>
<td>9</td>
<td>9</td>
<td>73.0%</td>
<td>-0.70 [-0.96, -0.41]</td>
</tr>
<tr>
<td>Suheda Baring-14</td>
<td>-0.2</td>
<td>0.2</td>
<td>6</td>
<td>-1</td>
<td>0.55</td>
<td>6</td>
<td>5</td>
<td>56.1%</td>
<td>1.20 [0.72, 1.68]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td>14</td>
<td>100.0%</td>
<td>-0.20 [-0.45, 0.04]</td>
</tr>
</tbody>
</table>

Total: C2 = 43.92, df = 1 (P < 0.00001), P = 0%
Test for overall effect Z = 1.62 (P = 0.10)

Jörg Wissel and Song-Jin Ri, Berlin 2016, unpublished data

## ESWT „shock wave“ compared with ES following BoNT injections

### 1) Early effect (MAS) at 1 month

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartolomeo A et al 2013</td>
<td>-2.13</td>
<td>0.18</td>
<td>16</td>
<td>-1.25</td>
<td>0.10</td>
<td>16</td>
<td>16</td>
<td>100.0%</td>
<td>-0.88 [-1.00, -0.76]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td>16</td>
<td>100.0%</td>
<td>0.88 [1.00, 0.76]</td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect Z = 13.86 (P < 0.00001)

### 2) Late effects (MAS) at 3 month

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartolomeo A et al 2013</td>
<td>-1.75</td>
<td>0.17</td>
<td>16</td>
<td>-1.44</td>
<td>0.16</td>
<td>16</td>
<td>16</td>
<td>100.0%</td>
<td>-0.31 [-0.42, -0.20]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td>16</td>
<td>100.0%</td>
<td>0.31 [0.42, 0.20]</td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect Z = 5.31 (P < 0.00001)

Jörg Wissel and Song-Jin Ri, Berlin 2016, unpublished data
Physical Treatment Adjunctive to BoNT A
Combining BoNT A injections and PT/ Activation of spasticity

\[ \text{PT} \quad n=20 \quad \text{+ stretching spastic muscles} \]
\[ \text{No PT} \quad n=18 \quad \text{... inducing activity in antagonistic muscles} \]

400 units BoNT A* in both groups (100 UE / 300 LL)

\* onabotulinumtoxinA
Giovannelli et al 2007

Vivantes is the biggest hospital chain of Germany located in one city: BERLIN – covering 30% of Berlin healthcare market

Departments of Neurological Rehabilitation & Physical Therapy
Vivantes North, Berlin, Germany
Spandau & Humboldt Hospital

- Vivantes 9 Hospitals in Berlin
- > 5,000 Beds
- Sales 2010 > 850 million €
- > 1,500 Physicians
- > 3,500 Nurses
- In total ca. 13,000 employees
- > 100 medical Departments
- 14 Nursing homes
- 1 Out-patient Rehab center
- Education and Training Facilities
- 200,000 In-patients/ Year
- 300,000 Out-patients/ Year

Source: Vivantes Corporate Development