TITLE: Botulinum Toxin for Spasticity: Clinical Effectiveness and Guidelines

DATE: 07 April 2016

RESEARCH QUESTIONS

1. What is the clinical effectiveness of botulinum toxin for spasticity in adults?

2. What are the clinical guidelines regarding the use of botulinum toxin for spasticity in adults?

KEY FINDINGS

Eight systematic reviews, five systematic reviews with meta-analyses, and 15 randomized controlled trials were identified regarding botulinum toxin for spasticity in adults. In addition, seven evidence-based guidelines were identified regarding the use botulinum toxin for spasticity in adults.

METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and March 23, 2016. Internet links were provided, where available.

The summary of findings was prepared from the abstracts of the relevant information. Please note that data contained in abstracts may not always be an accurate reflection of the data contained within the full article.
SELECTION CRITERIA

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Adults with spasticity in any setting; adults in long-term care (residential care homes are a subgroup of interest)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Botulinum toxin</td>
</tr>
<tr>
<td>Comparator</td>
<td>• No comparator</td>
</tr>
<tr>
<td></td>
<td>• Placebo</td>
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<td></td>
<td>• Alternate drug</td>
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<td></td>
<td>• Non-drug interventions (e.g., form of rehabilitation)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Q1: Effectiveness, clinical benefit or harm, safety</td>
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<td></td>
<td>Q2:</td>
</tr>
<tr>
<td></td>
<td>• Guidelines and recommendations for use and administration</td>
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<td></td>
<td>• Guidelines and recommendations for follow-up and management of patients receiving botulinum toxin</td>
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<td></td>
<td>• Guidelines and recommendations regarding which patients should receive botulinum toxin</td>
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<tr>
<td>Study Designs</td>
<td>Health technology assessment, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and evidence-based guidelines</td>
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</table>

RESULTS

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials and evidence-based guidelines.

Eight systematic reviews, five systematic reviews with meta-analyses, and 15 randomized controlled trials were identified regarding botulinum toxin for spasticity in adults. In addition, seven evidence-based guidelines were identified regarding the use botulinum toxin for spasticity in adults. No health technology assessments were identified, and non-randomized studies were not included due to the volume of systematic reviews and randomized controlled trials identified.

Additional references of potential interest are provided in the appendix.

OVERALL SUMMARY OF FINDINGS

Eight systematic reviews, five systematic reviews with meta-analyses, and 15 randomized controlled trials (RCTs) were identified regarding botulinum toxin for spasticity in adults.

Most of the systematic reviews, systematic reviews with meta-analysis, and the RCTs provided evidence regarding the efficacy and safety associated with botulinum toxin (types A, B, or unspecified) for the treatment of either lower limb and upper limb spasticity or both. Conversely, there were a few studies that did not observe benefits in patients with spasticity treated with botulinum toxin or observed weak benefits, however, these
studies did observe improvements in some other movements upon treatment. One systematic review recommended instrument-guided injections of botulinum toxin for spasticity treatment, another systematic review discussed the potential benefits of chemodenervation with botulinum toxin, while another systematic review focused on which muscles were used for injection and the effectiveness therein. Detailed study characteristics are provided in Table 2.

Table 2: Summary of Included Studies on Botulinum Toxin for Spasticity in Adults

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Study Characteristics</th>
<th>Botulinum Toxin-Type, Doses</th>
<th>Outcomes</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systematic Reviews and Meta-Analyses</strong></td>
<td></td>
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</tr>
<tr>
<td>Dashipour, 2016¹</td>
<td>• SR • 6 RCTs included • LL spasticity in various etiologies</td>
<td>• ABO-BTX-A • 500-2000 U (range)</td>
<td>• Efficacy • Safety • Dosing practices</td>
<td>• All studies showed statistically significant reduction in muscle tone • Generally well tolerated with most AEs considered un-related to tmt</td>
</tr>
<tr>
<td>Baker, 2015²</td>
<td>• SR and MA • LL spasticity • 12 PL-controlled RCTs included; various etiologies • MA of 6 UL and 6 LL studies</td>
<td>• BTX-A • One dose (NR)</td>
<td>• Relating to leg/arm spasticity • Active function measures • QoL measures</td>
<td>• BTX-A may improve active outcomes in UL</td>
</tr>
<tr>
<td>Baker, 2015²</td>
<td>• SR and MA • Ease of care in UL and LL • 32 PL-controlled RCTs included • MA of 11 UL and 3 LL studies</td>
<td>• BTX-A • Dose NR</td>
<td>• Efficacy regarding improving ease of care</td>
<td>• BTX-A improves ease of care in UL for up to 6 months • No conclusions possible for LL</td>
</tr>
<tr>
<td>Dashipour, 2015³</td>
<td>• SR • Tmt of UL spasticity • 12 RCTs included</td>
<td>• ABO-BTX-A • 500 – 1500 U (range)</td>
<td>• Efficacy • Safety • Dosing practices</td>
<td>• Strong evidence to support use of ABO for UL spasticity in stroke • ABO generally well tolerated with most AEs considered un-related to tmt</td>
</tr>
<tr>
<td>Grigoriiu, 2015⁴</td>
<td>• SR • Tmt of BTX-A on focal spasticity and dystonia • 10 studies included (7 RCTs)</td>
<td>• BTX-A • Dose NR</td>
<td>• Effectiveness of instrument guided BTX-A in focal spasticity and dystonia</td>
<td>• Results strongly recommend instrument guidance (ES or US) of BTX-A for spasticity tmt in adults and for tmt of focal dystonia such as spasmodic torticollis (EMG)</td>
</tr>
<tr>
<td>Baker, 2013⁵</td>
<td>• SR and MA • 37 studies included • MA on 21 for spasticity</td>
<td>• BTX-A • Dose NR</td>
<td>• Efficacy of BTX-A on spasticity</td>
<td>• Use of BTX-A for UL and LL spasticity is supported by moderate quality evidence</td>
</tr>
<tr>
<td>Foley, 2013⁶</td>
<td>• SR and MA • Post-stroke spasticity in UL • 16 RCTs (10 RCTs included in pooled</td>
<td>• BTX-A • Dose NR</td>
<td>• UL activity capacity or performance</td>
<td>• BTX-A associated with moderate UL activity capacity or performance</td>
</tr>
<tr>
<td>First Author, Year</td>
<td>Study Characteristics</td>
<td>Botulinum Toxin-Type, Doses</td>
<td>Outcomes</td>
<td>Conclusions</td>
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<tr>
<td>Intiso, 2013⁹</td>
<td>SR</td>
<td>BTX-A, Dose NR</td>
<td>Efficacy</td>
<td>Global functionality of activity daily living</td>
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<td></td>
<td>Post-stroke spasticity</td>
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<tr>
<td></td>
<td>16 RCTs included</td>
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<tr>
<td>Nalysnyk, 2013³</td>
<td>SR</td>
<td>ABO, Dose NR</td>
<td>Injection patterns</td>
<td>Most frequent muscles injected with ABO were wrist, elbow, finger flexors, and ankle plantar flexors</td>
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<tr>
<td></td>
<td>Adults with spasticity</td>
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<tr>
<td></td>
<td>70 studies included (28 RCTs, 5 NRS, 37 single-arm)</td>
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<tr>
<td>McIntyre, 2012⁰</td>
<td>SR</td>
<td>BTX-A, Dose NR</td>
<td>Effectiveness</td>
<td>Effective in reducing LL spasticity when initiated 6 months post-stroke</td>
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<td></td>
<td>BTX-A for reducing spasticity of LL in chronic stroke survivors</td>
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<td></td>
<td>9 RCTs included (n=605)</td>
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<tr>
<td>Wu, 2016¹¹</td>
<td>SR and MA</td>
<td>BTX: unspecified type, Dose NR</td>
<td>Effectiveness</td>
<td>BTX showed persistent clinical benefits in LL spasticity and Fugl-Meyer score</td>
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<td></td>
<td>LL spasticity in stroke</td>
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<td></td>
<td>7 RCTs (n=603) compared against PL or conventional therapy</td>
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<tr>
<td>Lui, 2015²¹</td>
<td>SR</td>
<td>BTX: unspecified type, Dose NR</td>
<td>Efficacy of chemodenervation</td>
<td>Chemodenervation with BTX may improve function and spasticity in patients with SCI</td>
</tr>
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<td></td>
<td>Limb spasticity after SCI</td>
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<td></td>
<td>19 studies included (9 involving BTX; 10 involving phenol/alcohol)</td>
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<tr>
<td>Phadke, 2014⁴⁴</td>
<td>SR</td>
<td>BTX: unspecified type, Dose NR</td>
<td>Impact of BTX treated spasticity on standing balance</td>
<td>Weak evidence for balance changes in post-stroke patients following BTX tmt</td>
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<tr>
<td></td>
<td>Spasticity post-stroke</td>
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<tr>
<td></td>
<td>Number of included studies NR</td>
<td></td>
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<tr>
<td>Randomized Controlled Trials</td>
<td></td>
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<tr>
<td>Elovic, 2016⁵⁵</td>
<td>PL-controlled</td>
<td>Inco-BTX-A, 1:1 400 U or PL</td>
<td>Efficacy</td>
<td>Tolerability</td>
</tr>
<tr>
<td></td>
<td>UL post-stroke spasticity</td>
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<tr>
<td></td>
<td>N=NR</td>
<td></td>
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<tr>
<td>Gracies, 2015¹⁵</td>
<td>DB, PL-controlled</td>
<td>ABO-BTX-A, 1:1:1 500 U, 1000 U, or PL</td>
<td>Efficacy in UL on muscle tone, spasticity, active movement, and function</td>
<td>ABO-BTX-A provided tone reduction and clinical benefit in hemiparesis</td>
</tr>
<tr>
<td></td>
<td>Patients 6 months post-stroke or post-brain injury</td>
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<td></td>
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<td>AEs were mild or</td>
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</tbody>
</table>
# Table 2: Summary of Included Studies on Botulinum Toxin for Spasticity in Adults

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<thead>
<tr>
<th>First Author, Year</th>
<th>Study Characteristics</th>
<th>Botulinum Toxin-Type, Doses</th>
<th>Outcomes</th>
<th>Conclusions</th>
</tr>
</thead>
</table>
| Nam, 2015<sup>16</sup> | DB, active comparator  
Post-stroke UL spasticity  
N=197  
O: NABOTA (n=99)  
O: ONA-BTX-A (n=98) | NABOTA  
ONA-BTX-A | Efficacy  
Safety | NABOTA was non-inferior in efficacy and safety for UL spasticity improvement compared to ONA-BTX-A |
| Seo, 2015<sup>17</sup> | Active comparator  
UL spasticity for stroke patients  
N=196 | Neuronox  
ONA-BTX-A | Efficacy  
Safety | Neuronox was equivalent to ONA-BTX-A with regard to efficacy and safety for treating UL spasticity in post-stroke patients |
| Tao, 2015<sup>18</sup> | PL-controlled  
Subacute stroke patients  
N=23  
O: BTX-A (n=11)  
O: PL (n=12) | Early, low dose electrical stimulation-guided BTX-A (200 U)  
PL | Gait improvement  
Spasticity improvement  
Improvement in daily living activities | Early low-dose BTX-A may improve gait, spasticity, and daily living activities |
| Fietzek, 2014<sup>19</sup> | DB, PL-controlled  
Patients with stroke, traumatic brain injury or hypoxic encephalopathy and spastic pes equinovarus (unilateral or bilateral)  
N=52 | ONA-BTX-A (230 U or 460 U)  
PL | Efficacy (muscular hypertonicity) | Given 3 months after lesions, ONA-BTX-A reduces muscular hypertonicity in spastic pes equines |
| Picelli, 2014<sup>20</sup> | Double active comparator  
Chronic stroke patients with spastic equinus  
N=NR | ONA-BTX-A  
Therapeutic ultrasound  
TENS | Efficacy | Results provide evidence that ONA-BTX-A is more effective for treating spasticity in this population that therapeutic ultrasound and TENS |
| Guarany, 2013<sup>21</sup> | DB, active comparator, crossover  
Patients with clinically meaningful spasticity  
N=57 | BTX-A (Botox[R])  
Prosigne[R] (new BTX serotype A) | Efficacy  
Safety | Both Botox[R] and Prosigne[R] are comparable in efficacy and safety for 3 month tmt of spasticity |
<p>| Yazdchi, | DB, active | BTX-A | Efficacy | In comparison with TZD, |</p>
<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Study Characteristics</th>
<th>Botulinum Toxin-Type, Doses</th>
<th>Outcomes</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>comparator • Post-stroke UL spasticity • N=68 o BTX-A (n=34) o TZD (n=34)</td>
<td>TZD</td>
<td>Safety</td>
<td>BTX-A was effective and safe in reducing post-stroke UL spasticity</td>
</tr>
<tr>
<td>Dunne, 2012</td>
<td>DB, PL-controlled • Post-stroke with plantarflexor overactivity • N=85 o ONA-BTX-A 200 U (n=28) o ONA-BTX-A 300 U (n=28) o PL (n=29)</td>
<td>ONA-BTX-A (at either 200 U or 300 U) o PL</td>
<td>Efficacy • Safety</td>
<td>ONA-BTX-A did not alter local spasticity at 12 weeks; however, it did reduce spasms and improve gait quality • No detectable differences between 2 doses • ONA-BTX-A was safe and well-tolerated</td>
</tr>
<tr>
<td>Rosales, 2012</td>
<td>PL-controlled • Asian patients with post-stroke patients with UL spasticity • N=163 o BTX-A (n=80) o PL (n=93)</td>
<td>Very early use of: o BTX-A (500 U) o PL</td>
<td>Effectiveness • Safety</td>
<td>BTX-A 500 U, within 2-12 weeks of stroke) provided sustained reduction in UL spasticity when combined with rehabilitation in patients with mild-to-moderate hypertonicity and voluntary movement • No differences in AS observed</td>
</tr>
<tr>
<td>Shaw, 2011</td>
<td>4 week therapy-controlled • Post-stroke patients with spasticity • N=333</td>
<td>BTX-A + 4-week therapy o 4-week therapy</td>
<td>Impairment • Activity limitation • Pain</td>
<td>BTX-A unlikely to be useful for spasticity post-stroke; however, may improve basic upper limb tasks and pain</td>
</tr>
<tr>
<td>Gracies, 2014</td>
<td>DB, PL-controlled • Post-stroke or traumatic brain injury hemiparetic patients with spastic UL muscles • N=24</td>
<td>Rima-BTX-B (10,000 U or 15,000 U) o PL</td>
<td>Efficacy • Safety</td>
<td>Rima-BTX-B (up to 15,000 U) improved active elbow extension and subject-perceived stiffness when injected into spastic UL muscles • Rima-BTX-B was well tolerated</td>
</tr>
<tr>
<td>Bollens, 2013</td>
<td>SB, active comparator • Chronic stroke patients with spastic equinovarus of the foot • N=16 o Selective tibial neurotomy (n=8) o BTX (n=8)</td>
<td>Selective tibial neurotomy o BTX unspecified</td>
<td>Effectiveness</td>
<td>Higher reduction in ankle stiffness was observed with selective tibial neurotomy • Both tmts induced improvement of ankle kinematics during gait • Neither induced muscle weakening</td>
</tr>
<tr>
<td>Lam, 2012</td>
<td>DB, PL-controlled • Long-term care patients • N=55</td>
<td>BTX-A o PL</td>
<td>Primary outcome: decrease of care burden • Secondary</td>
<td>Patients treated with BTX-A had significant decrease in care burden • Improved scores on</td>
</tr>
</tbody>
</table>
Of the seven identified guidelines containing information on the use of botulinum toxin for spasticity in adults, three provided recommendations regarding its use in patients with acute or post-acute stroke,\textsuperscript{30,32,35} two provided statements regarding the lack of recommendations in patients with multiple sclerosis (MS),\textsuperscript{31,34} one guideline provided recommendations for patients with motor neuron disease (MND),\textsuperscript{33} and the last guideline provided a statement for making no recommendation for the use of botulinum toxin in patients with MND.\textsuperscript{29}

For patients who have suffered a stroke, Health Quality Ontario and the Ministry of Health and Long-Term Care recommends the use of \textit{Clostridium botulinum} toxin to, a) relieve spasticity when is causes pain or interferes with physical functioning or the maintenance of hand hygiene, b) treat hemiplegic shoulder pain thought to occur due to spasticity (by injecting into the subscapularis and pectoralis muscles), c) relieve pain related to both spasticity and inflammation or injury in a subset of patients experiencing both (and as dual therapy with steroidal injections), and d) treat focal spasticity and/or symptomatically distressing spasticity of the lower extremities in order to decrease pain, to improve gait, and to increase the patient’s range of motion (specifically relates to botulinum toxin A).\textsuperscript{30} The Heart and Stroke Foundation (HSF) echoes the aforementioned recommendation to chemodenervate using botulinum toxin in order to both decrease pain and increase range of motion in patients with focal and/or symptomatically distressing spasticity in the shoulder, arm, or hand.\textsuperscript{32} In addition to being beneficial in decreasing pain and increasing range of motion, the HSF also recommends the use of botulinum toxin for improving gait in patients with lower limb focal and/or symptomatically distressing spasticity.\textsuperscript{32} The Royal College of Physicians’ Intercollegiate Stroke Working Party\textsuperscript{35} recommends the use of intramuscular botulinum toxin in patients with progressing or persistent troublesome focal spasticity affecting one or more joints and who have an identifiable therapeutic goal. Botulinum toxin should be provided in the context of a specialist multidisciplinary team service (including rehabilitation or physical maintenance therapy) over two to 12 weeks post-injection, with a subsequent functional assessment provided three to four months post-injection.\textsuperscript{35}

For patients with MS, the National Institute for Health and Care Excellence (NICE) did not make specific recommendations regarding the use of botulinum toxin for the treatment of spasticity.\textsuperscript{31} Instead, they provided a statement affirming that it may have a place for use in patients with severe spasticity or complications from their spasticity under the care of specialized services.\textsuperscript{31} The Spanish Society of Neurology\textsuperscript{34} also have stated that botulinum toxin A may be required in
selected cases of patients with MS; however, they did not provide any specific recommendations regarding its use for the treatment of spasticity.

For patients with MND, Esquenazi et al.\textsuperscript{33} recommends the use of botulinum neurotoxin type A, Abo-A, and Ona-A (Level A evidence), and Inco-A (Level B evidence) for the treatment of upper limb spasticity. For lower limb spasticity, Esquenazi et al.\textsuperscript{33} recommends the use of botulinum neurotoxin Ona-A and Type A in aggregate (Level A), and Abo-A (Level C); however, there was insufficient identified evidence to recommend either Inco-A or Rima-B (a form of botulinum neurotoxin type B). While NICE\textsuperscript{29} made no specific recommendations regarding the use of botulinum toxin in patients with MND, they did state that patients may benefit from receiving botulinum toxin from a specialist for focal spasticity when they are not responding to other treatments.
REFERENCES SUMMARIZED

Health Technology Assessments
No literature identified.

Systematic Reviews and Meta-analyses

Botulinum Toxin A

PubMed: PM26765447

PubMed: PM26150020

PubMed: PM25352614

PubMed: PM25299523

PubMed: PM25982240

PubMed: PM23864518

PubMed: PM23262381


Unspecified Botulinum Toxin Type


Randomized Controlled Trials

Botulinum Toxin A


Botulinum Toxin B


Unspecified Botulinum Toxin


Long-Term Care Specified


Guidelines and Recommendations

See: Section on Muscle stiffness, page 194
   See: Section 9.40.1, pages 76 and 125
   Section 9.47.4, pages 78 and 127
   Section 9.47.6, pages 78 and 127
   Section 9.54.1, pages 80 and 129

   See: Section 9 Pharmacological management of MS symptoms, page 124
   Table 48: Clinical evidence profile: Botulinum versus placebo, pages 149-151
   Botulinum versus placebo, page 166
   Botulinum Toxin not recommended, page 169

   See 5.5.2 page 43, 5.6.2 page 53

   PubMed: PM23220492

   PubMed: PM24289845

   See: Section 6.10 Impaired tone – spasticity and spasms and Recommendations 6.10.1, page 87
APPENDIX – FURTHER INFORMATION:

Previous CADTH Reports


Randomized Controlled Trials – Injection Site or Technique Comparisons


Clinical Practice Guidelines – Unspecified Methodology

See pages 32, 57


See pages 86-87 e.


PubMed: PM21847327

Management Pathway


Botulinum Toxin for Spasticity 15