



Review

Evidence-based review and assessment of botulinum neurotoxin for the treatment of adult spasticity in the upper motor neuron syndrome



Alberto Esquenazi^{a,*}, Alberto Albanese^b, Michael B. Chancellor^c,
Elie Elovic^d, Karen R. Segal^e, David M. Simpson^f, Christopher P. Smith^g,
Anthony B. Ward^h

^a MossRehab & Albert Einstein Medical Center, 60 Township Line Rd., Elkins Park, PA 19027, USA

^b Istituto Nazionale Neurologico Carlo Besta, Università Cattolica del Sacro Cuore, Fondazione IRCCS Istituto Neurologico Carlo Besta, Via G. Celoria, 1120133 Milano, MI, Italy

^c Oakland University, William Beaumont School of Medicine, Department of Urology, William Beaumont Hospital, 3535 W. 13 Mile Rd. #404, Royal Oak, MI 48073, USA

^d Salt Lake City, UT, USA

^e 10 West 66 Street, New York, NY 10023, USA

^f Clinical Neurophysiology Laboratories, Neuromuscular Division, Neuro-AIDS Program, Mount Sinai Medical Center, One Gustave Levy Place, Box 1052, New York, NY 10029, USA

^g Scott Department of Urology, Baylor College of Medicine, 6620 Main Street, Suite 1325, Houston, TX 77030, USA

^h North Staffordshire Rehabilitation Centre, Haywood Hospital/University Hospital on North Staffordshire, Hartshill Rd., Stoke on Trent ST4 7PA, United Kingdom

ARTICLE INFO

Article history:

Received 18 June 2012

Received in revised form 27 November 2012

Accepted 29 November 2012

Available online 5 December 2012

Keywords:

Botulinum neurotoxin

Adult spasticity

Upper motor neuron syndrome

Upper limb spasticity

Lower limb spasticity

Evidence-based review

ABSTRACT

Botulinum neurotoxin (BoNT) can be injected to achieve therapeutic benefit across a large range of clinical conditions. To assess the efficacy and safety of BoNT injections for the treatment of spasticity associated with the upper motor neuron syndrome (UMNS), an expert panel reviewed evidence from the published literature. Data sources included English-language studies identified via MEDLINE, EMBASE, CINAHL, Current Contents, and the Cochrane Central Register of Controlled Trials. Evidence tables generated in the 2008 Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (AAN) review of the use of BoNT for autonomic disorders were also reviewed and updated. The panel evaluated evidence at several levels, supporting BoNT as a class, the serotypes BoNT-A and BoNT-B, as well as the four individual commercially available formulations: abobotulinumtoxinA (A/Abo), onabotulinumtoxinA (A/Ona), incobotulinumtoxinA (A/Inco), and rimabotulinumtoxinB (B/Rima). The panel ultimately made recommendations on the effectiveness of BoNT for the management of spasticity, based upon the strength of clinical evidence and following the AAN classification scale. While the prior report by the AAN provided recommendations for the use of BoNT as a class of drug, this report provides more detail and includes recommendations for the individual formulations. For the treatment of upper limb spasticity, the evidence supported a Level A recommendation for BoNT-A, A/Abo, and A/Ona, with a Level B recommendation for A/Inco; there was insufficient evidence to support a recommendation for B/Rima. For lower limb spasticity, there was sufficient clinical evidence to support a Level A recommendation for A/Ona individually and BoNT-A in aggregate; the clinical evidence for A/Abo supported

* Corresponding author. Department of PM&R, MossRehab & Albert Einstein Medical Center, Gait & Motion Analysis Laboratory, 60 Township Line Rd., Elkins Park, PA 19027, USA.

E-mail address: aesquena@einstein.edu (A. Esquenazi).

a Level C recommendation; and there was insufficient information to recommend A/Inco and B/Rima (Level U). There is a need for further comparative effectiveness studies of the available BoNT formulations for the management of spasticity.

© 2013 Elsevier Ltd. All rights reserved.

1. Introduction

The motor behavior of patients with an upper motor neuron syndrome (UMNS) is characterized by highly variable mixtures of impaired voluntary movement control (negative signs of UMNS) combined with behaviors of involuntary muscle contraction (positive signs of UMNS). Spasticity is characterized by excess muscle tone and exaggerated tendon jerks occurring as part of the UMNS. Spasticity occurs commonly in a variety of diseases and conditions including cerebral palsy (CP), spinal cord or traumatic brain injury, multiple sclerosis, and as a consequence of stroke. Within these populations, spasticity is estimated to affect approximately 17%–38% (Lundstrom et al., 2008; Sommerfeld et al., 2004; Watkins et al., 2002; Welmer et al., 2006) of patients with stroke, 17%–53% of patients with multiple sclerosis (Barnes et al., 2003; Goodin, 1998; Rizzo et al., 2004), 40%–78% of those with spinal cord injury (Anson and Shepherd, 1996; Johnson et al., 1998; Maynard et al., 1990; Noreau et al., 2000; Skold et al., 1999; Walter et al., 2002), and as many as 34% of patients with traumatic brain injury (Wedekind and Lippert-Gruner, 2005).

Patients affected by UMNS are at risk of developing contractures and painful limb deformities. These are caused by combinations of voluntary and involuntary motor behaviors that produce a net balance of forces to promote stereotypic patterns of movements and posture, such as the flexed elbow, the clenched fist, and the equinovarus foot. The literature describes a number of UMNS patterns commonly observed by clinicians (Barnes et al., 2010; Brashear et al., 2004; Hesse et al., 1998; Kaji et al., 2010b; Smith et al., 2000) that often lead to problems of passive and active function or symptoms (Esquenazi and Mayer, 2004).

Clinical treatment strategies have focused on modifying the degree of muscle imbalance that characterizes these UMNS patterns, with a predominant emphasis on weakening the contractile effects of involuntary muscle overactivity within a given pattern. In simple terms, the principal objective of spasticity management is to reduce muscle overactivity and prevent irreversible soft-tissue changes and tendon contractures by maintaining muscle length and normalizing limb positioning.

Treatment options range from conservative to interventional measures, including physical and occupational therapies, oral and intrathecal medications, surgery, and focal chemical denervation with phenol, alcohol, and botulinum neurotoxin (BoNT) (Mayer and Esquenazi, 2003; Sheean, 2003). The choice of therapy is dictated by the duration and severity of disease, including the number of limb segments affected. The management of spasticity aims to meet individual patient needs with the overall goal of achieving enhanced functional capacity with the fewest adverse effects.

The use of BoNT to manage spasticity encompasses a wide range of underlying neuromuscular disorders. This

review will evaluate the evidence for the therapeutic application of BoNT to upper and lower limb spasticity in adults caused by stroke, multiple sclerosis, and spinal cord or brain injury. In general, the therapeutic benefit of BoNT in spasticity derives from its inhibitory actions on muscular contraction by blocking the release of the neurotransmitter acetylcholine at the neuromuscular junction (Sheean, 2003). Accordingly, the primary effect of BoNT is relaxation of the affected muscle. Recovery at the neuromuscular junction occurs a few weeks postinjection, and within 3–6 months postinjection, the neuromuscular junction function returns to the preinjection level (Sheean, 2003).

1.1. Objectives

The aim of this review of evidence is to assess the effectiveness of interventions involving injections of BoNT for the treatment of spasticity; the intent is to evaluate not only BoNT as a class but also individual BoNT formulations when the evidence allows. Two BoNT serotypes (A and B) are approved by the Food and Drug Administration (FDA) for clinical use in the United States and some countries in the European Union. Approved BoNT-A formulations are onabotulinumtoxinA (A/Ona; Allergan, Inc.), abobotulinumtoxinA (A/Abo; Ipsen Limited), and incobotulinumtoxinA (A/Inco; Merz Pharmaceuticals); the only approved BoNT-B formulation is rimabotulinumtoxinB (B/Rima; Solstice Neurosciences, LLC). These agents are marketed under the brand names Botox®, Dysport®, Xeomin®, and Myobloc® (Neurobloc® in Europe), respectively. In the United States, only onabotulinumtoxinA is FDA-approved for the treatment of spasticity, and only for the upper extremity. The use of other formulations and treatment of lower limb spasticity is considered “off label” in the United States.

2. Methods

2.1. Criteria for considering studies for this review

2.1.1. Types of studies

All studies comparing BoNT injection or BoNT injection plus other pharmacologic and nonpharmacologic therapies to placebo, no treatment, or active comparators or studies comparing doses of BoNT were considered.

2.1.2. Types of subjects

Adults with upper extremity or lower extremity spasticity and muscle overactivity within the selected diagnosis were included.

2.1.3. Types of interventions

Comparisons of BoNT injection to placebo, BoNT injection to other interventions, and different formulations/doses of BoNT were included.

Separate evidence tables were created for assessments of 1) effectiveness (placebo-controlled studies), 2) comparative effectiveness (active-controlled studies or multiple dose comparisons), and 3) methodology, defined as studies comparing different modes of administration including location, forms of guidance for injection, and non-pharmacologic treatments.

2.1.4. Types of outcome measures

From the reviewed literature, a variety of outcome measures were identified by the review authors as potential measures of effectiveness, taking into account the relevance of the outcomes to the disease/disorder of interest. Outcome measures could include variables related to body functions and body structures, and patient- and/or investigator-reported outcomes such as health-related quality of life and perceived improvements.

2.2. Search methods for identification of studies

The following terms were used to search several databases including MEDLINE, EMBASE, CINAHL, Current Contents, and the Cochrane Controlled Trials Register. In addition, clinicaltrials.gov was searched for additional studies that may not have been indexed in the former databases as of the cutoff data for inclusion (March 1, 2011). Only English-language articles were considered. Articles that were included were fully published (i.e., online and in print) or available as full text online. The search terms used were *botulinum toxin* (see below) and terms relevant to specific disorders of interest. In addition to the search terms for BoNT and those specific to each of the selected therapeutic interventions, the following criteria were considered: 1) relevance to the clinical questions of efficacy, safety, tolerability, or mode of use; 2) limited to human subjects; 3) limited to therapeutic studies. Mechanistic studies, abstracts, reviews, and meta-analyses were excluded as primary sources; however, publications of these types were searched manually for possible primary studies not detected by database searches.

The following search strategy was adapted as needed to accommodate the particulars of each of the databases:

1. Botulinum toxin/
2. Botulinum neurotoxin/
3. BoNT/
4. Botulinum toxin type a/
5. Botulinum toxin type b/
6. Botulin\$.tw
7. Botox.tw
8. Dysport.tw
9. Myobloc; Neurobloc
10. Xeomin; NT201
11. Onabotulinum
12. Rimabotulinum
13. Incobotulinum
14. Abobotulinum
15. Or/1–14

In addition, the result of the BoNT search was filtered with search terms relevant to the disease/disorder of

interest. The current article reviews the use of BoNT for upper- and lower-limb spasticity in adults. The following search terms were used to identify trials:

1. Spasticity; spastic paresis
2. Stroke; cerebrovascular accident
3. Upper extremity; upper limb
4. Lower extremity; lower limb
5. Traumatic brain injury
6. Spinal cord injury
7. Multiple sclerosis
8. Or/1–7

2.3. Data collection and analysis

2.3.1. Selection of trials

Evidence tables were obtained that had been generated in the 2008 Report of the Therapeutics and Technology Assessment (TTA) Subcommittee of the American Academy of Neurology (AAN) review of the use of BoNT for spasticity (Simpson et al., 2008). The literature search described above was conducted to update and expand the database and topics of inclusion, intending to capture all studies published since the TTA project.

2.3.2. Quality of trials

A centralized review staff evaluated the methodologic quality of the included trials according to a modification of the AAN quality of evidence scale classification. Studies previously classified by the TTA and identified in the present review as possibly requiring revised classification were separated for reassessment. Both the group of newly identified studies and the group of TTA studies for reassessment received second reviews by members of the expert panel. Differences of opinion were resolved by panel consensus.

The AAN Classification (see AAN Classification of evidence for therapeutic intervention on the Neurology Web site at <http://www.aan.com/globals/axon/assets/2371.pdf>) is shown below:

AAN Classification of Quality of Evidence for Clinical Trials.

Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population.

The following are required:

- a. Primary outcome(s) clearly defined
- b. Exclusion/inclusion criteria clearly defined
- c. Adequate accounting for drop-outs and crossovers, with numbers sufficiently low to have minimal potential for bias
- d. Relevant baseline characteristics presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences
- e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required:
 1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority
 2. The standard treatment used in the study is substantially similar to that used in previous

studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective)

3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment

Class II: Prospective, matched group cohort study in a representative population with masked outcome assessment that meets a–d above OR a randomized controlled trial in a representative population that lacks one criterion from a–d.*

*Note that numbers 1–3 in Class *Ie* are required for Class II in equivalence trials. If any one of the three is missing, the study is automatically downgraded to Class III.

Class III: All other controlled trials, including those with well-defined natural history controls or patients serving as their own controls in a representative population, where outcome assessment is independently assessed or independently derived by objective outcome measurement.*

*Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

In adapting these criteria to the present assessment, the panel considered that absence of reporting of the rate of premature study discontinuation or any information regarding safety at the time point for the primary outcomes assessment (i.e., not during open-label extension or long-term follow-up) warranted a downgrade in classification for studies otherwise meeting the requirements for Class I evidence. Furthermore, a premature discontinuation rate greater than 20% was considered to downgrade a trial otherwise deemed Class I evidence to Class II.

The criteria for Class I studies do not preclude active-comparator trials. However, the absence of a placebo control renders it difficult to estimate the effect size and hence the quantitative efficacy of either active treatment. To address this challenge, the panel considered, in addition to whether active-comparator studies met their pre-specified outcomes, the clinical relevance of the changes in outcome parameters within treatment groups.

2.4. Description of the analytic process

A panel comprised of specialists with experience in the therapeutic uses of BoNT for the indications under consideration or with expertise in basic and translational aspects of BoNT participated in the assessment was convened for this review. Panel members were selected because of their expertise with neurotoxin therapy as evidenced by years of clinical experience, participation in clinical trials, authorship of peer-reviewed literature, and/or prior involvement with guidelines methodology. The panel reviewed evidence tables, and on the basis of the strength of evidence regarding the quality and quantity of

evidence regarding the efficacy and safety of BoNT for each therapeutic indication, made a recommendation according to the AAN classification scale.

Classification of Recommendations

- A. Established as effective, ineffective, or harmful for the given condition in the specified population (Level A rating requires at least two consistent Class I studies)
- B. Probably effective, ineffective, or harmful for the given condition in the specified population (Level B rating requires at least one Class I study or at least two consistent Class II studies)
- C. Possibly effective, ineffective, or harmful for the given condition in the specified population (Level C rating requires at least one Class II study or two consistent Class III studies)
- U. Data inadequate or conflicting; given current knowledge; treatment is unproven

If there are two or more Class I studies for an individual product, there was no need to consider Class II studies unless specific studies provided additional insights regarding dosing, comparison between brands, or other unique attributes. In the event that there was only one placebo-controlled Class I study, a Class I comparator trial could provide confirmatory support if the efficacy was considered to be clinically meaningful by the reviewers. If only one Class I study was available, multiple Class II studies were considered. For a specific BoNT serotype, if insufficient quality evidence existed by individual brand but consistent results were observed across brands, recommendations were applied to the serotype. Recommendations for individual formulations must not be extrapolated to other brands.

The serotype and brand of BoNT used in specific studies are provided in the evidence tables. When sufficient evidence was available for each serotype and brand, the panel provided brand-specific recommendations. For each therapeutic indication, the panel summarized the evidence, indicated the level of recommendation supported by the available evidence, and suggested additional studies to fill current evidence gaps.

3. Results

Seven upper limb studies and two lower limb studies in the 2008 assessment of BoNT in the treatment of spasticity (Simpson et al., 2008) were reclassified from Class I to Class II in the present review because one or more criteria required for Class I status were either not explicitly described in the publication or not met; specifically, the method for randomization was not described and/or the rate of premature discontinuations was either not reported or exceeded 20% (Bakheit et al., 2000; Brashear et al., 2002; Hesse et al., 1998; Richardson et al., 2000; Simpson et al., 1996, 2009; Smith et al., 2000; Suputtitad and Suwanwela, 2005).

3.1. Upper limb spasticity

Commonly used outcome measures for assessing the effect of BoNT therapy in spasticity include the Ashworth

Scale (AS) and Modified Ashworth Scale (MAS), functional assessment of relevant activities of daily living, the Disability Assessment Scale (DAS), patient and caregiver subjective ratings, and active/passive range of motion (ROM).

Abundant high-quality evidence derived from placebo-controlled studies supports the use of BoNT for managing upper limb spasticity: two Class I studies of A/Abo (Bakheit et al., 2001; Bhakta et al., 2000), two Class I studies of A/Ona (Childers et al., 2004; Kaji et al., 2010b), and one Class I study each for B/Rima (Brashear et al., 2004) and A/Inco (Kanovsky et al., 2009) (see Table 1).

A Class I methodologic study evaluated A/Ona dilution and end-plate targeting in patients with upper limb spasticity, and demonstrated that high-volume or end-plate-targeted injections achieve greater neuromuscular blockade, co-contraction and spasticity reduction, and active range of elbow extension improvement, compared with low-volume, nontargeted injections (Gracies et al., 2009). A Class II methodologic study comparing 20 U/mL and 50 U/mL A/Inco dilutions showed no significant difference between dilutions (Barnes et al., 2010). Although there was no placebo control in this study, the improvements in both groups were deemed clinically meaningful to support the efficacy of A/Inco. There are no controlled active-comparator trials comparing two BoNT formulations. However, Simpson et al. compared BoNT to another therapy (tizanidine [TZD]) (Simpson et al., 2009). In this study, A/Ona reduced muscle tone in the fingers and wrist flexors significantly more than TZD at 3 and 6 weeks and was associated with a lower incidence of adverse events. In a two-by-two factorial design, Hesse et al. compared a single dose (1000 U) of A/Abo or placebo with and without an electrical stimulation regimen three times daily for three days postinjection (Hesse et al., 1998). This study showed that electrical stimulation plus BoNT-A was more effective than BoNT-A alone in reducing the caregiver burden for cleaning the palm of the affected hand.

All studies demonstrated that BoNT effectively reduced muscle tone. Functional improvement in relevant activities and subjective ratings of global satisfaction with treatment were also improved after BoNT therapy. Overall, the degree of functional improvement produced by BoNT therapy was consistently less robust than the improvements reported in muscle tone, spasticity, disability, and global clinical assessment (Bhakta et al., 2000; Childers et al., 2004; Simpson et al., 1996).

Trials reporting the effect of BoNT-A in poststroke upper limb spasticity generally showed reductions in muscle tone within 2 weeks after injection, with approximately 3–4 months durability of treatment effect (Bakheit et al., 2001, 2000; Bhakta et al., 2000; Brashear et al., 2004; Childers et al., 2004; Hesse et al., 1998; Kaji et al., 2010b; Simpson et al., 1996; Smith et al., 2000; Suputtitada and Suwanwela, 2005). The change in muscle tone/spasticity was about a one-point reduction more than placebo on the MAS, reflecting a clinically meaningful improvement.

The single study of BoNT-B (B/Rima) in 15 poststroke patients did not meet the primary efficacy end point of change in AS at 4 weeks and, in fact, showed a better reduction in muscle tone for the wrist compared with

placebo only at 2 weeks (Brashear et al., 2004). Consistent with this negative finding, there were no significant improvements in global assessments of change in the B/Rima group compared with placebo. However, it is important to consider the inconclusive findings of this study in the context of the very small sample size and the fact that only a single 10,000-U dose was evaluated. Future studies utilizing a higher dose in more patients may be able to detect a clinically meaningful difference from placebo of approximately 1 point on the MAS. The side-effect profile of B/Rima in this trial is consistent with the greater affinity of the type-B serotype for autonomic synapses compared with the type-A serotype, leading to greater muscarinic effects (Dressler and Benecke, 2007).

The effectiveness of BoNT-A appears to be dose dependent; however, most of the individual studies were not designed to evaluate the comparative effectiveness of different doses. Suputtitada et al. compared 350, 500, and 1000-U total doses of BoNT-A (A/Abo) and placebo in 50 poststroke adults to identify the lowest safe and effective dose (Suputtitada and Suwanwela, 2005). After five patients in the 1000-U dose group reported generalized weakness, particularly in the arms, and decreased global assessment of function according to the Barthel Index, no further patients were enrolled into this dose group. The primary end point—change in muscle tone of the elbow, wrist, and finger flexors using the MAS at 8 weeks post-injection—was significantly less in the 350-U group compared with both higher doses. Based on these findings, the investigators concluded that the 500-U dose was optimal, taking into consideration the excess weakening with the 1000-U dose noted above and the significantly reduced efficacy of the 350-U dose. Moreover, while all doses decreased tone, the 500-U dose produced the best functional change.

Smith et al., in their study combining data from doses of 500, 1000, and 1500 U A/Abo vs. placebo, reported significant reduction in spasticity at the wrist and fingers. This reduced spasticity was associated with an increased range of passive movement at the wrist and reduced finger curl at rest compared with placebo, but no differentiation among doses was noted (Smith et al., 2000). Childers et al. compared total doses of 90, 180, and 360 U A/Ona and placebo; they reported greater efficacy in reducing wrist muscle tone with the highest dose, but statistical significance was achieved only for each dose vs. placebo (Childers et al., 2004). Simpson et al. reported that 300 U A/Ona reduced tone in wrist and elbow flexors significantly more than placebo, while doses of 75 U and 150 U did not (Simpson et al., 1996).

3.1.1. Summary

Overall, there is Level A evidence supporting the effectiveness of BoNT-A for the treatment of upper limb spasticity. This recommendation is based on two Class I studies for A/Abo, two Class I studies for A/Ona, and one Class I placebo-controlled study of A/Inco. Individually, there is evidence to support Level A recommendations for both A/Abo and A/Ona and a Level B recommendation for A/Inco. There is insufficient evidence to support a recommendation for B/Rima.

Table 1
Upper limb spasticity in adults.

Ref	Class	Design	N	Treatment (Serotype/ brand/dose)	Targeting technique	Follow-up	Outcome measures (1-primary 2- secondary)	D/C	Safety	Efficacy	Comments
Placebo controlled Bakheit et al., 2001	I	R, DB, PC	59 >3 months poststroke	A/Abo 1000 U or PBO	Anatomic landmarks	16 w	1-Change in spasticity severity at 4 w 2-Joint ROM, pain severity, functional ability	1	No difference in any AEs; fatigue and pain in arm following A/Abo injection, probably due to study medication	1-Significant reduction in spasticity using MAS on 4 w ($p = 0.004$). 2-NS change in active ROM but significant mean magnitude of benefit in passive ROM at elbow with A/Abo at 16 w ($p = 0.036$). 1-Improved pt disability, caregiver burden, finger spasticity ($p < 0.001$) but not elbow flexor spasticity with A/Abo. 2-Finger flexor spasticity improved ($p < 0.001$); arm pain not improved with A/Abo.	
Bhakta et al., 2000	I	R, DB, PC	40 >6 mos poststroke	A/Abo 1000 MU or PBO	Anatomic landmarks	12 w	1-Subject disability and caregiver burden at 6 w 2-Muscle power, spasticity, grip strength, pain	2 PBO pts missing data	Self-limiting arm pain in 2 A/Abo pts at 1 w; worsening muscle spasm in 1 A/Abo pt		
Kanovsky et al., 2009	I	R, DB, PC	148 >6 mo poststroke	A/Inco 400 U or PBO	Stimulation technique or EMG	20 w	1-Wrist flexor responses at 4 w 2-DAS, Carer Burden Scale, Global Assessment of Benefit	3	AEs in 28.8% of A/Inco and 26.7% of PBO pts; most mild and resolved by final visit	1-68.5% A/Inco vs. 37.3% PBO had $>1\%$ improvement on AS ($p < 0.001$). 2-Greater improvement in DAS, Carer Burden, Global Assessment of Benefit scales with A/Inco. Median onset of benefit at 4 d; median duration 10 w in A/Inco pts. 1-NS differences in AS scores between groups. 2-NS differences between groups seen by MDs, pts, or OTs. A/Ona pts had greater improvement vs. PBO in principal target of treatment ($p < 0.001$), DAS at 6 w (83% vs. 53%; $p = 0.007$), flexor tone ($p < 0.001$), MD tone ($p < 0.001$) and pt global assessment ($p < 0.001$ at 6 w, $p = 0.002$ at 12 w).	
Brashear et al., 2004	I	R, DB, PC	15 >6 mo poststroke	B/Rima 10,000 U or PBO	Stimulation technique	16 w	1-AS at 4 w 2-MD/pt/OT global assessment of change	1	Dry mouth in 8 B/Rima pts vs. 1 PBO pt		Underpowered, with small number of pts
Brashear et al., 2002	II	R, DB, PC	126 >6 mo poststroke	A/Ona 200–240 U	Not specified	12 w	Functional disability by DAS, muscle tone, MD global assessment, pt global assessment	4	Muscle weakness in 6% of A/Ona pts vs. 0% PBO pts		Randomization method not specified

Richardson et al., 2000	II	R, DB, PC	32 (upper limb; + 20 lower limb spasticity)	A/Ona 50 U/mL	EMG	12 w	1-Passive ROM of target muscle by MAS; subjective rating of problem severity 2-Focal disability, gross motor function per Rivermead motor assessment scale, treatment goal	NR	Pain at injection site (4)	1-Muscle tone on MAS ($p < 0.02$) and ROM ($p < 0.03$) improved with A/Ona; sustained improvement in subjective rating or problem severity ($p < 0.02$) and AS ($p < 0.005$). 2-Rivermead scores significantly better for treated pts ($p < 0.05$); no treatment effects on gross motor function or goal attainment.	Lower limb pts also included; D/C NR
Comparator: Active comparator or multiple doses Kaji et al., 2010b	I	R, DB, PC	109 >6 mo poststroke	A/Ona 120–150 U (low dose), 200–240 U (high dose), or PBO	EMG or nerve stimulator; EMG injection	12 w	1- High dose: AUC of change in wrist flexor tone, using MAS 2- Low dose: AUC of change in MAS wrist score; wrist, fingers, thumb MAS, DAS scores	5	DRAEs: 6% A/Ona, 8% in PBO groups. All SAEs deemed unrelated to treatment.	1-Significant improvements with A/Ona vs. PBO ($p < 0.001$) in high-dose group, 2-In low-dose group, MAS wrist NS, finger differences significant at 6 w, DAS scores significant vs. PBO. Cycle 1: 1-Wrist flexor tone decreased more with A/Ona vs. PBO in 180-U ($p < 0.023$) and 360-U ($p < 0.001$) groups. 2-Elbow MAS significantly improved in 180-U and 360-U groups vs. PBO through week 9, Finger flexor tone results not significantly better with A/Ona vs. PBO. Global assessment responses not dose-dependent. Functional disability, pain, FIM: no difference among treatment groups. Cycle 2: No differences between groups in functional disability, subjective pain, function over 24 w. No strong dose response relationship seen.	2 PBO groups to mask treatment due to volume difference
Childers et al., 2004	I	R, DB, PC	91 >6 w poststroke Cycle 1: 91 pts Cycle 2: 67 pts	A/Ona 90, 180, 360 U or PBO	EMG guidance	6 w (cycle 1) and 24 w (cycle 2)	1-MAS wrist flexor tone by MAS 2-MAS elbow and finger flexor tone, MD/pt global assessment, pain, SF36, FIM	14 (cycle 1)	15 SAEs, all deemed not dose- or treatment-related; 9 TRAEs in 5 A/Ona pts		

(continued on next page)

Table 1 (continued)

Ref	Class	Design	N	Treatment (Serotype/ brand/dose)	Targeting technique	Follow-up	Outcome measures (1–primary 2– secondary)	D/C	Safety	Efficacy	Comments
Suputtiada and Suwanwela, 2005	II	R, DB, PC, dose ranging	50 poststroke	A/Abo 350, 500, 1000 U or PBO	EMG	24 w	Spasticity per MAS at 8 w, dexterity per Action Research Arm test, ADLs per Barthel Index, pain per VAS	NR	No AEs except weakness study drug (5/5) in 1000- U group	All A/Abo doses showed significant reductions per MAS vs. PBO at 8 w. Mean MAS approached lowest at 8 w, gradually increased through 6 mo in PBO, 350-, 500-U groups. Greater improvement per MAS in A/Abo 500-, 1000-U vs 350-U group at 8 w. 1-All A/Abo groups showed significant improvement vs. PBO on MAS. 2-No significant differences in functional disability.	Overall ANOVA NR; only pairwise comparisons, not controlled for multiplicity; arm weakness in 5/5 in 1000-U group led to dropping this arm (may have compromised trial integrity)
Bakhiet et al., 2000	II	R, DB, PC, dose finding	82 ≥3 mo poststroke	A/Abo 500, 1000, and 1500 U or PBO	Anatomic landmarks	16 w	1-Change of elbow, wrist, or finger joint ROM at 4 and 16 w; 2-Change in active passive muscle stretch and passive joint ROM, pain, function at 4 w	1	Between-group differences NS in frequency or nature of AEs	1-At 6 w, passive ROM significantly at wrist but not fingers with A/Abo; differences in dose groups NS, however, 1500 MU group showed improvement in passive elbow ROM. 2-NS differences in dressing time, Frenchay test, or postural alignment. Increasing the dose tended to increase magnitude of reduction in elbow and wrist spasticity but had little effect on duration of response.	Randomization method not specified; 1000 U appeared to be optimal dose
Smith et al., 2000	II	R, DB, PC, dose finding	21 >12 mo poststroke or TBI	A/Abo 500, 1000, 1500 MU or PBO	Not specified	12 w, then rerandomized	1-Passive and active ROM at 6 w 2-Dressing time, Frenchay Arm Test, postural alignment	None reported	Flulike symptoms for 2 d in 1 pt	1-At 6 w, passive ROM significantly at wrist but not fingers with A/Abo; differences in dose groups NS, however, 1500 MU group showed improvement in passive elbow ROM. 2-NS differences in dressing time, Frenchay test, or postural alignment. Increasing the dose tended to increase magnitude of reduction in elbow and wrist spasticity but had little effect on duration of response.	Randomization method not specified
Hesse et al., 1998	II	R, DB, PC	24 6–12 mo poststroke	Group A: A/Abo 1000 U + e-stim Group B: A/Abo 1000 U Group C: PBO + e-stim Group D: PBO	EMG guidance	12 w	Muscle tone per MAS, limb position at rest, difficulties during ADLs	NR	0	1-Between-group differences NS except in A vs. B and D (but not C) in performance of 1 ADL (cleaning of palm)	Randomization method not specified

Table 1 (continued)

Ref	Class	Design	N	Treatment (Serotype/ brand/dose)	Targeting technique	Follow-up	Outcome measures (1-primary 2- secondary)	D/C	Safety	Efficacy	Comments
Barnes et al., 2010	II	R, parallel groups	192	A/Inco 20 U/mL (low volume) or 50 U/mL (high volume); maximum dose, 400 U	EMG, electrical stimulation, or sonography	20 w	1- Noninferiority of 20 U/mL dilution by pt-chosen, MD- assessed therapeutic target on DAS at 4 w 2- Muscle changes per AS 3-Global assessment of treatment response	12	38% of pts experienced TRAEs, generally mild or moderate. No TRSAEs.	1-Noninferiority met; >1-point reduction in 57.1% of pts receiving 20-U dose, per DAS 2->1-point reduction in 62.2% receiving 20-U dose, per AS. 3-Minor differences in global improvement ratings by pts (80.2%) and investigators (89.0%) and between dosing groups.	Observer blind; otherwise not blinded

A/Abo, abobotulinumtoxinA; ADLs, activities of daily living; AE, adverse event; A/Inco, incobotulinumtoxinA; ANOVA, analysis of variance; A/Ona, onabotulinumtoxinA; AS, Ashworth Scale; AUC, area under the curve; B/Rima, rimabotulinumtoxinB; DAS, Disability Assessment Score; DB, double blind; D/C, discontinuation; DRAE, drug-related adverse event; EMG, electromyography; FIM, functional independent measure; IM, intramuscular; MAS, Modified Ashworth Scale; MD, doctor; MRV, mean rectified voltage; MU, mouse units; NR, not reported; NS, nonsignificant; OT, occupational therapy; PBO, placebo; PC, placebo-controlled; R, randomized; ROM, range of movement; SAE, serious adverse event; TBI, traumatic brain injury; TRAE, treatment-related adverse event; TRSAE, treatment-related serious adverse event; TZD, tizanidine; VAS, visual analog scale.

3.1.2. Evidence gaps

Additional controlled trials are needed to confirm the efficacy and tolerability of BoNT-B and A/Inco. Further investigation is also recommended to assess the comparative effectiveness and tolerability of the available BoNT formulations and to identify optimal injection techniques and dosing regimens for each formulation. In addition, the inclusion of standardized, clinically meaningful measures of functional capacity and disability would be important in future comparative effectiveness studies of BoNT therapy in upper limb spasticity, as such outcomes may be more relevant for patients than improvements in ratings-scale measurements of muscle tone.

3.2. Lower limb spasticity

For lower-limb spasticity in adults, there are two Class I studies of A/Ona (Kaji et al., 2010a; Verplancke et al., 2005) and one Class I study of A/Abo (Pittock et al., 2003) in a total of 382 patients (see Table 2). All these studies showed that BoNT improved range of motion and reduced muscle tone. Pittock et al. included objective assessment of gait velocity, measured by the distance in meters covered in 2 min (Pittock et al., 2003). After 12 weeks, the distance increased significantly within all groups, although there were no statistically significant differences among groups: placebo, 50.5 m; A/Abo 500 U, 49.5 m; A/Abo 1000 U, 50.6 m; and A/Abo 1500 U, 48.9 m. This finding was confirmed in another study, which also failed to show that BoNT improved gait velocity significantly more than placebo (Kaji et al., 2010a). While gait velocity is an objectively measured outcome, it is somewhat limited because walking production involves the trunk and all lower limb joints and it does not fully capture improvements in gait quality, balance, satisfaction with treatment, or changes in the need for orthoses or walking aids (Foley et al., 2010).

Two studies of A/Abo compared multiple doses: there were no significant differences in efficacy among doses, but there was a trend for more adverse events with the 1500-U dose of A/Abo compared with lower doses (Hyman et al., 2000; Pittock et al., 2003). The results of Pittock et al. suggest that the 500-U A/Abo dose may be too low to produce benefit, while the 1500-U dose may have caused excess muscle weakness in some patients (Pittock et al., 2003). A/Ona for lower-limb spasticity was studied in three trials (Kaji et al., 2010a; Richardson et al., 2000; Verplancke et al., 2005). One study compared 200 U A/Ona per leg or placebo in combination with serial casting to prevent worsening of ankle spasticity in patients with traumatic brain injury (Verplancke et al., 2005). Results showed no significant difference in improvement in the mean angle of ankle dorsiflexion for the A/Ona-plus-casting (13.59°) and casting-alone groups (11.69°). However, no patients who received A/Ona plus casting required rescue treatment because of substantially reduced range of motion, whereas about 30% of patients in the placebo-plus-casting and physical-therapy-alone treatment groups required rescue therapy. Overall, BoNT-A was administered effectively in the lower limb with electromyography or anatomic landmark guidance.

Table 2

Lower limb spasticity in adults.

Ref	Class	Design	N	Treatment (Serotype/ brand/dose)	Targeting technique	Follow-up	Outcome measures (1-primary 2-secondary)	D/C	Safety	Efficacy	Comments
Placebo controlled											
Kaji et al., 2010a	I	R, DB, PC	109 poststroke	A/Ona 300 U or PBO	EMG or nerve stimulator; EMG injection	12 w	1-AUC of change from baseline in MAS ankle score 2-Gait pattern, gait speed, CGI	7	AEs similar, resolved (A/Ona, 45%; PBO, 44%); not treatment- related except myalgia; SAEs in 9% of A/Ona, 2% of PBO pts; TRAEs similar, mild/moderate.	1-MAS AUC significantly superior with A/Ona vs. PBO ($p = 0.006$). 2-MAS ($p < 0.001$) and MD-assessed CGI ($p < 0.016$) superior in A/Ona pts at 4, 6, 8 w; gait speed, pt-assessed CGI NS	
Richardson et al., 2000	II	R, DB, PC	20 (lower limb + 32 upper limb spasticity)	A/Ona 75–400 U/mL	EMG guidance	12 w	1-Passive ROM of target muscle by MAS; subjective rating of problem severity 2-Focal disability, gross motor function per Rivermead motor assessment scale, treatment goal	NR	Pain at injection (4 pts)	1-Muscle tone on MAS ($p < 0.02$) and ROM ($p < 0.03$) improved with A/Ona vs. PBO; sustained improvement in subjective rating of problem severity ($p < 0.02$) and AS ($p < 0.005$). 2-Rivermead scores significantly better for treated pts ($p < 0.05$); no treatment effects on gross motor function or goal attainment.	D/C NR
Comparator: Active comparator or multiple doses											
Pitcock et al., 2003	I	R, DB, PC	234 ≥3 mo poststroke	A/Abo 500, 1000, 1500 U or PBO	Anatomic landmarks	12 w	1–2 min walking distance 2-Step length, stepping rate, Rivermead motor assessment, active and passive ROM at ankle	13	Any AE reported in 68/234 pts: 500 U, 29%; 1000 U, 25%; 1500 U, 33%; PBO, 29%. AEs similar across groups; AEs in ≥5%: pain, asthenia, convulsion, myasthenia	1-All measures improved vs. baseline, but differences among groups were limited. 2-In all treatment groups, more pts and investigators felt pts' condition was improved or much improved vs. the same or worse.	More pts said they were likely to, or would definitely use the treatment again than pts who said they would not do so.
Verplancke et al., 2005	I	R, BD, PC	35 post-brain injury	A/Ona 200 U Group 1: physical therapy only Group 2: casting + PBO injection Group 3: casting + A/Ona 200 U/leg	NR	12 w	1-Change in ankle dorsiflexion at 12 w 2-GOS and MAS	7 (4 D/C, 3 deaths)	3 deaths not related to study drug; well tolerated with 1 related 24-h reaction of flu like symptoms	1-Pts treated with casting + A/Ona improved vs. those treated with physical therapy alone ($p = 0.07$). 2-GOS improved more in casting + A/Ona vs. casting + PBO at 12 w.	~30% of casting alone and casting + saline pts required rescue vs. 0% of A/Ona pts

(continued on next page)

Table 2 (continued)

Ref	Class	Design	N	Treatment (Serotype/ brand/dose)	Targeting technique	Follow-up	Outcome measures (1-primary 2-secondary)	D/C	Safety	Efficacy	Comments
Hyman et al., 2000	II	R, DB, PC, dose ranging	74 MS	A/Abo 500, 1000, or 1500 U or PBO	Anatomic landmarks	12 w	1-Passive hip abduction sum of both legs, distance between knees at 4 w 2-Muscle tone, hygiene score, pain, global rating	14	AEs similar in all A/Abo and PBO groups except muscle weakness (A/Abo, 14%; PBO, 6%); twice as many AEs in 1500-U vs. 1000-U and 500-U groups. 6 SAEs, deemed unrelated to study drug	1-Few pts improved in hip abduction; maximum distance between knees significantly better with A/Abo 1500 U ($p = 0.02$) than other groups. 2-Global rating, pain scores similar across groups; muscle tone improved, spasm frequency reduced in A/Abo groups only; time to retreatment significantly longer in A/Abo groups (1500 U, $p = 0.015$; 1000 U, $p = 0.017$; 500 U, $p = 0.042$) vs. PBO; duration of benefit longer in A/Abo groups vs. PBO; hygiene improved in 1000-U and 1500-U vs. other groups.	Randomization method not specified

A/Abo, abobotulinumtoxinA; AE, adverse event; A/Inco, incobotulinumtoxinA; AS, Ashworth Scale; AUC, area under the curve; B/Rima, rimabotulinumtoxinB; CGI, clinical global impression; DB, double blind; D/C, premature discontinuation; EMG, electromyography; GOS, Glasgow Outcome Scale; MAS, Modified Ashworth Scale; MD, doctor; MS, multiple sclerosis; NR, not reported; Ona, onabotulinumtoxinA; PBO, placebo; PC, placebo-controlled; R, randomized; ROM, range of movement; SAE, serious adverse event; TRAE, treatment-related adverse event.

3.2.1. Summary

Overall, there are fewer studies of spasticity in the lower limb than for the upper limb, with less available data and few patients studied. There is sufficient clinical evidence to support Level A recommendations for A/Ona individually and BoNT-A in aggregate. The clinical evidence for A/Abo (one Class I study that did not demonstrate efficacy and one positive Class II study) supports a Level C recommendation: possibly effective. There is insufficient information to recommend A/Inco and B/Rima (Level U).

3.2.2. Evidence gaps

There is a need for further comparative effectiveness studies of the available BoNT formulations. Additional studies of A/Abo, A/Inco, and B/Rima in lower-limb spasticity are also needed. Although a number of studies included multiple BoNT doses, they were generally not powered for direct significance testing of differences in efficacy between doses. Thus, little objective evidence confirms clinical judgment regarding optimal BoNT dosing in lower-limb spasticity. Furthermore, given the limitations inherent in the outcome measures used in controlled trials, empirically derived dosing recommendations based on clinical experience and the complete evaluation of functional effects in large series of individual patients may provide valuable insights into optimal BoNT dosing regimens.

Conflict of interest

Alberto Esquenazi has performed research for Allergan and Ipsen.

Alberto Albanese has served on the editorial board of the European Journal of Neurology (Associate Editor) and Frontiers in Movement Disorders (Editor in Chief). He received speaker's honoraria from Merz and Ipsen and a research grant from Allergan. He also received royalties from publishing from Elsevier, Wiley-Blackwell.

Michael B. Chancellor has served as a consultant and investigator for Allergan.

Elie Elovic has served on advisory boards, speaker's bureaus, and as a consultant for Allergan, Merz, and Ipsen. She received research funding and grant support from Merz and Ipsen.

Karen Segal is currently employed by Mesoblast, Inc.

David Simpson has received consulting, research, and educational grants from Allergan, Merz, Ipsen, US Worldmeds Consulting, and Syntaxin.

Christopher P. Smith has served as a Consultant for Allergan, Inc.

Anthony B. Ward has received lectureship honoraria and fees from Allergan and Merz. He has received advisory board fees from Allergan and Medtronic.

References

Anson, C.A., Shepherd, C., 1996. Incidence of secondary complications in spinal cord injury. *Int. J. Rehabil. Res.* 19, 55–66.

Bakheit, A.M., Pittcock, S., Moore, A.P., Wurker, M., Otto, S., Erbguth, F., Coxon, L., 2001. A randomized, double-blind, placebo-controlled study of the efficacy and safety of botulinum toxin type A in upper limb spasticity in patients with stroke. *Eur. J. Neurol.* 8, 559–565.

Bakheit, A.M., Thilmann, A.F., Ward, A.B., Poewe, W., Wissel, J., Muller, J., Benecke, R., Collin, C., Muller, F., Ward, C.D., Neumann, C., 2000. A randomized, double-blind, placebo-controlled, dose-ranging study to compare the efficacy and safety of three doses of botulinum toxin type A (Dysport) with placebo in upper limb spasticity after stroke. *Stroke* 31, 2402–2406.

Barnes, M., Schnitzler, A., Medeiros, L., Aguilar, M., Lehnert-Batar, A., Minnash, P., 2010. Efficacy and safety of NT 201 for upper limb spasticity of various etiologies – a randomized parallel-group study. *Acta Neurol. Scand.* 122, 295–302.

Barnes, M.P., Kent, R.M., Semlyen, J.K., McMullen, K.M., 2003. Spasticity in multiple sclerosis. *Neurorehabil. Neural Repair* 17, 66–70.

Bhakta, B.B., Cozens, J.A., Chamberlain, M.A., Bamford, J.M., 2000. Impact of botulinum toxin type A on disability and carer burden due to arm spasticity after stroke: a randomised double blind placebo controlled trial. *J. Neurol. Neurosurg. Psychiatr.* 69, 217–221.

Brashear, A., Gordon, M.F., Elovic, E., Kassicheh, V.D., Marciniak, C., Do, M., Lee, C.H., Jenkins, S., Turkel, C., Botox Post-Stroke Spasticity Study, G., 2002. Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. *N. Engl. J. Med.* 347, 395–400.

Brashear, A., McAfee, A.L., Kuhn, E.R., Fyffe, J., 2004. Botulinum toxin type B in upper-limb poststroke spasticity: a double-blind, placebo-controlled trial. *Arch. Phys. Med. Rehabil.* 85, 705–709.

Childers, M.K., Brashear, A., Jozefczyk, P., Reding, M., Alexander, D., Good, D., Walcott, J.M., Jenkins, S.W., Turkel, C., Molloy, P.T., 2004. Dose-dependent response to intramuscular botulinum toxin type A for upper-limb spasticity in patients after a stroke. *Arch. Phys. Med. Rehabil.* 85, 1063–1069.

Dressler, D., Benecke, R., 2007. Pharmacology of therapeutic botulinum toxin preparations. *Disabil. Rehabil.* 29, 1761–1768.

Esquenazi, A., Mayer, N.H., 2004. Instrumented assessment of muscle overactivity and spasticity with dynamic polyelectromyographic and motion analysis for treatment planning. *Am. J. Phys. Med. Rehabil.* 83, S19–S29.

Foley, N., Murie-Fernandez, M., Speechley, M., Salter, K., Sequeira, K., Teasell, R., 2010. Does the treatment of spastic equinovarus deformity following stroke with botulinum toxin increase gait velocity? A systematic review and meta-analysis. *Eur. J. Neurol.* 17, 1419–1427.

Goodin, D.S., 1998. A questionnaire to assess neurological impairment in multiple sclerosis. *Mult. Scler.* 4, 444–451.

Gracies, J.M., Lugassy, M., Weisz, D.J., Vecchio, M., Flanagan, S., Simpson, D.M., 2009. Botulinum toxin dilution and endplate targeting in spasticity: a double-blind controlled study. *Arch. Phys. Med. Rehabil.* 90, 9–16. e12.

Hesse, S., Reiter, F., Konrad, M., Jahnke, M.T., 1998. Botulinum toxin type A and short-term electrical stimulation in the treatment of upper limb flexor spasticity after stroke: a randomized, double-blind, placebo-controlled trial. *Clin. Rehabil.* 12, 381–388.

Hyman, N., Barnes, M., Bhakta, B., Cozens, A., Bakheit, M., Kreczy-Kleedorfer, B., Poewe, W., Wissel, J., Bain, P., Glickman, S., Sayer, A., Richardson, A., Dott, C., 2000. Botulinum toxin (Dysport) treatment of hip adductor spasticity in multiple sclerosis: a prospective, randomised, double blind, placebo controlled, dose ranging study. *J. Neurol. Neurosurg. Psychiatr.* 68, 707–712.

Johnson, R.L., Gerhart, K.A., McCray, J., Menconi, J.C., Whiteneck, G.G., 1998. Secondary conditions following spinal cord injury in a population-based sample. *Spinal Cord* 36, 45–50.

Kaji, R., Osako, Y., Suyama, K., Maeda, T., Uechi, Y., Iwasaki, M., Group, G.S.K.S.S., 2010a. Botulinum toxin type A in post-stroke lower limb spasticity: a multicenter, double-blind, placebo-controlled trial. *J. Neurol.* 257, 1330–1337.

Kaji, R., Osako, Y., Suyama, K., Maeda, T., Uechi, Y., Iwasaki, M., Group, G.S.K.S.S., 2010b. Botulinum toxin type A in post-stroke upper limb spasticity. *Curr. Med. Res. Opin.* 26, 1983–1992.

Kanovsky, P., Slawek, J., Denes, Z., Platz, T., Sassini, I., Comes, G., Grafe, S., 2009. Efficacy and safety of botulinum neurotoxin NT 201 in post-stroke upper limb spasticity. *Clin. Neuropharmacol.* 32, 259–265.

Lundstrom, E., Terent, A., Borg, J., 2008. Prevalence of disabling spasticity 1 year after first-ever stroke. *Eur. J. Neurol.* 15, 533–539.

Mayer, N.H., Esquenazi, A., 2003. Muscle overactivity and movement dysfunction in the upper motoneuron syndrome. *Phys. Med. Rehabil. Clin. N. Am.* 14, 855–883. vii–viii.

Maynard, F.M., Karunas, R.S., Waring 3rd, W.P., 1990. Epidemiology of spasticity following traumatic spinal cord injury. *Arch. Phys. Med. Rehabil.* 71, 566–569.

Noreau, L., Proulx, P., Gagnon, L., Drolet, M., Laramée, M.T., 2000. Secondary impairments after spinal cord injury: a population-based study. *Am. J. Phys. Med. Rehabil.* 79, 526–535.

- Pittock, S.J., Moore, A.P., Hardiman, O., Ehler, E., Kovac, M., Bojakowski, J., Al Khawaja, I., Brozman, M., Kanovsky, P., Skorometz, A., Slawek, J., Reichel, G., Stenner, A., Timerbaeva, S., Stelmasiak, Z., Zifko, U.A., Bhakta, B., Coxon, E., 2003. A double-blind randomised placebo-controlled evaluation of three doses of botulinum toxin type A (Dysport) in the treatment of spastic equinovarus deformity after stroke. *Cerebrovasc. Dis.* 15, 289–300.
- Richardson, D., Sheean, G., Werring, D., Desai, M., Edwards, S., Greenwood, R., Thompson, A., 2000. Evaluating the role of botulinum toxin in the management of focal hypertonia in adults. *J. Neurol. Neurosurg. Psychiatr.* 69, 499–506.
- Rizzo, M.A., Hadjimichael, O.C., Preiningerova, J., Vollmer, T.L., 2004. Prevalence and treatment of spasticity reported by multiple sclerosis patients. *Mult. Scler.* 10, 589–595.
- Sheean, G., 2003. Botulinum toxin treatment of adult spasticity. *Expert Rev. Neurother.* 3, 773–785.
- Simpson, D.M., Alexander, D.N., O'Brien, C.F., Tagliati, M., Aswad, A.S., Leon, J.M., Gibson, J., Mordaunt, J.M., Monaghan, E.P., 1996. Botulinum toxin type A in the treatment of upper extremity spasticity: a randomized, double-blind, placebo-controlled trial. *Neurology* 46, 1306–1310.
- Simpson, D.M., Gracies, J.M., Graham, H.K., Miyasaki, J.M., Naumann, M., Russman, B., Simpson, L.L., So, Y., Therapeutics, Technology Assessment Subcommittee of the American Academy of, N., 2008. Assessment: botulinum neurotoxin for the treatment of spasticity (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 70, 1691–1698.
- Simpson, D.M., Gracies, J.M., Yablon, S.A., Barbano, R., Brashear, A., 2009. Botulinum neurotoxin versus tizanidine in upper limb spasticity: a placebo-controlled study. *J. Neurol. Neurosurg. Psychiatr.* 80, 380–385.
- Skold, C., Levi, R., Seiger, A., 1999. Spasticity after traumatic spinal cord injury: nature, severity, and location. *Arch. Phys. Med. Rehabil.* 80, 1548–1557.
- Smith, S.J., Ellis, E., White, S., Moore, A.P., 2000. A double-blind placebo-controlled study of botulinum toxin in upper limb spasticity after stroke or head injury. *Clin. Rehabil.* 14, 5–13.
- Sommerfeld, D.K., Eek, E.U., Svensson, A.K., Holmqvist, L.W., von Arbin, M.H., 2004. Spasticity after stroke: its occurrence and association with motor impairments and activity limitations. *Stroke* 35, 134–139.
- Suputtitada, A., Suwanwela, N.C., 2005. The lowest effective dose of botulinum A toxin in adult patients with upper limb spasticity. *Disabil. Rehabil.* 27, 176–184.
- Verplancke, D., Snape, S., Salisbury, C.F., Jones, P.W., Ward, A.B., 2005. A randomized controlled trial of botulinum toxin on lower limb spasticity following acute acquired severe brain injury. *Clin. Rehabil.* 19, 117–125.
- Walter, J.S., Sacks, J., Othman, R., Rankin, A.Z., Nemchausky, B., Chintam, R., Wheeler, J.S., 2002. A database of self-reported secondary medical problems among VA spinal cord injury patients: its role in clinical care and management. *J. Rehabil. Res. Dev.* 39, 53–61.
- Watkins, C.L., Leathley, M.J., Gregson, J.M., Moore, A.P., Smith, T.L., Sharma, A.K., 2002. Prevalence of spasticity post stroke. *Clin. Rehabil.* 16, 515–522.
- Wedekind, C., Lippert-Gruner, M., 2005. Long-term outcome in severe traumatic brain injury is significantly influenced by brainstem involvement. *Brain Inj.* 19, 681–684.
- Welmer, A.K., von Arbin, M., Widen Holmqvist, L., Sommerfeld, D.K., 2006. Spasticity and its association with functioning and health-related quality of life 18 months after stroke. *Cerebrovasc. Dis.* 21, 247–253.