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AbobotulinumtoxinA for the treatment of upper limb spasticity

Upper limb spasticity is a common feature of many conditions arising from stroke, brain injury or progressive neurological illness and can cause significant disability. Current guidelines recommend first-line treatment with botulinum neurotoxin type A. This paper provides a comprehensive overview of one type of botulinum neurotoxin type A – abobotulinumtoxinA – including its mechanism of action, efficacy and safety. Overall, there is a wealth of evidence supporting the clinical efficacy of abobotulinumtoxinA in the management of spasticity. Key findings from randomized controlled and open-label naturalistic studies support abobotulinumtoxinA as an efficacious long-term treatment for upper limb spasticity, with benefits extending to overall patient function as well as direct improvements in muscle tone.

Keywords: abobotulinumtoxinA • botulinum toxin • Dysport® • spasticity • upper limb

Spasticity, characterized by excess muscle tone and exaggerated tendon jerks, is a common feature of the upper motor neuron syndrome and is seen in a variety of diseases and conditions. For example, spasticity is estimated to affect 17–36% of patients with stroke [1–3], over half of patients with multiple sclerosis [4] or spinal cord injury [5,6] and up to a third of patients with traumatic brain injury [7]. The underlying pathophysiology of spasticity is complex and not well understood. Whereas it was once defined as a “velocity dependent increase in tonic stretch reflexes with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflexes” [8]. This definition has been heavily criticized as it only recognizes one motor loop and does not account for the complexity of changes that allow task performance after brain injury [9]. The burden of disability associated with spasticity can exert an immense impact on patient quality of life, as well as greater dependability on the caregiver and increased societal costs [10,11].

Key treatment goals in the management of spasticity are to maintain muscle length and enable normal positioning of the limbs

to prevent secondary soft tissue shortening [11,12]. Treatment options include conservative (physical and occupational therapies), oral and intrathecal medications, local injections of botulinum toxin (BoNT) and surgery. For patients with moderate-to-severe spasticity, physical treatments alone are often not effective enough, and therefore early intervention with pharmacological agents is advised [11].

Management of upper limb spasticity with botulinum neurotoxin type A

Botulinum neurotoxin type A (BoNT-A) is an acknowledged mainstay pharmacological treatment for the management of spasticity [11,13]. A robust body of evidence supports the use of BoNT-A as an effective focal intervention for reduction of spasticity. Guidelines consistently recommend that BoNT-A should be offered as a treatment option in adult spasticity as standard clinical practice [11–13].

The efficacy and safety of three of the commercially available BoNT-A preparations (abobotulinumtoxinA, Ipsen Biopharm Ltd, Wrexham, UK; incobotulinumtoxinA Merz Pharmaceuticals, Frankfurt am Main,

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Germany and onabotulinumtoxinA (Allergan, Inc., CA, USA) in treating spasticity have each been well established and there are numerous reviews regarding the efficacy and safety of the BoNT-A class for spasticity [12,14–16]. However, very few papers have looked at the efficacy and safety of specific products. This is important, as the injection dosing schemes (units used, volume of injection, and so on) of each product are not interchangeable. It is essential that practitioners understand the specifics of each product, as the lack of direct product comparability is a potential source of confusion. This review provides an overview of the use of abobotulinumtoxinA (Dysport®) in the management of upper limb spasticity (ULS).

In ULS, injections can be made into a variety of muscles to reduce muscle tone (Figure 1). Aside from improved muscle tone, patients may expect to experience improvement in function, increased ease of care and comfort, prevention of musculoskeletal complications and general cosmesis [17–19].

AbobotulinumtoxinA (Dysport)

The clinical development of BoNT-A began around 1970, when it was investigated for use as a nonsurgical alternative for the treatment of strabismus [20,21]. Since then, various BoNT-A products have been developed, each with their own characteristics. One of the first to be developed was given the commercial name Dysport, which was developed by the Centre for Applied Microbiology Research in Porton Down. In 2009, in order to reinforce the inherent differences and lack of interchangeability between different BoNT-A products, the US FDA recommended that all BoNT products be given a new established drug name specific to each drug product. Dysport was given the name abobotulinumtoxinA, and this unique name for the drug has been adopted in many other countries.

The abobotulinumtoxinA neurotoxin complex is composed of the active neurotoxin and associated proteins that stabilize and protect the neurotoxin.

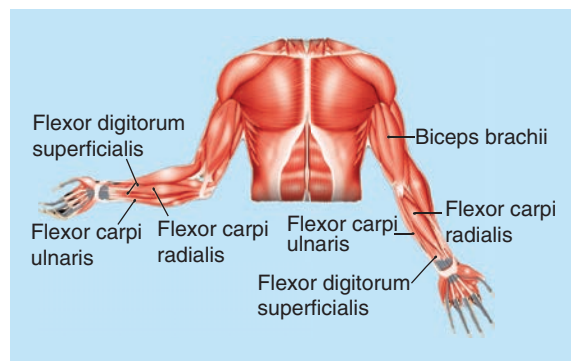


Figure 1. Muscles involved in upper limb spasticity. Image courtesy of Ipsen Pharma (Boulogne, France).

The active neurotoxin is produced by fermentation of *Clostridium botulinum* type A, Hall strain and purified from the culture supernatant by a series of proprietary precipitation, dialysis and chromatography steps. Since approval in 1990, all abobotulinumtoxinA batches have been produced using essentially the same method and have been reported to have a high degree of consistency [22].

Mechanism of action

Like all other BoNT-A products, abobotulinumtoxinA is a muscle relaxant agent that achieves its therapeutic effects on spasticity through the blockade of acetylcholine (ACh) release [23,24]. Following injection of abobotulinumtoxinA to the target muscle, the BoNT-A complex rapidly dissociates to separate associated proteins (hemagglutinin and nontoxic/nonhemagglutinin) from the neurotoxin [25,26]. The neurotoxin then diffuses and spreads to reach the target nerve terminals. Although various dermatologic studies [27–29] have reported differences in the diffusion characteristics of the different BoNT-A formulations, this has been disputed by several studies conducted under more strictly comparable laboratory conditions [30]. Once injected into tissue, there is a rapid dissociation between neurotoxin and associated proteins [26] and therefore there is no direct relationship between the complex size and the diffusion characteristics of abobotulinumtoxinA [30].

Thereafter, a four-step sequence of physiological events leads to the inhibition of ACh release: cell surface binding to peripheral nerve terminals; internalization (endocytosis); translocation and proteolysis. During the proteolysis step, the neurotoxin cleaves the SNAP-25 protein thereby impairing function of the neuroexocytosis machinery [31] and preventing ACh release. The main physiologic effect is the chemically induced loss of nerve input to the treated muscle, which results in a measurable decrease of the compound muscle action potential (muscle function) and consequent localized reduction of muscle activity. Very importantly, the effects of BoNT are not permanent; a final step in the sequence of physiological events associated with BoNT-A action is the gradual resumption of transmission as the neuromuscular junction recovers from the blockade of exocytosis and as new nerve endings are formed [32,33].

Efficacy of abobotulinumtoxinA in the management of ULS: evidence from clinical trials

The efficacy and safety of abobotulinumtoxinA in ULS has been established by several trials in the clinical development program and by further independent research. Official dosing recommendations for

abobotulinumtoxinA in ULS are largely based on the studies by Bakheit and colleagues who conducted two randomized placebo-controlled trials in patients with poststroke spasticity [34,35].

Pivotal studies

The first study was a dose-ranging trial to find effective and safe dose [34]. In this study, patients (n = 82) were randomized to receive injections with placebo (PBO), or three doses of abobotulinumtoxinA: 500, 1000 or 1500 U. Injections were made into the biceps brachii, flexor digitorum profundus, flexor digitorum superficialis, flexor carpi ulnaris and flexor carpi radialis using anatomic landmarks for guidance. Week 4 results showed a significant reduction in muscle tone as measured on the Modified Ashworth Scale (MAS) for all three abobotulinumtoxinA doses. Although not significantly different between groups, the authors noted an increase in range of motion at the elbow, wrist and fingers for all study groups. Importantly, the study found that 15.8% of the group who received 1500 U of abobotulinumtoxinA reported loss of the ability to voluntarily extend their fingers. The authors concluded that treatment with abobotulinumtoxinA at doses of 500, 1000 and 1500 U is effective and safe; however, for those individuals with residual voluntary movement in the affected limb, the optimal dose of abobotulinumtoxinA is 1000 U to achieve adequate spasticity control without negatively impacting voluntary movement.

The same investigators further evaluated the efficacy and safety of 1000 U abobotulinumtoxinA in 59 patients [35]. In this placebo-controlled study, patients randomized to abobotulinumtoxinA treatment received 1000 U in 2 ml of normal saline of abobotulinumtoxinA injected into the biceps brachii (300–400 U), flexor digitorum superficialis (150–250 U) and 150 U each into the flexor digitorum profundus, flexor carpi ulnaris and flexor carpi radialis, again using anatomic landmarks for guidance. The benefits of abobotulinumtoxinA injection in reducing muscle tone (MAS) were confirmed at week 4 of the study. Functional outcome measures, including active range of motion, Barthel Index and goal attainment did not show significance between group differences. However, global assessments of benefit (clinician and patient rated) demonstrated significant improvements for patients receiving abobotulinumtoxinA. The authors attributed this discrepancy to “the poor sensitivity of global functional outcome assessment scales in this situation.”

Randomized controlled trials

In 2008 the American Academy of Neurology conducted an evidence-based review of 14 randomized controlled trials (RCTs) of BoNT treatment for

spasticity, of which eight studies evaluated abobotulinumtoxinA (including the pivotal trials described above) [13]. Since then, at least six more RCTs (some of which have had an open-label design) have been completed and published. **Tables 1–7** present an overview of the 14 RCTs conducted to evaluate the efficacy and safety of abobotulinumtoxinA in the management of ULS [19,34–46].

All but one of the studies showed significant benefits of abobotulinumtoxinA versus placebo on the reduction of muscle tone as assessed by the MAS. The studies generally showed that clinically significant (≥ 1 point on MAS) [47] reductions in muscle tone were achieved within 2 weeks after injection. The trial by Hesse and colleagues was the only one not to show a significant difference in MAS and the authors attributed this finding to restricted selection of subjects with severe spasticity (mean MAS scores = 3), as well as the fact that the subjects did not participate in postinjection rehabilitation [45]. Nevertheless, the study showed significant improvements for abobotulinumtoxinA plus electrical stimulation in activities of daily living (cleaning the palm, cutting fingernails and putting affected arm through sleeve), which might be a very important goal for many patients.

When taken together, the 14 studies also show that, as well as improving muscle tone, treatment with abobotulinumtoxinA can, in some patients, also be helpful in improving associated reactions, disability, pain and caregiver burden (**Tables 1–7**).

By contrast, it was harder for the individual studies to demonstrate meaningful effects of abobotulinumtoxinA on functional improvement. Interestingly, meta-analytic approaches that combine data from many studies to produce a larger population of patients have found that reducing spasticity in the arm is associated with significant improvements in arm function. In the first exploratory meta-analysis conducted by Francis and colleagues in 2004, the authors used the MAS (elbow, wrist and fingers) from two RCTs to calculate a ‘Composite Spasticity Index’ and compared this with a ‘Composite Functional Index’ that had been similarly derived from the arm section of the Barthel Activities of Daily Living Index (dressing, grooming and feeding) and three subjective measures (putting arm through sleeve, cleaning palm, cutting fingernails) [48]. Using this targeted meta-analytic approach, the analysis found that there was a clear relationship between the changes in spasticity and in arm function in patients treated with abobotulinumtoxinA at 500 or 1000 U, but not in those treated with placebo or 1500 U. This led the authors to conclude, “...a moderate dose of BoNT reduces spasticity sufficiently to allow function to improve, without causing a substantial decrease in

Table 1. Pivotal trials of abobotulinumtoxinA.

Design	Patient population	Treatment (n)	Efficacy results ^a	Safety results	Author conclusions	Ref.
Bakheit et al. (2000)	<p>Randomized, double-blind, placebo-controlled, dose-ranging study</p> <p>Key eligibility criteria: Patients with moderate–severe muscle spasticity post hemiplegic stroke; ≥3 months after cerebrovascular event; muscle tone score ≥2 on MAS in wrist, elbow and finger flexors</p> <p>Key exclusion criteria: ABO 500 U (n = 22) Muscle contractures; ABO 1000 U (n = 22) previous treatment with BoNT</p>	<p>Injections were made into the motor endplate zone of the biceps brachii, flexor digitorum profundus, flexor digitorum superficialis, flexor carpi ulnaris and flexor carpi radialis</p> <p>Placebo (n = 19) ABO 500 U (n = 22) ABO 1000 U (n = 22) ABO 1500 U (n = 19)</p>	<ul style="list-style-type: none"> • Treatment with ABO (all three doses) significantly reduced MAS scores in any joint at week 4 compared with PBO • The number of patients who had an improvement of the MAS in all three joints was statistically higher for ABO (all doses) than in the placebo group (p < 0.02) • All ABO doses significantly improved MAS in elbow and wrist over 16 weeks (all p < 0.05). ABO 1000 U significantly reduced MAS in fingers (p = 0.04) • All groups had nonsignificant increases in ROM (active and passive) at the elbow, wrist and fingers • No statistically significant differences observed for measures of pain and functional assessment 	<p>AEs likely related to ABO: skin rashes (n = 6), flu-like symptoms (n = 3). Reduced active ROM with 1500 U dose, due to excessive weakening of muscles</p> <p>the upper limb appears to be 1000 U is safe in the doses used in this study”</p>	<p>“Treatment with ABO reduces muscle tone in patients with poststroke upper limb spasticity. Treatment was effective at doses of ABO of 500, 1000 and 1500 U. The optimal dose for treatment of patients with residual voluntary movements in the upper limb appears to be 1000 U is safe in the doses used in this study”</p>	[34]
Bakheit et al. (2001)	<p>Randomized, double-blind, placebo-controlled study</p> <p>Key eligibility criteria: Patients with moderate–severe muscle spasticity ≥3 months post hemiplegic stroke; muscle tone score ≥2 on MAS in at least two of the wrist, elbow and finger flexors and score (≥1 in remaining area)</p> <p>Key exclusion criteria: Muscle contractures; treatment with BoNT within 6 months</p>	<p>Injections were made into the biceps brachii flexor digitorum superficialis, flexor digitorum profundus, flexor carpi ulnaris and flexor carpi radialis</p> <p>Placebo (n = 32) ABO 1000 U (n = 27)</p>	<ul style="list-style-type: none"> • ABO treatment resulted in significant reduction in MAS in any joint at week 4 compared with PBO (p = 0.004) • No significant differences between groups in change from baseline to week 4 for active or passive ROM • Patient and physician global assessments of benefit showed “some or much improved” for significantly more ABO-treated patients (92.3 and 88.4%) 	<p>AEs possibly related to ABO included fatigue, tiredness and pain in the arm following the injection</p> <p>“Treatment with [ABO 1000 U] reduces muscle tone in patients with poststroke upper limb spasticity. This effect is sustained for at least 16 weeks. ABO is safe in the dose used in this study”</p>	<p>“Treatment with [ABO 1000 U] reduces muscle tone in patients with poststroke upper limb spasticity. This effect is sustained for at least 16 weeks. ABO is safe in the dose used in this study”</p>	[35]

^aResults in bold represent the primary efficacy variable.
ABO: AbobotulinumtoxinA; AE: Adverse event; BoNT: Botulinum toxin; MAS: Modified Ashworth Scale; PBO: Placebo; ROM: Range of movement.

Table 2. Randomized controlled trials of abobotulinumtoxinA up to 1000 U in upper limb spasticity.

Design	Patient population	Treatment (n)	Efficacy results*	Safety results	Author conclusions	Ref.
Bhakta et al. (2000)	Single-center, randomized, double-blind, placebo-controlled study	Injections were made into the biceps brachii, brachioradialis, flexor digitorum superficialis, flexor digitorum profundus and flexor carpi ulnaris	<ul style="list-style-type: none"> • Patients in the ABO group had significantly greater improvement in disability compared with PBO from week 0 to 2 (p = 0.004) and week 6 (p = 0.016). Greater improvement was also observed in the ABO group at week 12, but was not significant • Caregiver burden was significantly decreased from week 0 to 2 (p = 0.011), week 6 (p = 0.005) and week 12 (p = 0.027) • Finger flexor spasticity was significantly improved in the ABO group compared the PBO group at all time points (from week 0 to 2, p < 0.001; week 0 to 6, p < 0.001; week 0 to 12, p < 0.006) • Elbow flexor spasticity was significantly improved in the ABO group compared with the PBO group from week 0 to 2 (p = 0.002) • No significant differences between groups for active ROM, passive ROM at the elbow or shoulder, muscle strength or pain 	Patients in the ABO group reported self-limiting arm pain within 1 week of injection (n = 2) and worsening of muscle spasm (n = 1). No serious AEs were reported. Grip strength was reduced with ABO	"[ABO] is useful for treating patients with stroke who have self care difficulties due to arm spasticity. The decision to treat should also include relief of carer burden"	[19]
	<p>Key eligibility criteria: Patients with chronic hemiparesis; finger or elbow flexor (MAS >2) at least moderate difficulty with two out of eight items defining patient disability; at least 6 months poststroke</p> <p>Key exclusion criteria: Functionally useful movement in the paretic arm; previous treatment with BoNT or phenol block</p>	<p>Placebo (n = 20) ABO 1000 U (n = 20)</p>				

*Results in bold represent the primary efficacy variable.
ABO: AbobotulinumtoxinA; AE: Adverse event; AQoL: Assessment of quality of life; AR: Associated reaction; BoNT: Botulinum toxin; GAS: Goal attainment scaling; MAS: Modified Ashworth Scale; PBO: Placebo; ROM: Range of movement.

Table 2. Randomized controlled trials of abobotulinumtoxinA up to 1000 U in upper limb spasticity (cont.).

Design	Patient population	Treatment (n)	Efficacy results ^a	Safety results	Author conclusions	Ref.
Bhakta et al. (2008)	Randomized, placebo-controlled study Key eligibility criteria: Consecutive patients referred for management of upper limb spasticity; at least 6 months poststroke Key exclusion criteria: Previous treatment with BoNT or phenol block	Injections were made into the biceps brachii, brachioradialis, flexor digitorum superficialis, flexor digitorum profundus and flexor carpi ulnaris Placebo (n = 20) ABO 1000 U (n = 20)	<ul style="list-style-type: none"> • Peak ARs (unwanted involuntary movements) between week 1 and 6 were significantly reduced in the ABO group compared with the PBO group (mean group difference: 19.0; p ≤ 0.01) • 10/12 patients in the ABO group reported a reduction in the interference that AR have on their daily activities vs two of 12 in the placebo group (p = 0.02) 	None reported	"[ABO] reduces associated reactions and may be a useful adjunct to other rehabilitation interventions. The impact of associated reactions on daily activities may also be reduced"	[36]
McCrory et al. (2009)	Randomized, double-blind, placebo-controlled study Key eligibility criteria: Patients (aged ≥18 years) with moderate–severe spasticity of the arm (MAS score ≥2 in at least two of wrist, elbow and finger flexor and ≥1 in remaining area) Key exclusion criteria: Previous treatment with BoNT in past 120 days, phenol or neurolytic or intrathecal baclofen; severe contractures	Injections were made into the biceps brachii, brachialis, brachioradialis, triceps, flexor digitorum superficialis, flexor digitorum profundus, flexor carpi ulnaris, flexor carpi radialis and finger/thumb flexors Placebo (n = 42) ABO 750–1000 U (n = 54)	<ul style="list-style-type: none"> • No significant differences between groups for quality of life • No significant differences between groups for pain, mood disability or caregiver burden • A statistically significant functional benefit in GAS was observed for ABO compared with PBO from baseline to week 20 (GAS change: -5.20; p < 0.01) • Muscle spasticity was significantly reduced for ABO-treated patients compared with PBO-treated patients at all time points (p ≤ 0.001) • A significantly higher proportion of both patients and investigators reported a benefit from treatment in the ABO group vs placebo group at weeks 12 and 24 (p = 0.01) 	Treatment-related AEs occurred in 5.5% of ABO treated patients. AEs related to ABO were: atopic reaction (due to alcohol swabs), arm numbness, elbow twitch and thumb tremble	"Although no change in quality of life was demonstrated using the AQoL, [ABO] was found to be safe and efficacious in reducing upper limb spasticity and improving the ability to achieve personal goals"	[37]

^aResults in bold represent the primary efficacy variable. ABO: AbobotulinumtoxinA; AE: Adverse event; AQoL: Assessment of quality of life; AR: Associated reaction; BoNT: Botulinum toxin; GAS: Goal attainment scaling; MAS: Modified Ashworth Scale; PBO: Placebo; ROM: Range of movement.

Table 2. Randomized controlled trials of abobotulinumtoxinA up to 1000 U in upper limb spasticity (cont.).

Design	Patient population	Treatment (n)	Efficacy results [†]	Safety results	Author conclusions	Ref.
Lam et al. (2012)	<p>Randomized, double-blind, placebo-controlled trial in long-term care patients with a 24-week follow-up period</p> <p>Key eligibility criteria: Patients in long-term care with shoulder adductor, finger flexor or elbow flexor spasticity (MAS >2) and at least moderate difficulty with two of four items defining carer burden scale were eligible for the study. Patients had to have had spasticity for at least a year and be able to tolerate limb-stretching exercises and limb splints</p> <p>Key exclusion criteria: Patients with functionally useful movement in the spastic limb or rigid affected joints that are unlikely to respond to BoNT injection were excluded</p>	<p>Injections were made into the biceps brachii, brachioradialis, brachialis, pectoralis major, flexor digitorum profundus, flexor digitorum superficialis, adductor pollicis, flexor pollicis longus and flexor pollicis brevis</p> <p>Placebo (n = 25) ABO (n = 30); max dose 1000 U</p>	<ul style="list-style-type: none"> • At week 6 postinjection, 60% of had a significant four-point reduction of carer burden scale (p < 0.001 vs placebo) • Significant improvement in goal attainment scaling (p < 0.001 vs placebo) • Significant improvement in MAS, resting angle and passive range of movement of the three regions (shoulder, elbow and fingers) in the treatment group, which persisted until week 24 	<p>No statistical significance in cumulative incidence rates between the treatment and control groups regarding the pneumonia, bone fracture, fever, soft tissue swelling, pressure point or death</p>	<p>“Long-term care patients who were treated for upper limb spasticity with intramuscular injections of [ABO] had a significant decrease in the caregiver burden. The treatment was also associated with improved scores on patient-centered outcome measures”</p>	[38]

[†]Results in bold represent the primary efficacy variable.
 ABO: AbobotulinumtoxinA; AE: Adverse event; AQoL: Assessment of quality of life; AR: Associated reaction; BoNT: Botulinum toxin; GAS: Goal attainment scaling; MAS: Modified Ashworth Scale; PBO: Placebo; ROM: Range of movement.

Table 3. Dose-ranging studies for abobotulinumtoxinA.

Design	Patient population	Treatment (n)	Efficacy results [†]	Safety results	Author conclusions	Ref.
Smith <i>et al.</i> (2000)						
Randomized, double-blind, placebo controlled, dose-ranging study	Key eligibility criteria: Patients with troublesome flexor spasticity of the affected upper limb arising from stroke or traumatic brain injury >1 year previously	Injections were made into the muscles causing troublesome spasticity including biceps brachii, brachialis, wrist flexors and finger flexors (other muscles not specified) Placebo (n = 6) ABO 500 U (n = 6) ABO 1000 U (n = 7) ABO 1500 U (n = 6)	<ul style="list-style-type: none"> At 6 weeks, significant overall reductions in MAS (combined dose) were observed at the fingers and wrist after ABO treatment (p < 0.01 vs placebo) Passive ROM significantly increased at the wrist (p = 0.05) There were no significant differences between ABO and placebo on active ROM Significant improvements were observed in finger curl while at rest with ABO (combined dose) (p < 0.001 vs placebo) Statistically significant improvements in global rating scale were observed in 15 patients treated with ABO (combined dose; p < 0.02 vs placebo) There were no significant differences across groups for dressing time, postural alignment and the Frenchay arm test Six out of nine ambulant patients (who had an associated flexor reaction in the arm when walking) had improved gait after ABO injection into the biceps 	ABO was generally well tolerated. AEs included: hip pain (n = 1); flu-like symptoms (n = 1)	<p>"A single dose of [ABO] reduced spasticity and increased passive range of movement in the upper limb of patients with stroke and head injury for at least 6 weeks".</p> <p>"[ABO] was well tolerated and patients reported overall improvement but no change in upper limb function was demonstrated"</p>	[39]

[†]Results in bold represent the primary efficacy variable (when defined).

ABO: AbobotulinumtoxinA; AE: Adverse event; MAS: Modified Ashworth Scale; ROM: Range of movement; VAS: Visual analog scale.

Table 3. Dose-ranging studies for abobotulinumtoxinA (cont.).

Design	Patient population	Treatment (n)	Efficacy results [†]	Safety results	Author conclusions	Ref.
Supputitida et al. (2005)						
Randomized, double-blind, dose-ranging study	Key eligibility criteria: Patients (aged ≥15 years) with spasticity of any cause who were ambulatory and competent, and received at least 6 months of rehabilitative therapy	Injections were made into the biceps brachii, flexor digitorum superficialis, flexor digitorum profundus, flexor carpi ulnaris and flexor carpi radialis Placebo (n = 15) ABO 350 U (n = 15) ABO 500 U (n = 15) ABO 1000 U (n = 5)	<ul style="list-style-type: none"> All three ABO doses resulted in a significant decrease in MAS at week 8 vs placebo. The change in MAS was significantly higher in both the 500 and 1000 U groups compared with ABO 350 U (p < 0.05) Mean pain VAS decreased within 2 weeks post-treatment and approached its lowest value by week 8 in all three ABO groups Compared with placebo, ABO 500 U demonstrated a significant increase in the Action Research Arm test at weeks 8 and 24 (p < 0.05) 	The only AE considered related to ABO was “too much weakness” (n = 5 of 5 in the ABO 1000 U group)	“This study suggest that treatment with ABO reduces muscle tone in adult patients with upper limb spasticity. The optimal dose for treatment of patients with residual voluntary movement in the upper limb appears to be 500 U”	[40]
	Key exclusion criteria: Complete plegia, fixed contractures in the study limb, obvious atrophy of the muscles in the study limb					

[†]Results in bold represent the primary efficacy variable (when defined).

ABO: AbobotulinumtoxinA; AE: Adverse event; MAS: Modified Ashworth Scale; ROM: Range of movement; VAS: Visual analog scale.

Table 4. Studies of abobotulinumtoxinA for the management of poststroke shoulder pain.

Design	Patient population	Treatment (n)	Efficacy results*	Safety results	Author conclusions	Ref.	
Kong et al. (2007)	Randomized, double-blind, placebo-controlled study	Injections were made into the pectoralis major and biceps brachii Placebo (n = 9) ABO 500 U (n = 8)	<ul style="list-style-type: none"> No significant differences between groups in shoulder pain or passive shoulder abduction range Compared with placebo, patients treated with ABO had significantly greater improvements in shoulder adductor and elbow flexor MAS at week 4 ($p < 0.01$), but not at weeks 8 and 12 	Pain observed in six ABO-treated patients	"In patients with chronic hemiplegia pain associated with shoulder adductor and elbow flexor spasticity, [ABO] is effective in reducing spasticity compared with placebo. This reduction in spasticity did not impact on shoulder pain"	[41]	
Marco et al. (2007)	Randomized, double-blind, placebo-controlled study	Injections were made into the pectoralis major Placebo (n = 15) ABO 500 U (n = 14)	<p>Key eligibility criteria: Patients with moderate–severe shoulder pain and muscle spasticity (MAS ≥ 3) poststroke; at least 3 months after onset of cerebrovascular event</p> <p>Key exclusion criteria: Previous history of back or shoulder pain before stroke; poststroke central pain; previous BoNT treatment; reflex sympathetic dystrophy</p>	<ul style="list-style-type: none"> Patients in the ABO group showed significantly greater pain improvement vs placebo at 1, 3 and 6 months ($p = 0.035$) Patients in the ABO group showed increased shoulder abduction from the first week until month 6. However, the between group difference at month 6 was not statistically significant Patients in the ABO group showed significantly greater improvements in mean external rotation of the shoulder vs placebo ($p = 0.041$) No significant differences between treatment groups were observed for shoulder flexion or spasticity throughout the follow-up 	No important AEs were reported	"[ABO] is more effective than placebo in reducing pain and improving external rotation in patients with vascular hemiplegia with spastic shoulder pain"	[42]

*Results in bold represent the primary efficacy variable (when defined).

ABO: AbobotulinumtoxinA; AE: Adverse event; BoNT: Botulinum toxin; MAS: Modified Ashworth Scale; ROM: Range of movement; VAS: Visual analog scale.

Table 4. Studies of abobotulinumtoxinA for the management of poststroke shoulder pain (cont.).

Design	Patient population	Treatment (n)	Efficacy results [†]	Safety results	Author conclusions	Ref.
Yelnik <i>et al.</i> (2007)	Randomized, double-blind, placebo-controlled, two parallel group study	Injections were made into the subscapularis muscle Placebo (n = 10) ABO 500 U (n = 10)	<ul style="list-style-type: none"> Pain improvement was seen in week 1 in the ABO 500 U group and reached significance in week 4 (p = 0.025 vs placebo) Lateral rotation was improved with ABO treatment Spasticity decreased for upper limb muscles 	No AEs reported to be related to ABO treatment	“Subscapularis injection of [ABO] appears to be of value in the management of shoulder pain in spastic hemiplegic patients. The results confirm the role of spasticity in poststroke shoulder pain”	[43]
	<p>Key eligibility criteria: Upper limb spasticity related to a cerebral stroke; medial rotator and elbow flexor spasticity MAS ≥ 1; limited passive ROM of the shoulder</p> <p>Key exclusion criteria: Previous traumatic or neurological disease; retraction of ≥ 1 muscle; previous treatment with BoNT or alcohol in subscapularis</p>					
<p>[†]Results in bold represent the primary efficacy variable (when defined). ABO: AbobotulinumtoxinA; AE: Adverse event; BoNT: Botulinum toxin; MAS: Modified Ashworth Scale; ROM: Range of movement; VAS: Visual analog scale.</p>						

Table 5. Open-label study of abobotulinumtoxinA.

Design	Patient population	Treatment (n)	Efficacy results [†]	Safety results	Author conclusions	Ref.
Shaw <i>et al.</i> (2010)	<p>Open-label, parallel group, randomized, controlled trial and economic evaluation</p> <p>Key eligibility criteria: Patients with upper limb spasticity at the elbow (MAS >2), shoulder, wrist or hand and reduced upper limb function due to stroke ≥1 month previously</p> <p>Key exclusion criteria: Other significant upper limb impairment; fixed contracture; significant speech or cognitive impairments; use of BoNT in prior 3 months</p>	<p>Injections were made into the flexor digitorum superficialis, flexor digitorum profundus, flexor pollicis longus, forearm flexors, flexor carpi ulnaris, flexor carpi radialis biceps brachii, brachioradialis, pronator teres and pectoralis major</p> <p>Control (n = 163) ABO max 1000 U (n = 170)</p>	<ul style="list-style-type: none"> • No significant difference between groups for improved arm function at months 1, 3 or 12 • Treatment with ABO significantly reduced spasticity at the elbow vs control (p < 0.001) • Compared with control, patients treated with ABO showed improvements in upper limb muscle strength at 3 months (p = 0.055) and total motor impairment (p = 0.042) • Participants in the ABO group were more likely to be able to undertake specific basic functional activities (dress a sleeve, clean the palm and open the hand for cutting fingernails) at 1 month (p = 0.033) and 3 months (p = 0.027). Improvement was sustained at 12 months for opening the hand for cleaning the palm and opening the hand for cutting the nails but not for other activities • Pain rating was significantly improved in the ABO group vs control at 12 months (p = 0.004), but no significant differences were seen at 1 or 3 months 	<p>There was a higher incidence of general malaise/flu-like/cold symptoms in participants treated with ABO with a relative risk of 7.6. Only one serious AE (dysphagia) was potentially related to ABO treatment</p>	<p>“The addition of [ABO] to an upper limb therapy programme to treat spasticity due to stroke did not enhance improvement in upper limb function when assessed by the prespecified primary outcome measure at 1 month. However, improvements were seen in muscle tone at 1 month, upper limb strength at 3 months, upper limb functional activities related to undertaking specific basic functional tasks at 1, 3 and 12 months, and upper limb pain at 12 months”</p>	[44]

[†]Results in bold represent the primary efficacy variable.

ABO: AbobotulinumtoxinA; AE: Adverse event; BoNT: Botulinum toxin; MAS: Modified Ashworth Scale.

Table 6. Study of abobotulinumtoxinA given together with electrical stimulation.

Design	Patient population	Treatment (n)	Efficacy results	Safety results	Author conclusions	Ref.
Hesse <i>et al.</i> (1998)	<p>Key eligibility criteria: Randomized, double-blind, placebo-controlled study Patients with severe upper limb flexor (elbow, wrist, finger) spasticity (MAS score ≥ 3). Affected extremity had to be nonfunctional</p> <p>Key exclusion criteria: Muscle contractures; previous treatment with BoNT, neurolytic treatment or surgery for spasticity</p>	<p>Injections were made into the biceps brachii, brachialis, flexor digitorum superficialis, flexor digitorum profundus, flexor carpi ulnaris and flexor carpi radialis</p> <p>Placebo (n = 6) Placebo + electrical stimulation (n = 6) ABO 1000 U (n = 6) ABO 1000 U + electrical stimulation (n = 6)</p>	<ul style="list-style-type: none"> • Muscle tone reduction was most predominant in patients treated with ABO 1000 U and electrical stimulation, particularly with the elbow joint (p = 0.011) • No differences in muscle tone observed for finger or wrist • No significant differences in limb position at rest across groups. However, the most pronounced improvements (flexion from neutral) were seen in patients treated with ABO 1000 U and electrical stimulation • Patients treated with ABO 1000 U and electrical stimulation showed the best scores for ADLs (cleaning the palm, cutting fingernails and putting affected arm through sleeve; p = 0.004) 	Treatment was well tolerated with no study-related AEs reported	<p>“The placebo-controlled trial favours the concept that electrical stimulation enhances the effectiveness of [ABO] in the treatment of chronic upper limb flexor spasticity after stroke”</p>	[45]

ABO: AbobotulinumtoxinA; ADL: Activities of daily living; AE: Adverse event; BoNT: Botulinum toxin; MAS: Modified Ashworth Scale.

Table 7. Efficacy of abobotulinumtoxinA in early stroke.

Design	Patient population	Treatment (n)	Efficacy results [†]	Safety results	Author conclusions	Ref.
Rosales et al. (2012)						
Multicenter (Asian) randomized, placebo-controlled trial	Key eligibility criteria: Asian patients (aged 18–80 years) were recruited within 2–12 weeks after their first-ever stroke with impairment (MAS score of ≥1 in the elbow or wrist joint. Patient also had to have weakness of ≥2 according to MRC criteria in the relevant joint	Injections were made into the biceps brachii, brachioradialis, carpi ulnaris and the flexor carpi radialis Placebo (n = 83) ABO 500 U (n = 80)	<ul style="list-style-type: none"> At 4 weeks postinjection, ABO significantly improved MAS scores (most affected joint, wrist joint, elbow joint and combined joints); all $p < 0.0001$ Treatment effect-size estimates increased with higher baseline MAS scores from 0.45 (Q1) to 0.70 (Q3) Although not all participants reported pain, ABO-treated patients reported reductions in spasticity-related pain compared with baseline throughout the study, and this was significantly greater than placebo at weeks 4 and 24 No significant difference on the Functional Motor Assessment Scale 	Four AEs were reported to be related to ABO treatment: fatigue (two events), pyrexia and muscular weakness	“[ABO] 500 U can provide a sustained reduction in poststroke upper limb spasticity when combined with rehabilitation in Asian patients who have mild-to-moderate hypertonocity and voluntary movement, within 2–12 weeks of stroke. Functional use of the arm and hand was not affected”	[46]

[†]Results in bold represent the primary efficacy variable (when defined).

ABO: AbobotulinumtoxinA; AE: Adverse event; MAS: Modified Ashworth Scale; MRC: Medical Research Council.

strength, which may further impede function” [48]. More recently, Foley and colleagues performed a meta-analysis of 16 poststroke BoNT-A RCTs that included some sort of an activity outcome (e.g., Action Research Arm Test, Barthel Index) [49]. This large meta-analysis found that, while there was substantial variation of effect sizes in the individual studies due to the use of differing outcome measures, treatment with BoNT-A was overall associated with moderate improvement in upper-extremity activity capacity or performance after stroke [49].

These *post-hoc* analyses should be interpreted with caution, and the problem of how to best demonstrate functional improvement in an individual clinical trial has recently become the focus of much debate. A review of upper limb function measurement methods found that none of the methods currently used to assess function after BoNT treatment for upper limb spasticity satisfactorily fulfills all the criteria for a relevant outcome measure when used on their own [50]. The MAS is often criticized as being unable to distinguish between spasticity and soft tissue shortening, and experts suggest using the modified Tardieu scale as a better measure of spasticity [51–53]. Guidelines now also recommend that improved and reliable functional outcomes after BoNT-A therapy may be achieved when patient-specific goals that incorporate realistic expectations (e.g., improving passive as well as active functions and reducing pain) are used as functional outcome measures [11]. Emphasis is also placed on the duration of study so as to allow learning, rehabilitation and possibly even allow plasticity to occur [54]. Another aspect of current debate is the screening of suitable patients (inclusion criteria) for entry into clinical trials. Before starting treatment, it is important to assess if the patient has the “potential to improve” with spasticity reduction [55]. For example, it has been argued that studies such as the BOTULS study reported by Shaw and colleagues were unlikely to show a great functional benefit of treatment because they did not specifically include patients with the potential for functional change [44]. A patient with significant underlying plegia (weakness) is perhaps less likely to gain functional improvements through a reduction in spasticity.

Efficacy in real-world practice

In addition to randomized controlled studies, the efficacy of abobotulinumtoxinA in upper limb spasticity is supported by a number of open-label, ‘real-life practice’ studies. Two studies in particular provide confirmation that beneficial effects observed with abobotulinumtoxinA under clinical trial conditions also extend to real-world practice [18,56]. In their retrospective analysis of their clinics database, Mohammadi and colleagues

reviewed data from 137 patients with spasticity of various aetiologies who received 1221 BoNT-A treatments (at least eight consecutive treatments) for up to 12 years [56]. Of the 105 patients who were treated with abobotulinumtoxinA (7.5 years; range: 2–12 years), 16 patients were treated in the upper limb only. In these patients the mean latency between injection and response to abobotulinumtoxinA was 6.8 ± 3.6 days and the treatment effect was observed for a mean duration of 11.6 ± 3.1 weeks [56].

The ULIS-2 study reported by Turner-Stokes and colleagues was a large prospective, multicenter, observational study of patients with poststroke upper limb spasticity that included 456 patients who received one cycle of BoNT-A treatment under routine practice conditions [18]. The majority of patients ($n = 321$; 70%) received treatment with abobotulinumtoxinA. The primary outcome was achievement of the patient’s primary goal using goal attainment scaling (GAS) and the study showed that overall, 363 (79.6%) patients achieved (or overachieved) their primary goal and 355 (75.4%) mainly in terms of passive and active functions and pain reduction [18]. Importantly, GAS T-scores were correlated with global assessment of benefits (patient and investigator rated), as well as reductions in muscle tone. Baseline and mean change from baseline in GAS T-scores were similar between BoNT-A preparations.

Safety & tolerability

The safety and tolerability profile of abobotulinumtoxinA is also well established in patients with upper limb spasticity. In the pivotal placebo-controlled trials of patients with upper limb spasticity, the incidence of adverse events (AEs) was generally comparable between abobotulinumtoxinA and placebo and the overall frequency of AEs did not demonstrate a relationship with abobotulinumtoxinA dose [34,35]. Across the clinical trials of abobotulinumtoxinA in patients with spasticity, the most commonly experienced AEs were dysphagia and arm muscle weakness, abnormal gait and accidental injury or falls (Tables 1–7). Less frequently reported AEs that were considered possibly related to single-dose treatment included: skin rashes, flu-like symptoms, fatigue, tiredness and pain in the arm following injection [34,35]. However, these were mostly mild and transient in nature. Repeated treatment with abobotulinumtoxinA has also been shown to be well tolerated in upper limb spasticity, with no cumulative effect of dosing with abobotulinumtoxinA over multiple treatment cycles [57]. It must however be noted that, in the USA, all BoNT products (including abobotulinumtoxinA) carry a black box warning about the possible risk of spread of the toxin

away from the site of injection to other areas of the body producing symptoms consistent with botulism (including swallowing or breathing difficulties, which can be life-threatening) [58]. Similar warnings and precautions for use are in place for all BoNT in other countries.

Practical considerations

For the treatment of adult upper limb spasticity, abobotulinumtoxinA should be initially administered at a recommended dose of up to 1000 U, given as a divided dose at multiple injection sites depending on the affected limb. However, a lower dose may be advisable if target muscles are small or concomitant treatment of other muscle groups is intended. For subsequent treatment, the manufacturer recommends that the maximum abobotulinumtoxinA dose should not exceed 1000 U. Injections may be repeated approximately every 16 weeks, or as required to maintain a response, but not more frequently than every 12 weeks. This treatment interval is important for all BoNT-A formulations because, although the development of neutralizing antibodies is a relatively rare event, studies comparing patient groups with and without antibody-induced therapy failure have shown that shorter dosing intervals, more booster injections, higher BoNT-A

doses at each injection series and higher cumulative doses are clinically relevant risk factors for antibody formation [59]. No clinically relevant differences in immunogenicity between the various BoNT-A products have been reported. According to published data, only a small number of patients develop antibodies that neutralize the clinical effect of BoNT-A. When a patient develops neutralizing antibodies against a specific serotype, the patient will not respond to any preparation of the same serotype. Other considerations include the use of guidance techniques such as electrostimulation, electromyography and ultrasound to improve the accuracy of injections, but a review of these is out of the scope of this article.

Conclusion & future perspective

In summary, evidence-based clinical practice guidelines advocate BoNT-A as a mainstay treatment option for patients with spasticity. Injections of abobotulinumtoxinA have been consistently shown to provide significant clinical efficacy in the management of spasticity, as shown in numerous clinical trials and real-life studies. Key findings from clinical studies lend support to abobotulinumtoxinA as an efficacious long-term treatment for spasticity, with benefits extending to overall patient function.

Executive summary

- Spasticity is a common feature of the upper motor neuron syndrome and is seen in a variety of diseases and conditions. When present, the burden of disability associated with spasticity can exert an immense impact on patient quality of life, as well as greater dependability on the caregiver and increased societal costs.
- Botulinum neurotoxin type A is an acknowledged mainstay pharmacological treatment for the management of spasticity.
- The abobotulinumtoxinA neurotoxin complex is produced by fermentation of *Clostridium botulinum* type A, Hall strain and purified from the culture supernatant by a series of proprietary precipitation, dialysis and chromatography steps.
- Like all other *botulinum* neurotoxin type A products, abobotulinumtoxinA is a muscle relaxant agent that achieves its therapeutic effects on spasticity through the blockade of acetylcholine release.
- The efficacy and safety of abobotulinumtoxinA in upper limb spasticity has been established by several trials in the clinical development program and by further independent research, including large observational studies.
- All but one of the studies showed significant benefits of abobotulinumtoxinA versus placebo on the reduction of muscle tone as assessed by the Modified Ashworth Scale. The studies generally showed that clinically significant (≥ 1 point on modified Ashworth scale) reductions in muscle tone were achieved within 2 weeks after injection.
- By contrast, it was harder to demonstrate meaningful effects of abobotulinumtoxinA on functional improvement. However, meta-analytic approaches that combine data from many studies have suggested that reducing spasticity in the arm is associated with significant improvements in arm function.
- In the pivotal placebo-controlled trials, the incidence of adverse events (AEs) was generally comparable between abobotulinumtoxinA and placebo and the overall frequency of AEs did not demonstrate a relationship with abobotulinumtoxinA dose. The most commonly experienced AEs were dysphagia and arm muscle weakness, abnormal gait and accidental injury or falls. Repeated treatment with abobotulinumtoxinA has also been shown to be well tolerated in upper limb spasticity, with no cumulative effect of dosing over multiple treatment cycles.

Within the next years, we will hopefully get the approval to treat any focal spasticity. With support of electromyography and especially sonography the therapeutic results will be optimized.

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References

Papers of special note have been highlighted as:

• of interest; •• of considerable interest

- 1 Watkins CL, Leathley MJ, Gregson JM, Moore AP, Smith TL, Sharma AK. Prevalence of spasticity post stroke. *Clin. Rehabil.* 16(5), 515–522 (2002).
- 2 Sommerfeld DK, Eek EU, Svensson AK, Holmqvist LW, von Arbin MH. Spasticity after stroke: its occurrence and association with motor impairments and activity limitations. *Stroke* 35(1), 134–139 (2004).
- 3 Lundstrom E, Terent A, Borg J. Prevalence of disabling spasticity 1 year after first-ever stroke. *Eur. J. Neurol.* 15(6), 533–539 (2008).
- 4 Rizzo MA, Hadjimichael OC, Preiningerova J, Vollmer TL. Prevalence and treatment of spasticity reported by multiple sclerosis patients. *Mult. Scler.* 10(5), 589–595 (2004).
- 5 Walter JS, Sacks J, Othman R *et al.* 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(1), 53–61 (2002).
- 6 Noreau L, Proulx P, Gagnon L, Drolet M, Laramee MT. Secondary impairments after spinal cord injury: a population-based study. *Am. J. Phys. Med. Rehabil.* 79(6), 526–535 (2000).
- 7 Wedekind C, Lippert-Gruner M. Long-term outcome in severe traumatic brain injury is significantly influenced by brainstem involvement. *Brain Inj.* 19(9), 681–684 (2005).
- 8 Lance JW. What is spasticity? *Lancet* 335(8689), 606 (1990).
- 9 Malhotra S, Pandyan AD, Day CR, Jones PW, Hermens H. Spasticity, an impairment that is poorly defined and poorly measured. *Clin. Rehabil.* 23(7), 651–658 (2009).
- 10 Doan QV, Brashear A, Gillard PJ *et al.* Relationship between disability and health-related quality of life and caregiver burden in patients with upper limb poststroke spasticity. *PM R* 4(1), 4–10 (2012).
- 11 *Spasticity in Adults: Management Using Botulinum Toxin*. Royal College of Physicians. London, UK (2009).
- **Evidence-based guidelines on the use of botulinum neurotoxin type A in adult spasticity.**
- 12 Esquenazi A, Albanese A, Chancellor MB *et al.* Evidence-based review and assessment of botulinum neurotoxin for the treatment of adult spasticity in the upper motor neuron syndrome. *Toxicon* 67, 115–128 (2013).
- 13 Simpson DM, Gracies JM, Graham HK *et al.* 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(19), 1691–1698 (2008).
- 14 Teasell R, Foley N, Pereira S, Sequeira K, Miller T. Evidence to practice: botulinum toxin in the treatment of spasticity post stroke. *Top. Stroke Rehabil.* 19(2), 115–121 (2012).
- 15 Wissel J, Ward AB, Erztgaard P *et al.* European consensus table on the use of botulinum toxin type A in adult spasticity. *J. Rehabil. Med.* 41(1), 13–25 (2009).
- 16 Rosales RL, Chua-Yap AS. Evidence-based systematic review on the efficacy and safety of botulinum toxin-A therapy in post-stroke spasticity. *J. Neural. Transm.* 115(4), 617–623 (2008).
- 17 Simon O, Yelnik AP. Managing spasticity with drugs. *Eur. J. Phys. Rehabil. Med.* 46(3), 401–410 (2010).
- 18 Turner-Stokes L, Fhedoroff K, Jacinto J, Maisonobe P. Results from the Upper Limb International Spasticity Study-II (ULIS- II): a large, international, prospective cohort study investigating practice and goal attainment following treatment with botulinum toxin A in real-life clinical management. *BMJ Open* 3, e002771 (2013).
- **Large international study showing goal achievement in patients with upper limb spasticity following treatment with botulinum neurotoxin type A.**
- 19 Bhakta BB, Cozens JA, Chamberlain MA, Bamford JM. 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. Psychiatry* 69(2), 217–221 (2000).
- 20 Erbguth FJ. Historical notes on botulism, *Clostridium botulinum*, botulinum toxin, and the idea of the therapeutic use of the toxin. *Mov. Disord.* 19(Suppl. 8), S2–S6 (2004).
- 21 Truong DMD, Dressler D, Hallett M, Pathak M. *Manual of Botulinum Toxin Therapy*. Cambridge University Press, Cambridge, UK (2009).

- 22 Panjwani N, O'Keefe R, Pickett A. Biochemical, functional and potency characteristics of type A botulinum toxin in clinical use. *Botulinum J.* 1(1), 153–166 (2008).
- 23 Bakheit AM. The possible adverse effects of intramuscular botulinum toxin injections and their management. *Curr. Drug Saf.* 1(3), 271–279 (2006).
- 24 Wortzman MS, Pickett A. The science and manufacturing behind botulinum neurotoxin type A-ABO in clinical use. *Aesthet. Surg. J.* 29(Suppl. 6), S34–S42 (2009).
- 25 Friday D, Bigalke H, Frevert J. *In vitro* stability of botulinum toxin complex preparations at physiological pH and temperature. *Naunyn Schmiedebergs Arch. Pharmacol.* 365(Suppl. 2), R20 (2002).
- 26 Eisele KH, Fink K, Vey M, Taylor HV. Studies on the dissociation of botulinum neurotoxin type A complexes. *Toxicon* 57(4), 555–565 (2011).
- 27 Cliff SH, Judodihardjo H, Eltringham E. Different formulations of botulinum toxin type A have different migration characteristics: a double-blind, randomized study. *J. Cosmet. Dermatol.* 7(1), 50–54 (2008).
- 28 de Almeida AT, De Boule K. Diffusion characteristics of botulinum neurotoxin products and their clinical significance in cosmetic applications. *J. Cosmet. Laser Ther.* 9(Suppl. 1), 17–22 (2007).
- 29 Trindade de Almeida AR, Marques E, de Almeida J, Cunha T, Boraso R. Pilot study comparing the diffusion of two formulations of botulinum toxin type A in patients with forehead hyperhidrosis. *Dermatol. Surg.* 33(1 Spec No.), S37–S43 (2007).
- 30 Pickett A. Dysport: pharmacological properties and factors that influence toxin action. *Toxicon* 54(5), 683–689 (2009).
- 31 Blasi J, Chapman ER, Link E *et al.* Botulinum neurotoxin A selectively cleaves the synaptic protein SNAP-25. *Nature* 365(6442), 160–163 (1993).
- 32 de Paiva A, Meunier FA, Molgo J, Aoki KR, Dolly JO. Functional repair of motor endplates after botulinum neurotoxin type A poisoning: biphasic switch of synaptic activity between nerve sprouts and their parent terminals. *Proc. Natl Acad. Sci. USA* 96(6), 3200–3205 (1999).
- 33 Foran PG, Mohammed N, Lisk GO *et al.* Evaluation of the therapeutic usefulness of botulinum neurotoxin B, C1, E, and F compared with the long lasting type A. Basis for distinct durations of inhibition of exocytosis in central neurons. *J. Biol. Chem.* 278(2), 1363–1371 (2003).
- 34 Bakheit AM, Thilmann AF, Ward AB *et al.* 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(10), 2402–2406 (2000).
- Pivotal study for the use of abobotulinumtoxinA in the management of upper limb spasticity.
- 35 Bakheit AM, Pittock S, Moore AP *et al.* 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(6), 559–565 (2001).
- Pivotal study for the use of abobotulinumtoxinA in the management of upper limb spasticity.
- 36 Bhakta BB, O'Connor RJ, Cozens JA. Associated reactions after stroke: a randomized controlled trial of the effect of botulinum toxin type A. *J. Rehabil. Med.* 40(1), 36–41 (2008).
- 37 McCrory P, Turner-Stokes L, Baguley IJ *et al.* Botulinum toxin A for treatment of upper limb spasticity following stroke: a multi-centre randomized placebo-controlled study of the effects on quality of life and other person-centred outcomes. *J. Rehabil. Med.* 41(7), 536–544 (2009).
- 38 Lam K, Lau KK, So KK *et al.* Can botulinum toxin decrease carer burden in long term care residents with upper limb spasticity? A randomized controlled study. *J. Am. Med. Dir. Assoc.* 13(5), 477–484 (2012).
- 39 Smith SJ, Ellis E, White S, Moore AP. A double-blind placebo-controlled study of botulinum toxin in upper limb spasticity after stroke or head injury. *Clin. Rehabil.* 14(1), 5–13 (2000).
- 40 Suputtitada A, Suwanwela NC. The lowest effective dose of botulinum A toxin in adult patients with upper limb spasticity. *Disabil. Rehabil.* 27(4), 176–184 (2005).
- 41 Kong KH, Neo JJ, Chua KS. A randomized controlled study of botulinum toxin A in the treatment of hemiplegic shoulder pain associated with spasticity. *Clin. Rehabil.* 21(1), 28–35 (2007).
- 42 Marco E, Duarte E, Vila J *et al.* Is botulinum toxin type A effective in the treatment of spastic shoulder pain in patients after stroke? A double-blind randomized clinical trial. *J. Rehabil. Med.* 39(6), 440–447 (2007).
- 43 Yelnik AP, Colle FM, Bonan IV, Vicaut E. Treatment of shoulder pain in spastic hemiplegia by reducing spasticity of the subscapular muscle: a randomised, double blind, placebo controlled study of botulinum toxin A. *J. Neurol. Neurosurg. Psychiatry* 78(8), 845–848 (2007).
- 44 Shaw L, Rodgers H, Price C *et al.* BoTULS: a multicentre randomised controlled trial to evaluate the clinical effectiveness and cost-effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A. *Health Technol. Assess.* 14(26), 1–113, iii–iv (2010).
- 45 Hesse S, Reiter F, Konrad M, Jahnke MT. 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(5), 381–388 (1998).
- 46 Rosales RL, Kong KH, Goh KJ *et al.* Botulinum toxin injection for hypertonicity of the upper extremity within 12 weeks after stroke: a randomized controlled trial. *Neurorehabil. Neural Repair* 26(7), 812–821 (2012).
- Recent study evaluating the benefits of abobotulinumtoxinA when given within 12 weeks of stroke.
- 47 Esquenazi A, Mayer NH, Elia AE, Albanese A. Botulinum toxin for the management of adult patients with upper motor neuron syndrome. *Toxicon* 54(5), 634–638 (2009).
- 48 Francis HP, Wade DT, Turner-Stokes L, Kingswell RS, Dott CS, Coxon EA. Does reducing spasticity translate into functional benefit? An exploratory meta-analysis. *J. Neurol. Neurosurg. Psychiatry* 75(11), 1547–1551 (2004).

- 49 Foley N, Pereira S, Salter K *et al.* Treatment with botulinum toxin improves upper-extremity function post stroke: a systematic review and meta-analysis. *Arch. Phys. Med. Rehabil.* 94(5), 977–989 (2013).
- 50 Ashford S, Turner-Stokes L. Systematic review of upper-limb function measurement methods in botulinum toxin intervention for focal spasticity. *Physiother. Res. Int.* 18(3), 178–189 (2013).
- 51 Patrick E, Ada L. The Tardieu Scale differentiates contracture from spasticity whereas the Ashworth Scale is confounded by it. *Clin. Rehabil.* 20(2), 173–182 (2006).
- 52 Mehrholz J, Wagner K, Meissner D *et al.* Reliability of the Modified Tardieu Scale and the Modified Ashworth Scale in adult patients with severe brain injury: a comparison study. *Clin. Rehabil.* 19(7), 751–759 (2005).
- 53 Gracies JM, Burke K, Clegg NJ *et al.* Reliability of the Tardieu Scale for assessing spasticity in children with cerebral palsy. *Arch. Phys. Med. Rehabil.* 91(3), 421–428 (2010).
- 54 Rosales RL, Kanovsky P, Fernandez HH. What's the 'catch' in upper-limb post-stroke spasticity: expanding the role of botulinum toxin applications. *Parkinsonism Relat. Disord.* 17(Suppl. 1), S3–S10 (2011).
- 55 Burridge JH, Wood DE, Hermens HJ *et al.* Theoretical and methodological considerations in the measurement of spasticity. *Disabil. Rehabil.* 27(1–2), 69–80 (2005).
- 56 Mohammadi B, Balouch SA, Dengler R, Kollwe K. Long-term treatment of spasticity with botulinum toxin type A: an analysis of 1221 treatments in 137 patients. *Neurol. Res.* 32(3), 309–313 (2010).
- 57 Bakheit AM, Fedorova NV, Skoromets AA, Timerbaeva SL, Bhakta BB, Coxon L. The beneficial antispasticity effect of botulinum toxin type A is maintained after repeated treatment cycles. *J. Neurol. Neurosurg. Psychiatry* 75(11), 1558–1561 (2004).
- 58 Kuehn BM. FDA requires black box warnings on labeling for botulinum toxin products. *JAMA* 301(22), 2316 (2009).
- 59 Lange O, Bigalke H, Dengler R, Wegner F, deGroot M, Wohlfarth K. Neutralizing antibodies and secondary therapy failure after treatment with botulinum toxin type A: much ado about nothing? *Clin. Neuropharmacol.* 32(4), 213–218 (2009).