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SPECIAL REPORT

EUROPEAN CONSENSUS TABLE ON THE USE OF BOTULINUM TOXIN TYPE A IN ADULT SPASTICITY

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A group of clinicians from across Europe experienced in the use of botulinum toxin type A for the treatment of spasticity following acquired brain injury gathered to develop a consensus statement on best practice in managing adults with spasticity. This consensus table summarizes the current published data, which was collated following extensive literature searches, their assessment for level of evidence and discussion among the whole group. Published information is supplemented by expert opinion based on clinical experience from 16 European countries, involving 28 clinicians, who treat an average of approximately 200 patients annually, representing many thousand spasticity treatments with botulinum toxin per year.

Key words: botulinum toxin, upper motor neurone syndrome, adult spasticity, acquired brain injury.

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INTRODUCTION: DEVELOPMENT OF THE CONSENSUS TABLE

Botulinum toxin type A is a valuable treatment in the management of the focal problems of spasticity following acquired brain injury, which includes injury due to trauma, stroke, haemorrhage and hypoxia. This paper seeks to present a European consensus view on the management of adults with spasticity following an acute injury and was developed as a platform for defining and communicating the accepted best practice for the use of botulinum toxin type A.

This consensus statement was developed by drawing on the combined expertise of a number of renowned experienced users of botulinum toxin from 16 European countries. The process consisted of conducting a comprehensive literature search, identifying randomized controlled trials and other high-quality research papers, assessing the evidence, and forming consensus statements after extensive discussions.

The consensus statement was divided into 10 areas: Adult Spasticity; Service Configuration; Treatment Options; Medico-legal Considerations; Assessment and Goal Setting; Botulinum toxin type A Use and Dosage; Pharmacology of Botulinum

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Table I. *Consensus opinion*

Section Key area update	Key literature: selected clinical studies and reviews
Section 1: Adult spasticity following acute acquired brain injury	
Causes	Clinical studies
• Spasticity is one feature of the UMN syndrome	Incidence of spasticity after stroke (6–8)
• Spasticity can have a variety of causes and presentations depending on the location, age and size of the lesion following injury to the brain or spinal cord	Impact of spasticity on the individual (4, 5)
• Stroke damages descending pathways involved in sensory-motor control and is a major cause of severe disability	Impact of spasticity economically (16, 17)
• In stroke spasticity is a major feature of functional impairment	
• Incidence of spasticity in stroke: 19% at 3 months to 38% at 12 months	
• Early treatment of spasticity may avoid secondary mal-adaptation, functional impairment and loss of activity and participation	
Impact – on the individual	
• Impairments, e.g. pain, pressure sores, contractures depression	
• Activity limitation (disability)	
• Reliance on carers	
• Restriction of participation	
• Impaired quality of life	
Impact – economically	
• Financial burden on society Healthcare systems Social services Loss of employment.	
• Financial burden on individuals and carers.	
• 38% of stroke survivors will incur ongoing costs.	
Section 2: Service configuration	
Treatment of adult spasticity must be provided by a multidisciplinary team employing a shared-care approach	
• The rehabilitation team must be organized and supervised by a physical medicine and rehabilitation specialist or a neurologist specialized in rehabilitation	Clinical papers (4, 12)
• Recognition and referral Hospitals Acquired brain injury units General practitioners Community healthcare professionals Nursing homes Relatives Carers	Guidelines (community management of spasticity) (13, 41)
• Specialist spasticity services Consultant physician(s) Physiotherapist Occupational therapist Nurse Administrator Other clinicians	
• Wider teams who care for acquired brain injury patients Acute stroke specialists Neurologists Neurosurgeons In-patient departments Out-patient departments Professionals in community teams	
Competencies required of Specialist Spasticity Services	
• Trained clinicians in treatments for disabling neurological disease	
• Knowledge & experience of all available spasticity treatment modalities	
• Facilities to assess & treat patients	
• Location	
• Space	
• Equipment	
• Network	

- Referring units – virtual services
  - Community therapists and nurses
  - Surgeons
    - Orthopaedic surgeons – focal treatments
    - Neurosurgeons
      - Focal & segmental treatments
      - ITB pump placements
- Education & research activity
- Organizational commitment to accept referrals from outside
  - Business plan and financial security

Section 3: Treatment options for adult spasticity

Focal problems due to spasticity — Clinical studies

- Evidence from 20 RCTs and 2 meta-analyses has demonstrated significant decreases in muscle tone and improved passive function (reduced impairment and improved participation) with botulinum toxin therapy — See Table III for details of clinical studies (35, 38, 42–63)
- There is growing evidence to show that decreasing spasticity results in active functional improvements, i.e. reduced activity limitation. To date there have been no randomized clinical trials, but improving function through reducing a stiff knee gait has been reported — Stiff knee gait (62, 63)
- Decreased muscle tone improves possibility of functional training
- Botulinum toxin could therefore contribute to improved function
- Repeated doses of botulinum toxin produces significant improvement in activity performed and ability to manipulate affected limbs with reduced carer burden
- Additional studies are required that specifically address active function of the paretic limb

Botulinum toxin and shoulder pain

- Two randomized double-blind trials have demonstrated the value of botulinum toxin type A in relieving pain, as well as motion, in hemiplegic shoulder — Shoulder pain clinical papers (54, 64, 65)
- It has been suggested that this intervention is more effective than intra-articular steroid injections

Section 4: Medico-legal considerations

Botulinum toxin may be used off-label

- Some treatment with botulinum toxin is off-label since in some countries it is not licensed for indications other than stroke and upper limb spasticity
- Reimbursement of botulinum toxin treatment in non-licensed dose and indications result in problems for patients and physicians accessing effective treatment in many European countries

Cost-effectiveness

- There are no formal studies of the cost-effectiveness of botulinum toxin type A and this issue needs to be addressed. Two papers have estimated cost indirectly — Estimated cost of managing focal spasticity (16)
- However, the cost of stroke and complications such as fractures or pressure sores is considerable, so any intervention that reduces these costs will reduce the healthcare financial burden — Cost-effectiveness of botulinum toxin (derived not direct studies) (15, 17)

Section 5: Assessment and goal setting

Assessment

- The specialist should assess the neurological status of patient, and should note the positive and negative signs of the upper motor neurone syndrome — Clinical papers (59, 66–69)
- Confounding factors potentially influencing treatment response and post-injection treatment have to be considered

  Outcome measures should be based on the ICF model and be performed at the level of body functions and activities and participation

Goal setting

- Close cooperation between specialist team members, patient and caregivers is necessary to define realistic, individualized treatment goals and to achieve maximum benefit
- Goal attainment scoring may be useful in setting individual treatment goals

Section 6: Botulinum toxin type A use and dosage

Botulinum toxin type A use

- Botulinum toxin treatment is one part of an integrated programme of care and should not be given in isolation
- While access to a multidisciplinary team is possible in the early stage of treatment, this often become more challenging in the long-term and care may become more fragmented with time
- Physical therapy (physical, occupational, casting, motor-training) should follow injections — Clinical papers
- Maximum doses should not exceed: — Maximum dosing (70)

  Per injection session:
  - 1500 MU Dysport®
  - 600 U BOTOX®

Per injection site: 125 MU Dysport® 50 U BOTOX®	
In larger muscles, multiple injection sites. Note: These dosages are based on the maximum that can be used safely with acceptable side-effects. They do not represent equivalent efficacy of the 2 toxins and cannot be used to derive a dose conversion ratio (see p. 10). Each product has to be titrated for each individual patient for an optimal outcome in terms of both efficacy and safety	Tolerability of botulinum toxin (43, 51, 52, 57)
Tolerability of botulinum toxin type A • Doses must be assessed for each individual patient and common practice is to start at lower doses and titrate upwards • A single dose study of Dysport® (1000 U vs placebo) in upper limb spasticity did not show significant differences in adverse events between groups • A similar study in lower limb spasticity showed twice as many adverse events in the highest dose group (1500 U Dysport®) than the lower dose groups (500 and 1000 U Dysport®) • A dose ranging study of BOTOX® (75, 100 and 300 U) in upper limb spasticity showed no differences in adverse events between the groups • Single doses of 400 U of BOTOX® into calf muscles were well tolerated with no evidence of effects in adjacent muscles • Further studies are needed to clarify the side-effects of high doses in adults	
Section 7: Pharmacology of botulinum toxin type A	
Formulations of botulinum toxin type A • To date 2 different formulations of botulinum toxin type A: BOTOX® and Dysport® have demonstrated efficacy in adult spasticity The 2 products have different manufacturing processes, formulations, structure and levels of homogeneity • The 2 products use different biological assays and there is no internationally recognized dose comparison between the units for the different preparations	Pre-clinical papers (18, 71–74)
Safety of botulinum toxin A • There is extensive clinical experience with botulinum toxin-based products • In general, botulinum toxin type A has been shown to be efficacious and associated with few adverse events across many indications • A meta-analysis of 37 studies has confirmed the good safety profile of BOTOX® • There are differences in adverse event rates between botulinum toxin preparations, suggesting that use of these products should be based on individual dosing	Clinical papers (19, 75, 76) Meta-analysis (20)
Comparative safety • Pre-clinical studies have shown differences in dose-response curves for safety and efficacy between botulinum toxin preparations, suggesting that use of these products should always be based on individual dosing and fixed-dose ratios should not be derived for the products	
Section 8: Dilution and end-plate targeting	
• Muscle end-plate targeting is desirable, but not always possible in human studies	
• It is recommended that injections are made as near to the motor end-plates as possible, where the location is known. Otherwise, injections should be carried out in accordance with the available injection guidance charts	Pre-clinical papers (77, 78) Clinical papers (23, 24)
• In larger muscles with ill-defined or diffuse motor end-plates (e.g. soleus and gastrocnemius muscle), multiple injections and higher volumes may be preferable. Multiple injection sites and larger volumes may be impractical for small muscles	Injection guidance (25–28)
• Higher doses do not necessarily require higher volumes, so volumes can be kept low for small muscles	
• Injection guidance is recommended for deep-seated muscles and those difficult to locate using only anatomical landmarks	
• Patient comfort must be a consideration when considering injection volume	
Section 9: Follow-up	
Long-term use of botulinum toxin type A and follow-up • Botulinum toxin type A has shown sustained activity with repeated use up to 52 weeks and benefits are mainly seen in impairments	Clinical papers (12, 13, 20, 29–33, 74, 79, 80)
• One meta-analysis demonstrated that peak duration of response increased with time on repeated injections	
• Decisions to repeat injections must be informed by the response to the initial treatment and the improvements achieved	
• Follow-up is required and mechanisms should be put into place to ensure that it occurs, especially in the long-term	
• Follow-up decisions should involve the whole team involved in the patient's care, including the patient and carer	

Non-response
- May be affected by:
  - Inaccurate injections
  - Insufficient drug dosages
  - Inaccurate muscle selection
  - Development of changes in the muscle (fibrosis, contracture, etc.)
  - Rarely, the formation of neutralizing antibodies
- The incidence of neutralizing antibodies following repetitive botulinum toxin type A injections has been calculated from retrospective data from patients with cervical dystonia. The incidence of antibody formation was 3% –10% with Dysport® and the old formulation of BOTOX®
- Meta-analysis has revealed that antibody formation with current BOTOX® formulation is now a very rare event (1/191 adults) and is no longer considered a clinically relevant problem

Section 10: Research challenges

Unresolved issues
- The optimal method of muscle location
- Adoption of consistent terms for describing spasticity
- The timing, duration and intensity of post botulinum toxin physical therapy

Research challenges
- Costs of treating spasticity
  - Multidisciplinary team costs
  - Cost of botulinum toxin type A vs other treatments
- Optimal trial design, including tests and clinical measures, to demonstrate functional improvements with botulinum toxin type A
- Optimal pre- and post-injection treatment to increase efficacy from botulinum toxin type A injections

UMN: upper motor neurone; ICF: international classification of functioning, disability and health; RCT; randomized controlled trial; ITB: intrathecal baclofen; U: units; MU: million units.

Toxin type A; Dilution and End-plate Targeting; Patient Follow-up; and Research Challenges.

The literature search for each of the first 9 topic areas was conducted using the following databases: Medline, EMBASE, EMBAL, BIOSIS, SciSearch, PASCAL, HCAplus and IPA. Clinical studies focused on randomized controlled trials or meta-analyses of studies that used botulinum toxin type A to treat spasticity resulting from acquired brain injury. Review articles were also included where appropriate.

A preliminary summary was compiled and presented to the group at a consensus meeting held in Potsdam, Germany in October 2007. The material was discussed and the content of each section revised after the meeting in the light of the discussions. Authors then reviewed and endorsed the content of the revised presentations, which provided the basis for the first draft of the statement. The manuscript subsequently underwent review and revision by each member of the consensus group. The text provides a short summary of each section; the consensus statements are given in Table I.

Table II. *Positive and negative phenomena of the upper motor neurone syndrome (81)*

Positive features	Negative features
• Increased tendon reflexes with radiation	• Reductions in motor activity Weakness Loss of dexterity
• Clonus	• Fatigue
• Positive Babinski sign	
• Spasticity	
• Extensor spasms	
• Flexor spasms	
• Mass synergy patterns	
• Associated reactions – stereotypic spastic dystonias	

ADULT SPASTICITY

This paper considers the spasticity that occurs in adults as a result of acute acquired brain injury due to trauma, stroke (including subarachnoid haemorrhage) and hypoxia. Lance's definition of spasticity "a velocity-dependent increase in tonic stretch reflex" (1) was used as the basis for discussing the impact spasticity as part of the upper motor neurone (UMN) syndrome.

The UMN syndrome is a well-defined concept that involves both positive and negative clinical phenomena (Table II) following damage of the central nervous sensorimotor system. The constellation of phenomena form a clinical pattern that is useful for diagnostic purposes; however, this classification may be regarded as somewhat out of date and inconsistent in terms of the underlying physiology.

Gracies (2, 3) points out that patients with spasticity form a clinically and physiologically recognizable population. They are disabled by 3 main features: (*i*) paresis, i.e. reduced recruitment of skeletal motor units; (*ii*) soft tissue contracture, in particular muscle shortening and joint retraction; and (*iii*) muscle overactivity, i.e. reduced ability to relax muscle and co-contraction. These changes give rise to the commonly observed clinical picture of: shortened overactive muscles; velocity-dependent stiffness of limbs (by contrast to hypertonia which is not velocity dependent); loss of fine motor control; weakness masked by stiffness; muscle spasms; changes in limb posture; fatigue.

Besides acquired brain injury, the UMN syndrome also involves spinal cord injury, cerebral palsy and progressive neurological disease, but these conditions are not included in the current discussion as they have different clinical characteristics and courses and therefore, in some aspects, require different treatment considerations.

Spasticity is only one aspect of the UMN syndrome and other features also contribute to activity limitation and participation restriction. For instance, thixotropic changes in muscles, due to or as a consequence of spasticity, can impair people's physical abilities (e.g. as a result of increased muscle stiffness) and have a major impact on their lifestyle. The functional consequences of UMN syndrome and spasticity are highly variable. The most affected patients are unable to perform many activities of daily living, resulting in poor self-care and/or difficulty for carers in maintaining hygiene, for example because of finger contractures. They become dependent on assistance from family members and/or carers, may have impaired social participation, lose self-esteem and develop a poor body image. Less affected patients may present with a more limited movement disorder, for example equinovarus affecting gait. All patients may also experience pain, depression and impaired quality of life (4, 5).

The incidence of troublesome spasticity requiring treatment following acquired brain injury is not precisely known, as studies are lacking, but some have suggested that 19% of patients after stroke have spasticity at 3 months and 38% at 12 months after the original trauma (6–8). Upper extremity hypertonia (Ashworth score > 1) was seen in 63% of patients with initial paralysis due to acute supratentorial stroke during the first 26 weeks post-stroke (9). Lacunar infarction, most posterior infarctions and rostrally located anterior infarctions do not usually give rise to spasticity (10).

However, these studies use different quantitative criteria to define spasticity and, when the Lance definition is used, almost all hemiparetic patients can be considered as having spasticity (2, 3).

The development of spasticity following acquired brain injury also does not follow a predictable pattern (9), emphasizing the need for organized regular assessment and, where necessary, a treatment plan, on an individual basis. There is a lack of evidence-based clinical data on spasticity assessment; assessment protocols are only available for stroke survivors. In other causes of spasticity clinical experience has shown that there are some more predictable sub-groups of patients, but currently they are poorly documented.

SERVICE CONFIGURATION

Spasticity management must be undertaken by a multidisciplinary team, since optimal treatment involves physical therapy in conjunction with intermittent pharmacological treatment. It is very important that patients are referred to spasticity or rehabilitation services, which essentially include clinicians with the necessary training, competence, expertise and facilities, including space and equipment.

Table III. *Clinical trials of botulinum toxin A*

	Level of evidence*	Aetiology	No. of patients	Area	Dose	Effect on spasticity
Randomized controlled trials						
Bakheit et al. 2004 (42)	1b	Stroke	82	Biceps, wrist and finger flexors	D; 500, 1000, 1500 MU	Significant reduction in muscle tone at all doses
Bakheit et al. 2001 (43)	1b	Stroke	58	Biceps, wrist and finger flexors	D: 1000 MU	Spasticity reduced $p=0.004$ at week 4
Bhakta et al. 2000 (44)	1b	Stroke	40	Elbow, wrist, finger flexors	D; 1000 MU	Finger spasticity improved $p<0.001$ at 6 weeks
Brashear et al. 2002 (45)	1b	Stroke	126	Wrist, finger flexors, thumb flexors	B: 200–240 MU	Improved flexor tone $p<0.001$ at 12 weeks
Burbaud et al. 1996 (46)	1b	Stroke, trauma	23	Lower limb muscles	D: 1000 MU	Reduced spasticity $p<0.0001$ ankle extensors
Carda & Molteni 2005 (38)	2b	Stroke, trauma	65	Finger flexors		Taping vs electrical stimulation and splinting
Childers et al. 2004 (47)	1b	Stroke	91	Biceps, wrist and finger flexors	B: 90–360 MU	Decreased muscle tone $p<0.05$ wrist, elbow and fingers. No effect on global QoL or disability
Cardoso et al. 2005 (48)	Meta-analysis	Stroke	5 studies	Upper limb	B: 75–300MU D: 500, 1000, 1500 MU	BTX-A superior to placebo in reducing muscle tone
Grazko et al. 1995 (49) (mixed upper and lower)	1b	Stroke, MS, traumatic brain injury, perinatal hypoxia	20	Involved muscles	B: 138 U	At least 2-point reduction in Ashworth scale in all patients. Reduced pain in 5/5
Francis et al. 2004 (50)	Meta-analysis	Stroke	2 studies	Biceps, wrist and finger flexors	D: 500, 1000, 1500 MU	Improvement in spasticity is associated with improvement in arm function

Hesse et al. 1998 (35)	1b	Stroke	24	Upper limb flexors	D: 1000 U ± electrical stimulation vs placebo ± stimulation	Most improvement occurred in botulinum toxin plus stimulation group
Hyman et al. 2000 (51)	Ib minus (the groups receiving Dysport® were receiving more muscle relaxant than the placebo group)	MS	74	Hip adductors	D; 500, 1000 MU	Dysport® reduced spasm and improved muscle tone in hip adductors
Kirazli et al. 1998 (52)	1b (Rated 1b minus by some authors because of differences in baseline clonus duration in subjects)	Stroke	20	Soleus, tibialis posterior, gastrocnemius	B: 400 MU compared with phenol 3 ml 5% solution	Both treatments were effective; more significant at weeks 2 and 4 for BOTOX® – no difference in groups at week 8 and 12
Mancini et al. 2005 (53)	1b	Stroke	45	Lower limb muscles	B: GI 167; GII 322; GIII 540 MU	Significant effect on MAS at 4 weeks for GII and GIII compared with GI. Prolonged effect on spasticity, gait velocity, gait function, pain and clonus in Groups II and III
Marco et al. 2007 (54)	1b	Stroke	29	Pectoralis major	D: 500 MU vs placebo	Less pain with BTX-A
Pittock et al. 2003 (55)	1b	Stroke	234	Calf muscles	D: 500, 1000, 1500 MU	1500 units: greatest benefit $p<0.02$ at 4, 8, 12 weeks
Richardson et al. 2000 (56) (mixed upper and lower)	1b	Mixed (stroke, trauma, tumour, CP, anoxia)	52	Upper and lower limb muscles identified by EMG	B: 30–500 MU	Reduced spasticity $p<0.02$ at 3 weeks – no further decrease
Simpson et al. 1996 (57)	1b	Stroke	39	Biceps, flexor carpi radialis, flexor carpi ulnaris	B: 75, 150, 300 MU	300 U dose reduced wrist and elbow spasticity $p<0.05$ at 2, 4 weeks
Smith et al. 2000 (58)	1b minus (the study combined all doses for analysis)	Stroke or trauma	21	Elbow, wrist, finger flexors	D: up to 1500 MU	Fingers and wrist spasticity reduced $p<0.001$
Snow et al. 1990 (59)	1b	MS	9	Hip adductors	B: 400 MU	Spasticity reduced $p=0.009$ at 6 weeks
Suputtitada & Suwanwela 2005 (60)	1b minus (the 1000u groups only recruited 5 patients – should have been 15 – because of excessive muscle weakness)	Mixed (stroke, traumatic brain injury, spinal cord lesion, MS, degenerative disease)	50	Biceps, wrist and finger flexors	D: 350, 500, 1000 MU	Significant reduction in MAS at week 8. 1000 MU caused unacceptable weakness
Verplancke, et al. 2005 (61)	1b	Acquired severe brain injury	243 screened 35 randomized	Gastrocnemius, soleus	B: 200 U per leg	Reduction in ankle deformity $p=0.07 – 0.41$
Non-randomized trials						
Stoquart et al. 2008 (62)	n/a	Stroke	18	Rectus femoris	B: 200 U	Stroke impairment assessment set (SIAS) improved ($p=0.005$) as did Duncan-Ely score ($p<0.001$). Increases were seen in maximum knee flexion during swing phase ($p<0.001$), knee flexion speed ($p=0.009$) and knee negative joint power ($p<0.001$).
Caty et al. 2008 (63)	n/a	Stroke	20	Rectus femoris (RF), semitendinosus (ST), triceps surae (TS)	B: 100 U-ST; 200 U RF and TS	Reduced RF and ST muscle tone ($p<0.001$). Increased knee flexion during swing phase ($p=0.03$); decreased external mechanical work ($p=0.04$) and lower energy cost ($p=0.03$). Locomotion ability (ABILOCO) was improved ($p=0.03$)

*Level of evidence was rated as defined by the Oxford Centre for Evdence Based Medicine (2002). Available at: www.cebm.net/index.aspx?0=1047

BTX-A: botulinum toxin type A; QoL: quality of life; MAS: magic-angle spinning; n/a: not applicable; EMG: electromyography; MS: multiple sclerosis; CP: cerebral palsy; B: BOTOX®; D: Dysport®; U: units; MU: million units; No.: number; G: group. .

Guidelines for rehabilitation of adults with stroke have been published in the US (11). Specific guidance on the use of botulinum toxin therapy in the management of spasticity has also been published and endorsed by the Royal College of Physicians (UK) (12, 13) and has gained wide acceptance.

It is important that multidisciplinary teams have access to both secondary and primary (community) medical services, so that patients can receive the necessary physiotherapy and occupational therapy services. Appropriate rehabilitation programmes are defined for each patient with emphasis on the new rehabilitation techniques that exploit the neuroplasticity of the brain.

Specialist spasticity and rehabilitation services have an advantage over *ad hoc* arrangements, in that their healthcare professionals have the experience and expertise of guiding patients to realistic and timely goals in order to achieve optimal outcomes. They are also able to raise awareness amongst patients and carers about spasticity, the availability of new treatments and treatment strategies and how good referrals may be made to them.

TREATMENT OPTIONS

A variety of treatment options is available and clinical experience has shown that a multi-modal approach has many benefits in combining physical therapies with surgical and/or pharmacological treatments.

There is ample evidence (12 studies in upper limb, 7 in lower limb, 2 mixed upper and lower limb and one meta-analysis) that botulinum toxin type A significantly decreases muscle tone and improves passive function (Table III). The demonstration of functional gains has proved more difficult (14). Some studies of single treatments with botulinum toxin produce conflicting results, which could be related to methodological problems in showing the improvement. However, combining toxin injections with physical therapy has shown functional improvements, lending support to the idea that this should be part of a comprehensive spasticity service.

MEDICO-LEGAL CONSIDERATIONS

The licensed indications for botulinum toxin type A use vary throughout Europe, with licensing often restricted to stroke and upper limb (Table IV) and much usage off-label. This may pose problems for patients and physicians in accessing effective treatment, and contributes to an inequitable access to specialist spasticity services across Europe.

There is a paucity of studies addressing the direct cost-effectiveness of botulinum toxin type A in adult spasticity. Three studies have been carried out using panels of physicians and other healthcare professionals to provide treatment scenarios and anticipated improvement for typical patients with post-stroke spasticity (15–17). These scenarios were then used to calculate costs. The studies concluded that botulinum toxin type A gave significant benefit for little additional cost and, when calculated as cost per successful month of treatment ratio, using botulinum toxin type A actually cost less than not including it in the treatment regimen. These studies suggest therefore that botulinum toxin type A would be a cost-effective treatment for post-stroke spasticity.

More information is available on the costs associated with the complications following stroke, such as falls, fractures, or the pressure sores that may develop as a consequence of spasticity. The costs of these complications are considerable and will have significant impact on healthcare budgets.

Table IV. *Licensed indications for botulinum toxin type A in upper limb, lower limb and hand and wrist spasticity**

	Spasticity hand and wrist following stroke		Upper limb spasticity		Lower limb spasticity		
Country	BOTOX®	Dysport®	BOTOX®	Dysport®	BOTOX®	Dysport®	Comment
Austria	No	No	No	No	No	No	Treatment is only possible in hospital and out-patient departments
Belgium	Yes	Yes	No	Yes	No	No	
Finland	Yes	No	No	No	Only for children with CP	Only for children with CP	
France, Italy, Spain, Turkey	Yes	Yes	Yes	Yes	Yes	Yes	
Germany	Yes	Yes	No	Yes	Only for pes equinovarus in children with CP >2 years old	No	
Poland	Yes	Yes	No	Elbow	Children with CP	Children with CP	
Switzerland	Yes	No	Yes	Post-stroke	Yes	No	
UK	Yes	No	Yes	In conjunction with PT	No	Only in CP	

*This is not a comprehensive list of the licensed indications for botulinum toxin type A. In the majority of countries, both preparations are also licensed for the treatment of cervical dystonia, blepharospasm, hemifacial spasm, torticollis, pes equinus, and hyperhydrosis. There are also cosmetic indications for both preparations.
CP: cerebral palsy; PT: physiotherapy.

There is a potential risk of adverse events associated with distant spread of toxin and, for this reason, the summary of product characteristics (SmPC) for both Dysport® and BOTOX® have recently introduced some additional statements about patient monitoring. The SmPC for Dysport® states that "Side-effects related to spread of toxin distant from the site of administration have been reported (exaggerated muscle weakness, dysphagia, aspiration/aspiration pneumonia, with fatal outcome in some very rare cases)". The BOTOX® SmPC states "Side-effects related to spread of toxin distant from the site of administration have been reported, sometimes resulting in death, which in some cases was associated with dysphagia, pneumonia and/or significant debility". All patients receiving botulinum toxin therapy should be advised to contact their doctor and seek medical attention immediately if they develop breathing, swallowing, or speech difficulty or any severe allergic reaction.

ASSESSMENT AND GOAL SETTING

An essential part of treating spasticity is a proper assessment of the individual's clinical status including a full neurological assessment, noting positive and negative signs of the UMN syndrome (Table II). Functional problems must be addressed and any confounding or exacerbating conditions, such as infection, pain, constipation and other nociceptive influences should be identified and treated (12). Treatment plans can then be devised on an individual basis.

The specialist will need to assess the patient, involving family and carer(s) fully in the planning of treatment, which allows the multidisciplinary management team to define realistic goals and the expectation of outcomes. Briefly, these goals can be related to functional use, especially in the lower limbs; to comfort, especially in the upper limbs or proximal part of the lower limb; or to pain-related spasticity.

Methods of assessing the effectiveness of treatment must be in place and individualized outcome measures should be based on the World Health Organization (WHO) International Classification of Functioning, Disability and Health (ICF) model. Assessments should be performed at regular intervals and continuing treatment should be refined in light of these assessments.

BOTULINUM TOXIN TYPE A USE AND DOSAGE

Botulinum toxin type A treatment should be given as part of an integrated treatment programme involving all the available relevant treatment modalities. Dosages are determined by the individual patient's condition and the goals of treatment and can be reassessed according to the response. It is common clinical practice to initiate therapy at low, but effective, doses and titrate upwards as effects become evident. In order to have a uniform uptake of botulinum toxin within muscles, the muscle is injected in more than one site and this is particularly important in larger muscles, where the dose is divided across multiple sites. A single muscle is rarely treated in isolation and it is important that the pattern of muscle under- and over activity, at rest and while moving, is understood, so that relevant muscles can be treated appropriately.

As there is a lack of uniformity in terms used to describing the anatomical pattern of injections, the consensus group proposes that:

- where muscles in a close anatomical region, including only one or two joints (excluding finger and toe joints, e.g. hand and forearm or foot and ankle) are injected, the term *focal treatment* is appropriate;
- where several adjacent anatomical regions (e.g. hand, forearm, elbow and/or shoulder) are injected, the term *segmental treatment* is appropriate;
- where anatomically separate and distant sites (e.g. arm and leg) are injected, the term *multifocal or multisegmental treatment* is appropriate.

PHARMACOLOGY

To date, 2 formulations of botulinum toxin type A are widely available: BOTOX® (Allergan) and Dysport® (Ipsen); a third preparation, Xeomin® (Merz) has become available recently in some European countries, but its efficacy has not yet been demonstrated in adult spasticity. These preparations are manufactured by different processes, have different formulations and potencies, which are determined by different biological assays. This results in differences in potency of the "units" used for each preparation. *Since there is no simple or accurate way of converting the unit potency of one preparation to another, it is important that clinicians are familiar with the characteristics and dosages of each preparation they use and do not try to convert or extrapolate from one preparation to another* (18). Whichever preparation is used, dosages, dilutions and injections should be tailored to each individual patient.

Extensive clinical experience with botulinum toxin type A has shown it to be well-tolerated and associated with few adverse events across a variety of indications. A meta-analysis of 37 studies (19) has confirmed the excellent safety profile of BOTOX® (grade A evidence) which continues with long-term use (20).

An important consideration in terms of side-effects is the propensity for toxin to migrate away from the injection site. A low migration potential is desirable to restrict the action of the toxin to the injected muscle and minimize both local unwanted spread and systemic effects that could occur subsequent to diffusion. Clinical studies comparing the migration of BOTOX® and Dysport® have not been carried out in patients with spasticity; however, studies in both hyperhidrosis and cervical dystonia have concluded that BOTOX® shows less migration than Dysport® (21, 22).

DILUTION, END-PLATE TARGETING AND INJECTION GUIDANCE

As botulinum toxin type A acts by blocking acetylcholine release at the neuromuscular junction, injection into the region of the motor end-plate should maximize efficacy. While some

muscles, such as biceps brachii, have well-defined motor end-plates, which can be located from external landmarks (23), the anatomical location of the motor end-plates is unknown for many others. Where the end-plate location is not known, or for muscles with diffuse end-plates, such as the gastrocnemius muscle, a more even spread of injections across the muscle (with possibly higher injection volumes) may be necessary. One study has shown greater efficacy for higher dilutions of botulinum toxin type A when injections were not targeted to end-plate regions (24).

Targeting of botulinum toxin type A injections is another important issue. So far 2 controlled studies have shown that for deeply localized or small muscles needle placement based solely on anatomical landmarks is unsatisfactory and most muscles were only correctly located in less than 50% of cases (25, 26). Therefore injection guidance with electrical stimulation or sonography for deep-seated muscles may be a better alternative (27, 28) and should be standard practice. A specific intramuscular injection into the target muscle is more effective and safe since the toxin is delivered to the right place; injecting outside the muscle increases the potential for the toxin to migrate away from the target. However, muscle targeting by EMG or electrical stimulation, while effective, can be difficult, is time-consuming and may cause discomfort and thus is not always carried out in a routine clinical setting, although practice does vary between countries.

Patient comfort should always be a consideration in determining the number and location of injection sites and volume of injections as well as injection guidance techniques.

FOLLOW-UP

Botulinum toxin type A has shown sustained activity with repeated use for up to a year (29). The peak duration of response has been shown to increase with time and the interval between injections may also lengthen. It is important that patients are followed up carefully and that subsequent injection regimens are based on the patient's response to previous treatment in terms of the gains obtained, such as increases in passive or active functioning.

Where there is a lack of response, the patient should be assessed at review to determine the possible responsible factors confounding efficacy. Inaccurate selection of the correct muscle, or its identification for injection, are possible causes, or there may have been an inadequate injection technique. There may be a biomechanical component of hypertonia and an assessment of the neural and non-neural contributions to muscle stiffness that could be contributing to outcome may be necessary. Rarely, lack of response may have been due to the presence of neutralizing antibodies or muscle fibrosis and shortening of soft tissue (e.g. ligaments and capsule).

The incidence of neutralizing antibodies following repetitive botulinum toxin type A injections has been calculated from retrospective data from patients with cervical dystonia. The incidence of antibody formation was 3–10% with the old formulation of BOTOX® and up to 5% with Dysport® (30–32). However, neutralizing antibodies are really no longer seen in adult spasticity treatment. As measured after the reformulation of BOTOX® in 1997, the formation of antibodies with this lower total protein preparation is now a rare occurrence, and deemed to be of minimal clinical significance (33).

RESEARCH CHALLENGES

Muscle identification and injection guidance

While many techniques are available to aid muscle localization, there are no recommendations as to which techniques are most suitable for which muscles, nor is there concrete guidance as to which muscles require imaging techniques for accurate placement of the injections. Studies are needed to clarify these issues.

Cost-effectiveness

The cost-effectiveness of botulinum toxin type A has been estimated, but is not known with real accuracy; this is an area that could benefit from proper cost-efficacy studies and one is currently underway.

Recommendations on pre- and post-injection treatment

Currently, there is little information on the measures that can modify and/or increase the efficacy of botulinum toxin injections. Electrical stimulation of the nerve or the injected muscles (34–36) and muscle activity itself (37) can increase efficacy of botulinum toxin type A. Also, physiotherapy including muscle stretching, casting, taping or splinting is able to act in the same way (38, 39). However, more studies are required to ascertain the optimal timing, duration and intensity of post botulinum toxin physical therapy and the contribution of learning processes based on repeat-attention-reward methodology (40).

Trial design

It is an acknowledged problem that designing trials and using clinical scales capable of demonstrating functional improvements is very difficult. Attention needs to be focused on optimal trial design, e.g. the use or development of valid and sensitive clinical scales for measurement of motor control and functional improvements in upper and lower limb spasticity following botulinum toxin This assessment should follow the WHO's ICF model, i.e. assess the impairment, activity limitation and participation restriction; utilise the combination of modern physiotherapy and training methods with botulinum toxin treatment to elucidate the impact of reduced spasticity in creating a therapeutic window for employing interventions to produce functional improvement.

CONCLUSION

In conclusion, botulinum toxin type A provides a valuable tool in the multi-modal treatment of adult spasticity. This paper provides a European consensus opinion on the condition and best practice in its treatment and defines the research challenges that still exist.

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