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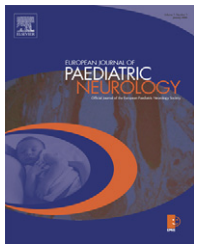

Review article

European consensus table 2006 on botulinum toxin for children with cerebral palsy

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ABSTRACT

An interdisciplinary group of experienced botulinum toxin users and experts in the field of movement disorders was assembled, to develop a consensus on best practice for the treatment of cerebral palsy using a problem-orientated approach to integrate theories and methods. The authors tabulated the supporting evidence to produce a condensed but comprehensive information base, pooling data and experience from nine European countries, 13 institutions and more than 5500 patients. The consensus table summarises the current understanding regarding botulinum toxin treatment options in children with CP.

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Contents

Development of the consensus table

The use of botulinum neurotoxin (BoNT) in European countries is established but is far from standardised. A large variety of treatment strategies and applications of BoNT in children with cerebral palsy (CP) are recognised; however, subtle differences in therapy seem crucial in determining success or failure. This has been convincingly shown in two recent papers on the treatment of the upper extremity spasticity.[1,2] A UK position paper on BoNT in CP was published 8 years ago[3] and guidelines have been produced by acknowledged experts in the field.[4,5] However, there is a recognised need for an updated orientation in this rapidly evolving and expanding field.

An interdisciplinary group of renowned experienced users of BoNT (in children with CP) and experts in the field of movement disorders was assembled, to work using a problem-orientated approach to integrate theories and methods[6] and develop a consensus on best practice for the treatment of CP. This group actively supports the rights of children to the highest attainable standard of health and access to health care as set forth in the resolution of the executive board of the World Health Organisation.[7]

The authors decided to tabulate the supporting evidence to offer the reader a comprehensive and condensed information base. Each reader is encouraged to draw the relevant information from the table that is specific to their own treatment setting. The corresponding author (F.H., University of Munich) proposed a first draft of the table that was sent out to the other authors for comment. The draft consensus table covered 10 key areas of BoNT therapy in children with CP. A comprehensive literature search in PubMed (including MEDLINE, NLM Gateway, PreMEDLINE, HealthSTAR, publisher supplied citations) and SCOPUS was performed for each area. The available literature on BoNT (>7500 papers) was screened. Studies included in the table were those that used BoNT to treat children (search items: BOTULINUM CHILDREN, >550 papers) or added other relevant information to the specific research domain. Additional papers were included according to their relevance in this setting, e.g. pathogenesis and imaging[8] or injection technique.[9] Each therapy study to be cited in the table was assigned there a value of I–V as suggested by the AACPDM and used by e.g. Lannin et al.,[10] according to the level of evidence represented.

Following circulation of the draft table a 1-day meeting, of invited participants, was held in June 2005 on behalf of the University of Munich. During the meeting the 10 key areas were discussed in detail, further data from clinical studies were collected and clinical experience from each participant was included to build on the knowledge base. In a 3-month period after the meeting, the participants formed teams according to their expertise to confirm details and, before submission, the table was updated with relevant new papers published up to June 2006.

The consensus table summarises the current understanding regarding BoNT treatment options in children with CP. The text serves as a short introduction to the 10 key areas and should be read as a commentary on the table. The table pools data and experience from nine European countries, 13 institutions and more than 5500 patients.

Section 1 Cerebral palsy

CP is the most common cause of spastic movement disorders in children.[11,12] Our understanding of the aetiology, or at least the pathogenesis, of the disease has been greatly advanced by the development of magnetic resonance imaging, which allows the identification of the underlying structural changes in the brain[13] and gives information on topography and the extent and potential timing of the causative lesion.[8] The development of a European consensus on CP definition and classification[14] and its illustration by a video-based manual (the reference and training manual of the SCPE) provides a practical basis for a unified approach with respect to diagnosis.[15] A whole body approach to classification is facilitated by the use of tools such as the gross motor function classification system (GMFCS), which describe both disease severity and course.[16,17] An International Committee has proposed a more standardised and comprehensive classification system.[18] As these classifications represent specific problems in children with CP, associated with

possible causes, they can ultimately be connected with specific treatment strategies.

Section 2 Medico-legal and medico-economical aspects

BoNT treatment of children with CP is often performed under unlicensed conditions. However, the off-label use of medications is common practice in many paediatric fields. In a number of countries the licence for BoNT treatment is restricted to specific preparations, specific indications and limited dosages. Considered variations in BoNT dosage, clinical indication(s) and the muscle group(s) treated represent appropriate, although unlicensed, use where such treatment is in line with clinical experience.[19]

Section 3 Botulinum toxin and integrated therapy

The use of BoNT in children with CP represents a major therapeutic intervention and should not be considered a stand-alone treatment. The treatment approach to the spastic movement disorders associated with CP must include the whole range of conservative and surgical strategies and regularly requires an interdisciplinary team approach. Recent developments in the field show that the advanced use of BoNT i.e. combined with different conservative (or non-conservative) treatment options, has the potential to achieve functional benefits for children with CP.[1,20,21] However, there is insufficient evidence to either support or refute the use of interventions after BoNT injections.[10]

Section 4 Botulinum toxin therapy approach

The spastic movement disorders in children with CP are a result of the involvement of the brain, central motor pathways, spinal circuits and musculo-skeletal system. With ongoing child motor development spastic movement disorders develop into distinctive motor patterns, which need to be recognised and should be used to guide treatment. The use of a disease pattern-guided treatment approach will help to establish standards of therapy.[22] To achieve optimal results in patients with a non-focal condition such as CP a number of muscle groups may need to be targeted.[22,23] This has led to the development of a multi-muscle treatment approach, in which a number of muscle groups are treated with BoNT to achieve optimal limb alignment.[24,25]

Section 5 Pharmacological aspects of botulinum toxin therapy

To date two preparations of BoNT Serotype A—Botox® (Allergan Inc.) and Dysport® (Ipsen Ltd.)—have demonstrated focal efficacy and functional gains for children with CP. The two products have different formulations, molecular structures, manufacturing processes and use different methods for determining biological activity.[26,27] For children with CP, these pharmacological differences can have implications for clinical use; individual dosages must be calculated independently for the preparations and fixed dose-conversion factors are not applicable in the treatment of spasticity in children with CP.[24] The authors suggest the use of dosages as presented in the table.

Section 6 Botulinum toxin therapy and procedures

In children with CP pain management is an important issue, especially because repeated, elective procedures are performed. Therefore, appropriate, effective analgesia and sedation is a fundamental and an ethical necessity. The optimal regimen will vary between individuals and will be influenced by the age of the child, the number of muscles to be treated and the institutional setting and resources.

Children should receive injections delivered using an accurate localisation technique.[28,1] Classical neurophysiological localisation methods (EMG, electrical stimulation) have recently been fine-tuned and amended by sonography which allows precise and painless identification of any target muscle using readily available, non-invasive equipment.[29,30]

Section 7 Assessment and evaluation of treatment with BoNT in children with CP

Ongoing development of new CP assessment tools has been stimulated by the therapeutic possibilities offered by BoNT therapy. For optimal CP evaluation it is crucial to use a combination of validated instruments and methods, with respect to the dimensions of the international classification of functioning, disability and health (ICF).[31]

Section 8 Botulinum toxin therapy continuation or discontinuation

Randomised controlled trials for the initial BoNT treatment of pes equinus deformity show efficacy rates of 50%[32] and 61%.[33] Initial reports on long-term treatment show that, while about 75% of patients achieve their treatment goals following the initial injection sessions, a considerable number discontinue therapy for various reasons.[34] Further research will need to delineate and quantify what factors determine continuation or discontinuation of therapy.

Non-responsiveness to BoNT can occur as a result of (i) insufficient injection accuracy, (ii) development of muscle fibrosis or (iii) the formation of antibodies. In children undergoing BoNT treatment in the 90s up to 30% were reported to develop antibodies.[35] Although higher dosages per session have recently been administered to children with CP, secondary non-response due to the presence of antibodies is no longer experienced as a clinically relevant problem due to the use of reformulated BoNT.[21,24] This is in line with reports that have demonstrated reduced antigenicity of the reformulated preparation in adults with cervical dystonia.[36]

Section 9 Safety of botulinum toxin

Looking back on more than 15 years of widespread use BoNT therapy has proved a safe treatment option[24,37,38] and the dosing recommendations given in the table are drawn from this long-term experience.

Section 10 CP is a research challenge

Studies conducted in children with CP have received increasing recognition over recent years and are now considered on a par with the research-excellence seen in other movement disorder fields. CP as a lesional cerebral disease has the potential to serve as a model to investigate the structure–function relationships and the compensatory potential of the young brain during development.[39] A sample of six research topics addressing basic and clinical aspects is outlined in the table to stimulate future work.

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A.1. Consensus table

See Table A.1.

Table A1

Section	Key areas-updated consensus	Key literature—selected clinical studies and reviews
Section 1. Cerebral palsy: epidemiology, aetiology phenomenology		
	Epidemiology • CP is the most prevalent cause for motor disorders in childhood • The socio-economic impact of CP is high • The prevalence is 2–3 per 1000 live births • The prevalence increases up to 100 per 1000 live births in extreme pre-maturity	**Clinical studies** • Epidemiological studies on CP[11,40–42]
	Etiology Time of lesion–lesion pattern • 1st+2nd trimester–maldevelopments • Early 3rd trimester–periventricular leucomalacia (PVL), intraventricular hemorrhage (IVH) • Late 3rd trimester–cortical-subcortical and deep grey matter lesions The motor disorder in CP involves supra-spinal motor centres, cortico-spinal tracts, segmental spinal circuits and the musculo-skeletal system	**Reviews** • Actual classification of CP[18,43] • Classification of cerebral lesions in CP acc. to MRI[8] • Epidemiology[44] • Definitions of dystonia, rigidity and spasticity in children[45] • Pathophysiology on paediatric motor disorders[46] • Musculo-skeletal aspects of CP[4,47,68]
	Phenomenology • Type (spastic, dyskinetic or ataxic CP) • Distribution (bilateral or unilateral) • Severity (GMFCS Level I-V) • Comorbidity (e.g. epilepsy, mental retardation, sensory impairment, etc.)	
Section	Key areas-updated consensus	Key literature—selected clinical studies and reviews
Section 2. Medico-legal and medico-economical aspects		
	Medico-legal aspects • Users should be familiar with the guidelines for registration of BoNT applicable in their countries • Comprehensively explain the proposed therapy to parents and caregivers and obtain written consent	**Clinical studies** • Socio-economic impact of CP[48–51] • Off-label use in paediatrics[52] • Off-label therapy in Germany[53]

Table A1 (*continued*)

Section	Key areas-updated consensus	Key literature—selected clinical studies and reviews
	• Meticulously document treatment details including evaluation of functional outcome	**Reviews** • Minimal acceptable standards of health care[54] • BoNT is elemental part of spasticity treatment[55] • Statement of the Society for Neuropediatrics[56] • Social outcomes of children with CP[57]
Section	Key areas-updated consensus	Key literature—selected clinical studies and reviews
Section 3. BoNT and integrated therapy		
	Therapeutic options should consider all dimensions of the International Classification of Functioning Disability and Health (ICF of the WHO)	**Clinical studies** • BoNT combined with other treatments (selection of studies) ([32] [II], [58] [II], [59] [II], [60] [II], [61] [II], [62] [II], [63] [II], [64] [II], [65] [IV])
	Integrative aspect • BoNT can be combined with all other treatment modalities, e.g. ○ BoNT & functional therapy ○ BoNT & orthoses, casting, splinting ○ BoNT & surgical intervention ○ BoNT & intrathecal baclofen or other pharmacotherapy	**Reviews** • WHO/ICF/CP[31] • BoNT & physical therapy[66] • BoNT & occupational therapy[67] • Pharmacotherapy of spasticity[55] • Existing consensus[3,4] • Minimal acceptable standards for healthcare[54] • Effectiveness of therapy after BoNT[10]
	Key Therapists (in alphabetical order) ○ Developmental paediatrician ○ Functional therapist (physiotherapy, occupational therapy etc.) ○ Orthopedic surgeon ○ Orthotist ○ Paediatric neurologist ○ Rehabilitation specialist	
Section	Key areas-updated consensus	Key literature—selected clinical studies and reviews
Section 4. BoNT therapy approach		
	General considerations • A developmental disorder needs an adaptive approach to cope with the changing patterns that occur during the course of development • During the time of the most rapid motor development, the reversibility of any treatment option is of great value • The reduction of the M-response as a measure for the paralysing effect of BoNT seems to be effected more readily in dystonic muscles compared to spastic muscles	**Clinical Studies** • Spastic quadriplegia ([69] [IV]) • Spastic pes equinus ([32] [II], [33] [II], [70] [IV], [71] [II], [72] [II], [73] [II]) • Crouch-gait ([74] [IV]) • Adductor spasticity ([60] [II], [75] [II]) • Upper limb flexor deformity ([1] [II], [2] [IV], [76] [IV], [77] [II], [78] [II], [79] [II], [80] [II]) • Analgesic effects of BoNT therapy ([59] [II], [81] [IV]) • Quantification of the M-response in dystonic and spastic muscles ([33] [I], [82] [IV])
	Therapy goals should be established by mutual consent between the therapist and the patient/parent before therapy • (Multi)-focal problem • Functional relevance may include improved mobility, ease of care, deformity or pain **The therapy goals should address specific clinical problems, e.g.** • Spastic quadriplegia (bilateral spastic CP) • Spastic pes equinus (unilateral or bilateral spastic CP) • Crouch-gait, hip flexion (bilateral spastic CP) • Adductor spasticity (bilateral spastic CP)	**Reviews** • Rehabilitation of children with CP[83] • Family-centred service for children with CP[84] • On CP and BoNT[85,86] • Cochrane review: BoNT as an adjunct to treatment in the management of the upper limb[87] • Cochrane review: treatment of lower limb spasticity in CP[88]

Table A1 (*continued*)

	• Upper limb flexor deformity (unilateral or bilateral spastic CP) • Amelioration of pain (unilateral or bilateral spastic CP)	
Section	Key areas-updated consensus	Key literature—selected clinical studies and reviews
Section 5. Pharmacological aspects of BoNT therapy		
	Preparations In children with CP the available preparations cannot be exchanged with a fixed ratio due to different pharmacokinetic and pharmacodynamic characteristics Upper dose limits (U = Units; kg bw = kilogram body weight) BoNT Serotype A • Preparation Botox® ○ Safe range (U/kg bw) 6–25 ○ Total dose (U) 400–600 • Preparation Dysport® ○ Safe range (U/kg bw) 15–25 ○ Total dose (U) 900 BoNT Serotype B • Preparation Neurobloc®/Myobloc® ○ Safe range (U/kg bw) 150–400 (?) ○ Total dose (U) 10,000 (?)	**Pharmacology** • Mechanism of action of BoNT serotype A[89–92] and Serotype B[93] **Clinical studies** • Preparation Botox® ○ Up to 12 U Botox®/kg body weight (pes equinus) ([33] [I]) ○ Up to 30 U Botox®/kg body weight (multi-level, multi-muscle approach) ([24] [IV], [25] [IV]) • Preparation Dysport® ○ Up to 30 U Dysport®/kg body weight (pes equinus, adductor spasticity) ([32] [II], [75] [II], [94] [I]) • Preparation Neurobloc® ○ Up to 400 U Neurobloc®/kg body weight in a small pilot study ([95] [IV]) **Reviews** • Pharmacology of botulinum toxins[96] • Physiological effects of BoNT in spasticity[97] • Upper dose limits ○ Up to 23 U Botox®/kg bw[19] ○ Up to 25 U Dysport®/kg bw[98] **Internet resources** • BoNT dosing tables: www.mdvu.org/library/dosingtables
Section	Key areas-updated consensus	Key literature—selected clinical studies and reviews
Section 6. BoNT and therapy procedures		
	Administration by an experienced team in an equipped paediatric setting • The therapy setting has to be adapted accordingly ○ Analgesia and sedation ○ Technique of injection (sonography, electrical stimulation, EMG)	**Clinical studies** • Accuracy of palpation/electrical stimulation[28] • BoNT injection using sonography[29] • Sonography-guided psoas injection[30] • Repeated injections without general anaesthetic[99] • N_2O in paediatric patients[100,101] **Reviews** • EMG, pro/contra[102,103] • Management of pain and anxiety[104] • Methodology of sonography-guided injection[105]
Section	Key areas-updated consensus	Key literature—selected clinical studies and reviews
Section 7. Therapy evaluation		
	Documentation and evaluation should use validated methods (according to ICF/WHO).	**Clinical Studies** • ICF in CP[106]

Table A1 (*continued*)

Section	Key areas- updated consensus	Key literature—selected clinical studies and reviews
	Body structure/function • Range of Motion • (modified) Ashworth Scale • Tardieu Scale • 3D gait analysis • Video documentation • Goal Attainment Scale (GAS) **Activity/participation** • 3D gait analysis • Gross motor function measure (GMFM) • Manual ability classification system (MACS) • WeeFIM™ (Functional Independence Measure) • Paediatric evaluation of disability inventory (PEDI) • Canadian occupational performance measure (COPM) • Quality of upper extremity skills test (QUEST) • Bimanual fine motor function (BFMF) • AHA (assisting hand Assessment) • Physician Rating Scale, Observational Gait Scale • Edinburgh Visual Gait Analysis Interval Testing Scale • Energy expenditure measures • Goal Attainment Scale (GAS)	• Joint range of motion[107,108] • Ashworth Scale[109] • Tardieu Scale[110] • GMFCS[17,111,112] • GAS[113–116] • Video documentation[68] • Energy expenditure[117–119] • Edinburgh Visual GAIT[120,121] • Physician Rating Scale, Observational Gait Scale[122] • PEDI[123] • BFMF[106] • AHA: Assisting Hand Assessment[124] • MACS[125] • Longitudinal health outcome[126] • Health-related quality of life[127–129] • 3D gait analysis[21,62,130] **Reviews** • ICF approach[31] • Evaluating therapy[131–133] • Measures for muscles and joint in lower limb[134] • Systematic literature review of assessment measures[135]
Section	Key areas-updated consensus	Key literature—selected clinical studies and reviews
Section 8. BoNT therapy continuation or discontinuation		

	Continuation
	• Improved function
	• Improved posture of extremities
	• Improved pain and comfort
	Discontinuation
	• Continued benefit without further injections
	• No significant gain or unacceptable side effects
	• Secondary non-response
	  ○ Fibrosis
	  ○ Neutralising antibodies against BoNT
	• Continuation to orthopaedic treatment
		Clinical Studies
		• Antibody screening in children with CP (mouse protection bioassay)[136]
		• Antibody screening in children with CP (mouse hemidiaphragm assay)[35]
		• Rate of AB formation for BoNT (preparation Botox®) in adults[36]
		• Why children discontinue treatment[34]

Section	Key areas-updated consensus	Key literature—selected clinical studies and reviews
Section 9. Safety of BoNT		
	Local adverse events • Haematoma (rare when small gauge needles (27-30G) are used) • No reports on local infections following BoNT injections have been published or reported by the users of BoNT • Local weakening beyond the therapy goal can occur when muscle size, dosing guidelines and dilution guidelines are not respected or when inadequate localisation techniques are applied • Distal local adverse events (e.g. bladder dysfunction) can be observed when dosing and dilution guidelines are neglected or inadequate localisation techniques are applied	**Clinical Studies** • Report on the safety and occurrence of adverse events after repeated injections (preparation Dysport®)[137] • Report on safety of treatment and frequency of adverse events in large cohort (preparation BOTOX®)[24] • Safety profile of BoNT treatment in children (preparation Dysport®)[37] • Accuracy is relevant for the safety of treatment[1]

Table A1 (*continued*)

	Generalised adverse events	**Reviews**
	• Generalised weakness has been observed and reported and can occur when preparation specific dosing and dilution guidelines are not respected	• Meta-analysis on safety, incl. data from adults and children[38]
Section	Key areas-updated consensus	Key literature—selected clinical studies and reviews
Section 10. Research challenge CP		
	• Muscle pathology in children with CP—the molecular biology of fibrosis • The spastic movement disorder in children with CP—system physiology • Plasticity and neuromodulation in children with CP—intervention vs. natural course • Aetiology and pathogenesis of CP—biology and neuroimaging • Computational neuroscience—robotics in children with CP • Evidence-based medicine vs. poly-pragmatical approach • To bundle epidemiologic competency and to conduct international cooperation studies	

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