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Review article

The updated European Consensus 2009 on the use of Botulinum toxin for children with cerebral palsy

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ABSTRACT

An interdisciplinary European group of clinical experts in the field of movement disorders and experienced Botulinum toxin users has updated the consensus for the use of Botulinum toxin in the treatment of children with cerebral palsy (CP). A problem-orientated approach was used focussing on both published and practice-based evidence. In part I of the consensus the authors have tabulated the supporting evidence to produce a concise but comprehensive information base, pooling data and experience from 36 institutions in 9 European countries which involves more than 10,000 patients and over 45,000 treatment sessions during a period of more than 280 treatment years. In part II of the consensus the Gross Motor Function Measure (GMFM) and Gross Motor Function Classification System (GMFCS) based Motor Development Curves have been expanded to provide a graphical framework on how to treat the motor disorders in children with CP. This graph is named "CP^{Graph} Treatment Modalities – Gross Motor Function" and is intended to facilitate communication between parents, therapists and medical doctors concerning (1) achievable motor function, (2) realistic goal-setting and (3) treatment perspectives for children with CP. The updated European consensus 2009 summarises the current understanding regarding an integrated, multidisciplinary treatment approach using Botulinum toxin for the treatment of children with CP.

Contents

1. Part I: update of the table

1.1. *Legend to the consensus table*

The Consensus update 2009 presents a conceptual framework for best practice in the use of Botulinum toxin (BoNT) in children with cerebral palsy (CP). Since the first European consensus table on Botulinum toxin for children with CP in 2006[1] basic research, clinical trials, new treatment strategies and safety regards have evolved in the expanding field of CP management. The aim of this updated, annotated, and tabulated evidence report (Table 1) is to incorporate the recent advances in knowledge into all sections of the earlier consensus table. A comprehensive literature search in PubMed (including MEDLINE, NLM Gateway, PreMEDLINE, HealthSTAR, as well as publisher supplied citations) was performed as described in the first European consensus[1] including literature from June 2006 until June 2009. Previously cited literature was only removed if there was more accurate literature published on a topic or level of evidence could be increased with new literature.

Besides literature enhancement, the updated European consensus table is based on data from an extended number of 36 European treatment centres. The authors were able to draw upon the combined experience of more than 280 treatment years, more than 10,000 treated patients, and more than 45,000 treatment sessions to condense the knowledge in the consensus table.

1.2. *Essentials of 2009*

(1) Changing the Paradigm from ''Botulinum toxin'' to ''Activity is supported by Botulinum toxin'': Activity is supported by BoNT and *vice versa*: due to its mechanism of action, BoNT only reduces muscle tone in the active, non fibrotic, ''non-contractured'' part of the muscle. However, by reducing tone in the muscle it allows stretch to be applied, which is in itself a stimulus for muscle growth. Activity, which means function, (e.g. dorsiflexion of the foot during the gait cycle) is dependant on the agonistic activity of a particular muscle (in this case tibialis anterior muscle). BoNT supports the agonist's activity by reducing muscle tone and regulatory circuits of the antagonist (here triceps surae muscle). To improve function, activity, participation and development of a child with CP additional therapies have to be included (see also Sections 3 and 4).
(2) ''Safety and publicity'': BoNT reflects all the benefits and controversies of modern medicine: strong and ongoing medical success as well as a fashion-driven presence on ''how to design a perfect body'', oversimplified enthusiasm, mass media presence, and headline catching criticism. Due to the wide number of indications Pharm Allergan (Preparation Botox® and Vistabel®), Ipsen Pharma (Preparation Dysport®), Merz Pharmaceuticals (Preparation Xeomin®) and Solstice Neuroscience (Preparation Neurobloc/Myobloc®) have had to document the possibility of severe systemic side effects in a ''red hand letter'' in Europe in June 2007 (download at: The German Federal Institute for Drugs and Medical Devices (BfArM http://www.bfarm.de/), followed by an FDA statement in February 2008 (http://www.fda.gov), and a statement produced by Swissmedic (http://www.swissmedic.ch) in June 2008. In September 2008 the German BfArM published the conclusive statement that currently ''there is no evidence showing a causal connection'' between the fatal outcome of 5 patients and their prior treatment with Botulinum toxin.[2] A follow-up statement of the FDA was published in May 2009 stating that FDA has notified the manufacturers of licensed Botulinum toxin products of the need to strengthen warnings in product labelling and that manufacturers have to develop and implement a Risk Evaluation and Mitigation Strategy (REMS) to provide more information regarding the risk for distant spread of Botulinum toxin effects after local injection in the future.[3] It rests in the hand of the treating physician to be up to date on the ongoing safety and labelling discussions using the above mentioned health agencies and their internet domains. Additional information can be accessed at the European Medicines Agency (EMEA: http://www.emea.europa.eu/).

The members of the consensus group are strongly committed to emphasise the ongoing need for a careful, unbiased and transparent documentation of any adverse events in the children with CP who are treated with BoNT, ideally stratified by GMFCS levels (see also Section 2.6).

2. Sections 1–10

2.1. *Cerebral palsy (section 1)*

CP is the most common cause of spastic movement disorders in children.[4,5] Epidemiologic data has shown that with the advanced care in neonatal medicine the incidence and severity of CP in premature children of very low birth weight in Europe[6] and northern America[7] is decreasing. Our

(Continued on page 10)

Table 1 – Updated European consensus table on the use of Botulinum toxin for children with cerebral palsy

Section	Key areas – updated consensus	Key literature – selected clinical studies and reviews
1 Cerebral palsy: epidemiology, etiology 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 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. 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.)	Clinical studies • Epidemiological studies on CP[6,7,84–87] Reviews • Actual classification of CP[88–92] • Classification of cerebral lesions in CP acc. to MRI[11,93] • Epidemiology[94] • Definitions of dystonia, rigidity and spasticity in children[95] • Pathophysiology on paediatric motor disorders[96] • Musculo-skeletal aspects of CP[97,98]
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 care-givers and obtain written consent. - Meticulously document treatment details including evaluation of functional outcome. - Enhance pharmaco-vigilance by rigorously reporting all adverse events	Clinical studies • Socio-economic impact of CP[99–102] • Off-label use in paediatrics[103] • Off-label therapy in Germany[104] Reviews • Minimal acceptable standards of healthcare[105] • BoNT is elemental part of spasticity treatment[106] • Statement of the Society for Neuropediatrics[107] • Social outcomes of children with CP[108]
3 Botulinum toxin, integrated therapy (see also: Fig. 1: CP^{Graph} Treatment Modalities – Gross Motor Function)	Therapeutic options should consider all dimensions of the International Classification of Functioning Disability and Health (ICF of the WHO): - Body structure - Body function - Activity - Participation - Environmental factors Integrative aspect BoNT can be combined with all other treatment modalities, e.g. - BoNT + all modalities of functional therapy: Physiotherapy, OT, speech therapy, constraint-induced movement therapy (CIMT), robotic assisted therapy, etc. - BoNT + orthoses, casting, splinting - BoNT + intrathecal baclofen or other pharmacotherapy - BoNT + surgical intervention	Clinical Studies • BoNT combined with other treatments ([II],[21] [II],[77] [II],[109] [II],[110] [II],[111] [II],[112] [II],[69] [II],[113] [II],[114] [II],[115] [II],[116] [II],[117] [II],[118] [II],[119] [II],[120] [II],[121] [IV][122]) • Evidence based treatment in CP ([V][123])

	Key therapists (in alphabetical order) - Developmental Paediatrician - Functional therapist (physiotherapy, occupational therapy etc.) - Orthopaedic surgeon - Orthotist - Paediatric neurologist - Rehabilitation specialist	Reviews • WHO/ICF/CP[68,124] • Therapeutic interventions in CP[125,126] • Pharmacotherapy of spasticity[125–127] • BoNT & physical therapy[128–130] • BoNT & occupational therapy[131] • BoNT & casting[132] • CIMT in CP[133] • Existing consensus[1,98,134] • Minimal acceptable standards for healthcare[105] • Effectiveness of therapy after BoNT[24] • Effectiveness of casting, physical therapy interventions and orthoses in CP[135,136]
4 Botulinum toxin and common indications	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 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 ([IV][137]) • Spastic pes equinus ([I],[138] [II],[139] [II],[140] [II],[141] [II],[142] [II],[77] [III],[143] [IV],[144] [IV][145]) • Crouch-gait/flexed-knee gait ([II],[119] [IV][146]) • Adductor spasticity ([II],[114] [II][147]) • Upper limb flexor deformity ([II],[148] [II],[149] [II],[21] [II],[117] [II],[120] [II],[116] [II],[121] [III],[150] [IV][136]) • Analgesic effects of BoNT therapy ([II],[110] [IV][151]) • Quantification of the M-response in dystonic and spastic muscles ([I],[138] [IV][152])
	Therapy goals should be established by consent prior to therapy, adapted to: - GMFCS or MACS (see also Section 3, 8, and the CP^{Graph} Treatment Modalities – Gross Motor Function) - Focal, multifocal or multi-level approach - Functional relevance may include improved mobility (function, activity, participation), ease of care, prevention of deformity or pain The therapy goals should address specific clinical problems and patterns in paediatric lower and upper extremity spasticity (the following terminology is used in the cited studies but is not seen as ''up to date'' by the consensus group. The corresponding SCPE terminology is displayed in parentheses: - 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) - Upper limb flexor deformity (unilateral or bilateral spastic CP) - Amelioration of pain (unilateral, bilateral spastic, or dyskinetic CP)	Reviews • Rehabilitation of children with CP[153] • Clinical value of BoNT[154] • Family-centred service for children with CP[155] • On CP and BoNT[156,157] • Cochrane review: BoNT as an adjunct to treatment in the management of the upper limb[158] • Cochrane review: treatment of lower limb spasticity in CP[159]

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Table 1 (*continued*)

Section	Key areas – updated consensus	Key literature – selected clinical studies and reviews
5 Dosage and dose modifiers of Botulinum toxin therapy[a]	Preparations In children with CP the available preparations can not be exchanged with a fixed ratio due to different pharmacokinetic and pharmacodynamic characteristics (no conversion factors). Physicians need to be aware of national/local licensing restrictions Cautions - dose per muscle should not be increased - dose per site should not be increased - number of muscles treated should follow the clinical need - undertreatment should be avoided - carefully calculation of total dose, see dose modifiers below Dose ranges [U = Units; kg bw = kilogram body weight][a] BoNT Serotype A - Preparation BOTOX® range [U/kg bw] 1–20 (–25) max total dose [U] 400 (–600) range max dose/site [U] 10–50 - Preparation Dysport® range [U/kg bw] 1–20 (–25) max total dose [U] 500–1000 range max dose/site [U] 50–250 - Preparation Xeomin® (adult studies suggest dosage equivalence with Botox®,[160, 161] but for children this needs to be confirmed) range [U/kg bw] not established yet max total dose [U] not established yet max dose/site [U] not established yet BoNT Serotype B - Preparation Neurobloc® (mainly used as second line preparation in adult neurology in case of secondary non-response to BoNT/A) range [U/kg bw] not established max total dose [U] not established max dose/site [U] not established Dose modifiers - Severity of CP according to GMFCS - Accompanying diagnoses (e.g. dysphagia, aspiration pneumonia, hypopnea) - Predominant type of movement disorder (spastic versus dyskinetic), - Activity of the injected muscle (dynamic versus fibrotic compounds of the muscle) - Muscle bulk size - Nutritional status, body mass index - Knowledge about the distribution of motor endplates in the injected muscle - Experience from previous BoNT injections Dilution can be adapted to body region and muscle size (e.g. forearm: lower dilution, lower leg: higher dilution).	Pharmacology • Mechanism of action of BoNT Serotype A[162–165] and Serotype B[166] Clinical studies • Preparation Botox® • 4 U Botox®/kg body weight (pes equinus) ([I][138]) • 20–30 U Botox®/kg body weight (multi-level, multi-muscle approach) ([IV],[33] [IV][167]) • Dilution of 1–4 ml/Vial preparation Botox® ([III][41]) • Preparation Dysport® • 15–30 U Dysport®/kg body weight (pes equinus, adductor spasticity) ([II],[77] [II],[114] [I][168]) • Dilution of 1–5 ml/Vial preparation Dysport® ([II][169]) • Preparation Neurobloc® • Up to 400 U Neurobloc®/kg body weight in a small pilot study ([IV],[170] [IV][171]) • Low versus high dosage (upper and lower limb) ([I],[168] [II],[150] [II],[172] [III][52]) • Dosage in multi-level treatment ([V],[34] [II],[69] [V],[33] [IV][51]) • Dose modifiers[39] Reviews • Pharmacology of Botulinum Toxins[173] • Physiological effects of BoNT in spasticity[174] • Dose ranges: • Up to 16 U Botox®/kg bw[39] • Up to 23 U Botox®/kg bw[20] • Up to 25 U Dysport®/kg bw[175] Internet sources • BoNT dosing tables: http://www.mdvu.org/(Login required)

6 Safety of Botulinum toxin	Three types of adverse events: (1) Focal adverse events - 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. - Distant adverse events (e.g. bladder dysfunction) can be observed when dosing and dilution guidelines are neglected or inadequate localisation techniques are applied. (2) Generalised adverse events - Generalised weakness has been observed and reported and can occur when preparation specific dosage and dilution guidelines are not respected. (3) Procedural adverse events - Haematoma (rare when small 27–30 gauge needles are used). - No reports on local infections following BoNT injections have been published or reported by the users of BoNT. - procedural complications due to analgo-sedation or general anaesthesia Specific risks of mortality and morbidity according to GMFCS need to be addressed in future evaluations [54]	Clinical studies safety • Report on the safety and occurrence of adverse events after repeated injections (preparation Dysport®)[176] • Report on adverse events in severe CP after repeated injections (preparation BOTOX®) ([V][54]) • Report on safety of treatment and frequency of adverse events in large cohort (preparation BOTOX®) ([IV][33]) • Report on safety of treatment with high-dose BoNT/A (BOTOX®) ([IV],[51] [IV],[50] [IV],[52] [IV][53]) • Safety profile of BoNT/A treatment in children (preparation Dysport®)[42] • Report on dysphagia after BoNT/B ([V][177]) • Secondary non-response after repeated injections (BoNT/B) ([V][178]) • Accuracy is relevant for the safety of treatment ([II][21]) • Case-report on systemic effect of BoNT ([V][54]) • Report on the safety and adverse effects of BoNT/A, both BOTOX® and Dysport®, in children below 2 year of age ([IV][47]) Reviews • Meta-analysis on safety, incl. data from adults and children[43] • Safety of long-term use[44] • Safety of BoNT-A[49]
7 Botulinum toxin therapy and procedures	Administration by an experienced team in a setting appropriate for children The therapy setting has to be adapted according the patients needs adequate analgesia (in combination with sedation if necessary) - Technique of injection (sonography, electrical stimulation, EMG)	Clinical studies procedure • Accuracy of palpation/electrical stimulation[59,66] • BoNT injection using sonography[60,67] • Sonography-guided psoas injection[61,65] • Repeated injections without general anaesthetic[179] • N_2O in paediatric patients[56,57,180,181] Reviews • EMG, pro/contra[182,183] • Management of pain and anxiety[184] • Methodology of sonography-guided injection[62,64]
8 Assessment and evaluation of treatment with BoNT in children with CP	Documentation and evaluation should use validated methods (according to ICF/WHO).	Validity and reliability • Joint Range of Motion[185,186] • Ashworth Scale[187,188] • Tardieu Scale[188,189] • QEK, Deep-tendon reflexes, Clonus[139] • GMFM[14,15,190,191] • GAS[192–194] • Video documentation,[195] Edinburgh Visual GAIT,[196,197] Physician Rating Scale, Observational Gait Scale[198] • PEDI,[199] BFMF,[200] MACS[201,202] • AHA: Assisting Hand Assessment,[203] Melbourne Assessment[204–206] • Longitudinal health outcome,[207] Health-related quality of life[b208–210]

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Table 1 (*continued*)

Section	Key areas – updated consensus	Key literature – selected clinical studies and reviews
	Body structure/function e.g.: - Range of motion (ROM) - (modified) Ashworth Scale [(M)AS)] - Tardieu Scale - Quantitative Electromyographic Kinesiology (QEK) - Deep-tendon reflexes - Clonus - 3D gait analysis - Video documentation - Goal Attainment Scale (GAS)	Clinical Studies containing BoNT intervention • ICF in CP ([III][124]) • Ashworth Scale ([III][187]), Tardieu Scale[189] • SMS, QEK, Deep-tendon reflexes, clonus ([II][139]) • GMFM ([II],[139] [II][119]) • GAS ([IV],[211] [IV],[212] [II][21]) • Energy cost ([II][118]) • Video documentation, Edinburgh Visual GAIT ([II][118]), Observational Gait Scale ([I][138]), PEDI ([II],[120] [II][213]), COPM ([II],[21] [II][120]) • Melbourne Assessment ([II][120]), QUEST ([II],[21] [II][120]) • 3D gait analysis ([II],[69] [IV],[214] [III],[70] [IV][71]) • 3D kinematics in upper limb ([V][215]) • VAS ([IV][216])
	Activity/participation e.g.: - 3D gait analysis - 3D kinematics in upper limb - 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) - Child Health Questionnaire (CHQ) - Quality of Upper Extremity Skills Test (QUEST) - Melbourne Assessment of unilateral upper limb function - 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) - Visual Analogue Scale (VAS) Caregiver Priorities & Child Health Index of Life with Disabilities (CPCHILD©) questionnaire[b]	Reviews • ICF approach[68] • Evaluating therapy[217–219,133] • Measures for muscles and joint in lower limb[220] • Systematic literature review of assessment measures[221] • Review of spasticity assessment measures[222,188] • Review of measurements of activity level[223]

9 Botulinum toxin therapy adherence	Continuation • Improved function • Improved balance/posture • Improved pain and comfort • Crucial factors for treatment success: - Number of treatments (although repeated treatments are successful, the largest functional improvement usually occurs after the first treatment) - dosages (different dosages may produce different levels of response - Follow-up care (combination with functional therapy, orthotic management, casting) seems crucial for a good result - Age (younger children seem to respond better) - Functional level (can influence a positive outcome) - Individualised treatment approach with respect to muscle selection Discontinuation • Continued benefit without further injections • No significant gain or unacceptable side effects • Secondary non-response • Fibrosis • Neutralizing antibodies against BoNT • Continuation to orthopaedic treatment, intrathecal baclofen, or others	Clinical studies • Antibody screening in children with CP (mouse protection bioassay) ([II][78]) • Antibody screening in children with CP (mouse hemidiaphragm assay,[80,178] [V]) • Rate of antibody formation for BoNT (preparation BOTOX®) in adults[81] • Long-term use ([IV],[224] [II],[213] [II][225]) • Why children discontinue treatment[79]
10 Research challenge CP	(1) Evaluation of injection techniques and follow-up: - Effect of BoNT within the muscle - dilution, distribution, spreading within the muscle - location of injection sites - motor endplate targeting (2) Evaluation of patient and treatment characteristics of high and low responders. (3) The effects of BoNT in combination with a goal directed therapy and follow-up care.	(1) Follow up: Muscle biopsy substantiates longterm MRI alterations one year after a single dose of Botulinum toxin injected into the lateral gastrocnemius muscle of two healthy volunteers. [226] (3) Activity focused and goal directed therapy for children with cerebral palsy. [227]

Level of evidence in parentheses behind clinical trials: I–V according to AACPDM Methodology to Develop Systematic Reviews of Treatment Interventions (Revision 1.2) 2008 Version[83]:
I = systematic review of randomized controlled trials (RCTs), Large RCTs (with narrow confidence intervals; $n > 100$).
II = smaller RCTs (with wider confidence intervals; $n < 100$), Systematic reviews of cohort studies, 'Outcomes research' (very large ecological studies).
III = cohort studies (must have concurrent control group), systematic reviews of case–control studies.
IV = case series, cohort study without concurrent control group, case–control study.
V = expert opinion, case study or report; bench research, expert opinion based on theory or physiologic research, common sense/anecdotes.
Citations are sorted chronologically, alphabetically and by level of evidence, if possible.
a Dose rests in the hand of treating physician (read carefully Sections 2, 4, 6).
b CPCHILD Questionaire to be downloaded at http://www.sickkids.ca/Research/CPCHILD-Questionaire/CPCHILD-Project/CPChild-questionaire/index.html.

understanding of the etiology, or at least the pathogenesis, of the disease has been greatly advanced by the development of Magnetic Resonance Imaging techniques, which allow the identification of the underlying structural changes in the brain[8,9] and gives information on topography and the extent and potential timing of the causative lesion.[10,11] Although the cerebral lesion in CP is viewed as caused by a single event, CP has to be understood as a developmental disorder described over time as an individual develops. The development of the European consensus on CP definition and classification[12] 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.[13] A whole body approach to classification (and reclassification) is facilitated by the use of the Gross Motor Function Classification System (GMFCS), which describes both disease severity and course.[14,15]

Reclassification of a child is recommended during every appointment, especially when the child is under the age of four years. Classification according to GMFCS may also be used for decision-making concerning which treatment intervention is appropriate over the course of time (see also Section 3). The GMFCS classification system is a useful tool for hip surveillance programs as was shown by a Swedish group in 2007.[16] Classifications by GMFCS and 'limb distribution' or by GMFCS and 'type of motor impairment' are significantly correlated.[17] However, an analysis of function (GMFCS) by impairment (limb distribution) indicated that the limb distribution did not add prognostic value over GMFCS, although classification of CP by impairment level seems useful for clinical and epidemiological purposes.[17,18] These recommendations are in line with a report on the definition and classification of cerebral palsy as published by an international consensus group.[19]

2.2. *Medico-legal and medico-economical aspects (section 2)*

BoNT treatment of children with CP is often performed under unlicensed conditions, using dosages and body segments or muscles which are not supported by the relevant licensing bodies. However, the off-label use of medications is accepted and common practice in many paediatric fields and will continue until there is a significant increase in research directed at children. Typically the licences for BoNT treatment show a great variety between countries (in Europe and all other continents) and are restricted to specific preparations, specific indications and dose limitations. Licensing does not reflect the clinical need, especially for children with CP. Individualised variations in BoNT dosage, BoNT dilution, clinical indication(s) and the muscle group(s) treated represent appropriate, although unlicensed, use where such treatment is in line with clinical experience.[20] A strong level of pharmaco-vigilance is required due to the broad spectrum of indications ranging from single muscle injections in children with e.g. unilateral CP, GMFCS Level I versus multi-level injections in severely affected children with bilateral CP, GMFCS Levels III–IV (-V) suffering from multiple additional impairments. In order to assess adverse events sufficiently, a new system of pharmaco-vigilance documentation in the field of off-label use was addressed by the NIH to be developed for the future. In conclusion, careful decision-making on dosage, dilution and injection control rests in the hands of the treating physician and has to be adapted to the individual patient (see Sections 2.5 and 2.6).

2.3. *Botulinum toxin and integrated therapy (section 3)*

The use of BoNT in children with CP represents a major therapeutic intervention but should never be considered as 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 multi-modal 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.[21–23] However, there is insufficient evidence to either support or refute the use of these interventions before or after BoNT injections.[24]

A combination of therapy procedures is common in daily practice, but addressing this by research is far from being easy. Robotic assisted therapy can serve as an intervention model where activity parameters can be measured during therapy intervention.[25–30] This may allow a better understanding about the correlation of effect of dosing to activity and whether this has any effect on participation.

2.4. *Botulinum toxin and common indications (section 4)*

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. Starting in the 1990s an increasing number of ''focal'' indications emerged such as *pes equinus, pes equinovarus*, knee and hip flexion spasticity, adductor spasticity, and spasticity of the upper extremity (e.g. finger flexion, wrist flexion, ulnar deviation, elbow flexion, and shoulder adduction). In a non-focal condition such as CP, a number of muscle groups may need to be targeted.[31,32] This has led to the development of a multi-muscle, multi-level treatment approach, in which a number of overactive muscle groups are treated with BoNT to achieve an improvement of limb motion and posture.[33,34] The use of classifications, e.g. for sagittal gait patterns[31] may facilitate the development of more standardized pattern-guided treatment approaches.

2.5. *Dosage and dose modifiers of Botulinum toxin therapy (section 5)*

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. A third BoNT/A preparation (Xeomin®, Merz Pharma, Germany) was introduced to the market in 2005 with anecdotal reports on beneficial effect in children with neuropaediatric indications.[35] All Botulinum toxin products are distinct concerning their molecular structure and manufacturing process and methods used for determining

biological activity are different.[36–38] For children with CP, these pharmacological differences have significant implications for clinical use. Individual dosages must be calculated independently for each BoNT preparation and fixed dose-conversion factors are not applicable in the treatment of spasticity in children with CP.[3,33,39]

Dosage calculation for each preparation is based on: (1) total units per treatment session, (2) total units per kg body weight per session, (3) units per muscle, (4) units per injection site, (5) units per kg body weight per muscle (U/kg/muscle). It has to be respected that the term ''Unit'' represents a different biologic potency for each BoNT preparation.

Additional dose modifiers which have to be considered when planning the injection protocol may be: severity of CP according to GMFCS, accompanying diagnoses (e.g. dysphagia, aspiration, breathing problems), predominance of movement disorder (spasticity, dystonia), activity of the injected muscle, muscle size, dynamic *versus* fibrotic muscle, knowledge about the distribution of motor endplates in the injected muscle, and experience from previous BoNT injections. Dilution will depend on body region and muscle size (e.g. forearm versus upper leg). In animal models higher dilutions showed greater dissemination,[40] but clinical evidence to support this information is missing.[41]

2.6. *Safety of Botulinum toxin (section 6)*

BoNT therapy has been widely used for over 20 years during which time it has proved to be a safe treatment option.[33,42–49] In general, the occurrence and severity of CP adverse events are rare. With the development of the multi-level treatment strategy over the last years it has become apparent that an adequate focal treatment effect can only be achieved when the injected dose/muscle remains the same.[34] Consequently, the total dose/session increases with the number of treated muscles, but this needs to be differentiated from ''overdosing'' a single muscle. Adverse events can be differentiated into focal (local, distant), generalised and procedural adverse events. With the development of the multi-level treatment strategy a dose dependency of adverse events is discussed[50] although this observation could not be supported by other groups.[51–53]

Heightened interest concerning safety has occurred since severe adverse events (deterioration in respiratory and oro-motor function) were reported in a child with CP after BoNT treatment (see introduction).[54] With the report of severe adverse events to national health institutions a so-called ''red hand letter'' was published in Germany by the German Federal Institute for Drugs and Medical Devices (BfArM, http://www.bfarm.de/) on June 1, 2007.[55] In the United States the national non-profit ''Public Citizen'' interest Organisation followed with a petition in January 2008, insisting on transparency of Botulinum toxin treatment in the USA (http://www.citizen.org/publications/release). Following this petition a warning was issued by health institutions from several countries: the Food and Drug Administration (FDA, http://www.fda.gov) in the USA, Health Canada (http://www.hc-sc.gc.ca) and by the Swiss Agency for Therapeutic Products (www.swissmedic.ch) in Europe 2008. In September 2008 the BfArM published a conclusive statement that currently ''there is no evidence showing a causal connection'' between the fatal outcome of five reported patients in Germany and their prior treatment with Botulinum toxin.[2] The ongoing discussion concerning safety and licensing of BoNT needs to be followed carefully by each treating physician using the websites of the above mentioned health institutions. It is important to emphasise that it remains the responsibility of the treating physician to ''check and balance'' dosing, dose modifying effects and procedural risks (as general anaesthesia) for each child on an individual basis keeping in mind the treatment goal(s), national and institutional rules. The GMFCS helps to anticipate severity-related co-morbidities which should be taken into account in every BoNT treatment session. According to the Surveillance of Cerebral Palsy in Europe the GMFCS was distributed at Level I in 32%, Level II in 29%, Level III in 8%, Level IV in 15%, and Level V in 16%. Learning disability was present in 40%, epilepsy in 33%, and severe visual impairment in 19% of the children. More severe GMFCS levels correlated with larger proportions of accompanying impairments[18] and a greater incidence of brain stem pathology and cranial nerve dysfunction, that needs to be assessed prior to BoNT treatment. The potential additional risk for the different subgroups of GMFCS evolving from treatment with BoNT remains to be clarified and is currently under investigation in different centres worldwide.

2.7. *Botulinum toxin therapy and procedures (section 7)*

In children with CP, pain management is an important issue. Procedural pain such as BoNT injections requires appropriate, effective analgesia, especially because BoNT therapy requires repeated multiple, painful, but elective injections. Therefore, appropriate, effective analgesia and as the case arises in combination with 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 GMFCS, the number of muscles to be treated and the institutional setting and resources.[56,57] The procedural pain management includes pharmacological as well as non-pharmacological techniques and already starts prior to the procedure. Useful comprehensive guidelines can be found at the webpage of The Royal Australasian College of Physicians Sydney (http://www.racp.edu.au/page/health-policy-and-advocacy/paediatrics-and-child-health).[58] Children should receive injections delivered using an accurate localisation technique.[21,59] Classical neurophysiological localisation methods (EMG, electrical stimulation) have recently been fine-tuned and amended by sonography which allows precise identification of any target muscle using readily available, non-invasive equipment.[60–67]

2.8. *Assessment and evaluation of treatment with BoNT in children with CP (section 8)*

The development of new CP assessment tools has been stimulated by the therapeutic possibilities offered by BoNT therapy. Purpose-built classification tools and standardized clinical assessments enable people to speak the same language and to evaluate interventions using consistent and

valid instruments, matched to the dimensions of the international classification of functioning, disability and health (ICF).[68] The cited literature in the table represents an excerpt of the assessment and evaluation tools for treatment with BoNT in children with CP. A large number of studies in literature report about the effect of BoNT predominantly only on the level of body structure and function (e.g. Ashworth and/or, Tardieu scores and Range of Motion). Gait analysis data provide important information for delineating the problems of children with CP.[23,69–71] With respect to study design, attempts are necessary to further improve the quality to allow meta-analysis of studies. The following issues are important: (1) Stratification of patients according to age, Gross Motor Function/Manual abilities and type/characteristic of movement disorder, (2) randomization centrally organized, independent from the physician doing the intervention, (3) Blinded rating of treatment effects, e.g. through blinded video analysis in conjunction with appropriate outcome measures, (4) standardization of co-interventions, (5) intention-to-treat analysis of drop-out patients. Qualitative research which aims to make sense of, or interpret experiences of individuals,[72–75] and aids in evaluating the complexity of evidence-based clinical decisions[76] will also be valuable.

2.9. *Botulinum toxin therapy adherence (section 9)*

In a randomized controlled clinical trial 48% of children treated with BoNT showed clinical improvement of initial foot contact using a video gait analysis compared to 17% of placebo treated children.[77] A multicenter open label clinical trial enrolling 207 children with CP showed an improvement of dynamic gait pattern on the Physician Rating Scale in 46% of patients (86/185) at first follow-up. BoNT injections (4 U/Kg, Botox®) were given approximately every 3 months. The mean duration of BoNT/A exposure was 1.46 years per patient and the response was maintained in 41–58% of patients for 2 years.[78] Initial reports on long-term adherence show that, while about 75% of patients achieve their treatment goals following the initial injection sessions, a considerable number discontinue therapy for various reasons.[79] 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) predominant muscle fibrosis or (iii) the formation of antibodies. In children undergoing BoNT treatment in the 1990s up to 30% were reported to develop antibodies.[80] 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.[23,33] This is in line with reports that have demonstrated reduced antigenicity of the reformulated preparation in adults with cervical dystonia.[81] In conclusion antibody formation does not seem to affect clinical decision and any ''new'' BoNT formulations that are introduced would have to prove their superiority to established preparations.[82]

2.10. *CP is a research challenge (section 10)*

A sample of three exemplary research topics addressing some clinical aspects of BoNT treatment with the multi-modal treatment concept are named to stimulate future work.

3. Part II: introduction of the CP^{Graph} treatment modalities – gross motor function

3.1. *The need and chance for visualisation*

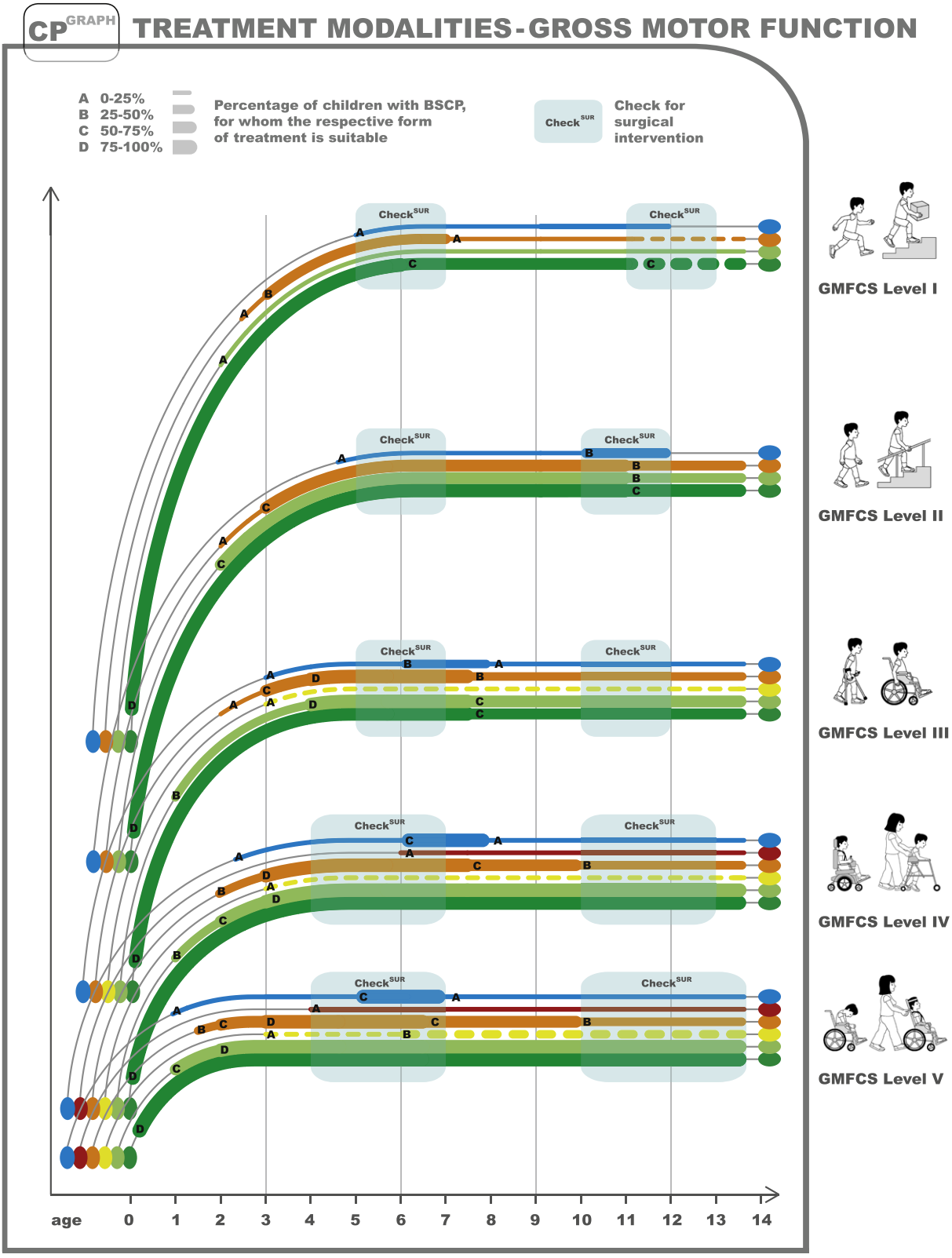
A further development of this updated consensus table is the introduction of an integrative treatment graph for children with bilateral spastic cerebral palsy (CP^{Graph} Treatment Modalities – Gross Motor Function (Fig. 1)).

This graph was presented as a draft and discussed at the consensus meeting and has been adapted on the basis of vivid discussions. It represents the likely path of motor development in a group of children with bilateral spastic CP based on the GMFM/GMFCS-based Motor Development Curves.[228] It describes the principles of common treatment options which can be considered in an interdisciplinary setting. The goal is to provide parents and caretakers, physicians and therapists with a means to plan treatments and interventions within the multidisciplinary treatment approach and to help answer questions concerning: What? When? How much? How long?

At the same time the limitations of a graphical conclusion have to be considered: The graph is not designed to show a predictable and detailed course of development for the individual child and it does not serve as a fixed protocol for the interdisciplinary treatment team.

The basal (green) curve represents all functional therapies. It forms the foundation to which all other therapies can be added on demand. These other therapies are coded with other colours (bright green = orthoses/aids, yellow = oral medication, orange = Botulinum toxin, red = intrathecal baclofen, blue = orthopaedic surgery):

Functional therapies (basal, green line): support of motor development in children with CP is the continuous principle of care. Besides adaptive support of motor development, negative alterations can be uncovered and addressed as they appear by e.g. short term intensification of treatment blocks.[135,229–231]
Orthoses/aids (bright green line): goal and therapeutic benefit need to be defined ideally in conjunction with the orthotist, paediatric neurologist, and paediatric orthopaedic. Improvement of function in daily activity, but also prevention of structural deformities are the two most important therapeutic goals.[132,232] Ambulatory aids are essential for participation in daily activities.
Oral medication (yellow line): oral, anti-spasticity medication aims to generally reduce muscle tone in children with CP. Due to frequent habituation to applied dosages, treatment often is limited to short- or medium-term benefit. Generalised systemic side effects frequently limit the application of adequate dosages for a sufficient tone reduction.[233,234]
Botulinum toxin (orange line): its indication has been applied to all grades of severity in children with CP (GMFCS I–V). As a focal treatment for a non-focal disease it ranges from focal



Florian Heinen. GMFM-Graph and GMFCS-Illustrations by courtesy of Peter Rosenbaum, Bob Palisano, Canada, and H Kerr Graham, Australia. version 1.0/2009

1: European Medicines Agency (EMEA: www.wmwa.europe.eu), The German Federal Institute for Drugs and Medical Devices (BfArM: http://www.bfarm.de), Swiss Agency for Therapeutic Products (Swissmedic: www.swissmedic.ch), Food and Drug Administration (FDA: www.fda.gov).

Fig. 1 – CP^{Graph} treatment modalities – gross motor function.

to multi-level injections. Distant action and systemic action of substance may occur when dose recommendations and dose modifiers are not regarded.[45,70]

Intrathecal baclofen (red line): the indication for ITB has been established for GMFCS levels IV and V, rarely III. The monitoring needs to be performed in an experienced centre in order to minimize the occurrence of systemic adverse events or complications.[235–238]

Orthopaedic surgery (blue line): developmental paediatrician, paediatric neurologist, and rehabilitation specialist often are the initial treating physicians in children with CP. To optimize motor development it is essential to include paediatric orthopaedic surgeons into the therapeutic team as early as possible. Depending on the severity of CP frequent consultations or shared evaluations of the patient should be performed. GMFCS levels IV and V need to be monitored as early as possible for "hips at risk".[16,111] The correct indication for surgery at the right time has to be established in the future with respect to GMFCS level, long-term outcome, effects and side effects on the levels of body structure and function as well as activity and participation.

Conflicts of interest

Dr. Heinen and Dr. Berweck have received speaker's honoraria, research support and travel grants from manufacturers of the different BoNT preparations available (Allergan, Germany, IPSEN, Germany, Merz Pharmaceuticals, Germany). Dr. Schroeder reports having received lecture fees and travel grants from Allergan, Germany.

Dr. Molenaers and Mrs. Desloovere have received unrestricted educational grants, research support, speaker's honoraria and travel grants from Allergan. Dr Hustedt and Dr. Pascual-Pascual have received speakeŕs honoraria, research support and travel grants from Allergan. Dr Papavasiliou has received grants to attend scientific meetings form Allergan and Ipsen. Ms van der Ploeg has received an honaraorium from Allergan for lecturing. Dr Tedroff has chaired the Swedish Committee for Botulinum toxin A which was funded by an unrestricted grant from Allergan, and has conducted an investigator-driven randomized clinical trial where Botulinum toxin A was provided by Allergan Inc. Dr. Mall has received speaker's honoraria, research support and travel grants from manufacturers of the different BoNT preparations available (Allergan, Germany, IPSEN, Germany, Merz Pharmaceuticals, Germany). The remaining authors have received grants to attend scientific meetings from Allergan or did not state a conflict of interest.

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Supplementary data

The graph can be downloaded from the online version, at doi:10.1016/j.ejpn.2009.09.005.

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