Botulinum toxin assessment, intervention and after-care for lower limb spasticity in children with cerebral palsy: international consensus statement

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Botulinum neurotoxin type-A (BoNT-A) has been used in association with other interventions in the management of spasticity in children with cerebral palsy (CP) for almost two decades. This consensus statement is based on an extensive review of the literature by an invited international committee. The use of BoNT-A in the lower limbs of children with spasticity caused by CP is reported using the American Academy of Neurology Classification of Evidence for therapeutic intervention. Randomized clinical trials have been grouped into five areas of management, and the outcomes are presented as treatment recommendations. The assessment of children with CP and evaluation of outcomes following injection of BoNT-A are complex, and therefore, a range of measures and the involvement of a multidisciplinary team is recommended. The committee concludes that injection of BoNT-A in children with CP is generally safe although systemic adverse events may occur, especially in children with more physical limitations (GMFCS V). The recommended dose levels are intermediate between previous consensus statements. The committee further concludes that injection of BoNT-A is effective in the management of lower limb spasticity in children with CP, and when combined with physiotherapy and the use of orthoses, these interventions may improve gait and goal attainment.

Introduction & objectives

Botulinum neurotoxin type-A (BoNT-A) has been used in the management of spasticity in the lower limbs of children with CP for more than 15 years, with the first reports by Koman et al. from the United States in 1993 [1] and Graham et al. in the United Kingdom in 1994 [2]. The original indication, which remains the most common today, was injection of the gastrocsoleus for the correction of spastic equinus or improvement of equinus gait (toe-walking). Since the first reports, indications have been extended to almost every major muscle in the lower limb, with varying degrees of success and variable levels of evidence.

This international consensus statement reviews the evidence for the use of BoNT-A therapy in the lower limbs of children with spasticity caused by CP, formulates them into appropriate treatment recommendations and identifies areas for future research based on gaps in the literature. In addition, areas of clinical relevance without high levels of evidence have been reviewed including assessments, outcome measures, adjunctive therapies, recommended doses, dilution, muscle localization techniques and screening for adverse events. A suggested management algorithm is also provided.

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Literature was searched and appraised using a conventional evidence hierarchy. The highest levels of evidence available were used to develop recommendations, with randomized controlled trials (RCTs) and systematic reviews preferentially sought. Only when RCT or systematic review evidence was not available, were lower level evidence and practice-based evidence included to answer clinical questions raised at the International BoNT Consensus Workshop. Expert opinion where included has been clearly labelled and should be interpreted with judicious caution. Recommendations for research were made based on the gaps identified in the literature. All recommendations were graded based on the American Academy of Neurology evidence classification [3].

Definition and classification of cerebral palsy

CP is the most common cause of physical disability of childhood in the developed world, with an incidence of 2–2.5 per 1000 live births [4]. The heterogeneity of clinical phenotypes is one of the most striking features in CP. Impairment of gross motor function and abnormalities of tone are defining features of CP [5]. Spasticity affects between 70 and 80 per cent of children with CP [6]; however, precise diagnosis of the movement disorder can be difficult as spasticity often co-exists with dystonia. Management of spasticity will be the focus in this review because it is the most common movement disorder in cerebral palsy. The treatment of dystonia is beyond the scope of this review.

The Upper Motor Neurone syndrome
CP is the most common cause of UMN syndrome in children. Spasticity, defined as a velocity-dependent increase in tonic stretch reflexes [5], is but one manifestation of the Upper Motor Neurone (UMN) Syndrome.

The UMN syndrome presents both positive and negative features [4]. The positive features include spasticity, co-contraction and hyper-reflexia. The negative features include weakness, impaired selective motor control, balance deficits and fatigability of skeletal muscle. There has been a tendency for health professionals to concentrate on the positive features of the UMN syndrome because they are clinically obvious and amenable to modulation. However, the negative features may be more important to long-term locomotor prognosis [7]. In younger children, spasticity is very prominent, resulting in toe-walking and equinus gait patterns [7]. In older children and adolescents, weakness of antigravity muscles frequently results in various types of flexed knee gait including crouch gait [8,9].

CP may be classified by aetiology (when known), brain imaging, type and topographical distribution of movement disorder and gross motor function. In recent years, the Gross Motor Function Classification System (GMFCS) [10] has been adopted as the common language for health professionals to communicate about gross motor ability in children with CP. The GMFCS is a five-level ordinal grading system, which describes gross motor function with different descriptors used for children of different ages. The Gross Motor Function Classification System (GMFCS) is valid, reliable, relatively stable with time and clinically relevant. It is a classification system and not an outcome measure but is relevant in all discussions in respect of management of CP, because management goals and selection of relevant interventions must be based on a sound knowledge of long-term gross motor prognosis. For example, children at GMFCS levels I and II walk independently in the community. They often have relatively mild gait disorders amenable to management with BoNT-A combined with therapy interventions. Children at level III need extensive assistive devices but still manage to ambulate for shorter distances. Children at GMFCS level IV have very limited standing and walking ability, and children at GMFCS level V are non-ambulant. The Children with GMFCS V may have severe generalized hypertonia, of which spasticity may be only one component, and may benefit from interventions more global than BoNT-A. BoNT-A may be indicated for focal tone management in these children, and when used in this way, indications are more difficult to define and outcomes are less predictable.

Methods: inclusion and exclusion criteria

A literature search completed in April 2008, using the following search terms:
1 'cerebral palsy' and
2 'spasticity' and
3 'botulinum neurotoxin' or 'BOTOX®' or 'BoNT-A' or 'BTA' or 'Dysport®'.

The search revealed a very large number of studies of varying quality. Only randomized clinical trials (RCTs) that met the inclusion criteria (Table 1) were retained and included. Each full article was then reviewed and classified by two committee members using the American Academy of Neurology (AAN) Classification of Evidence for therapeutic intervention and classification of recommendations [3]. Where classifications were not congruent, a third reviewer's opinion and committee consensus was sought. It was recognized that much useful information exists in studies and reviews other than RCTs, especially in relation to methods of

Table 1 Inclusion criteria

Inclusion criteria
Participants with spasticity caused by CP
Age ≤ 18 years
Use of BoNT-A (BOTOX® & Dysport®)
Randomized Controlled Trials
English language

assessment, outcome measures and adjunctive interventions. Therefore, these other studies have been reviewed and information reported as 'expert opinion'.

What is the best way to assess children with CP for BoNT-A therapy?

Selection for, and/or targeting of, BoNT-A injection in the lower limb is dependent upon many factors, in particular, the specific goals of intervention. Because of the heterogeneity of children with CP, the aim of treatment using BoNT-A will vary significantly between individuals. It is important to separate assessment into (i) patient selection/screening of children for BoNT-A therapy and (ii) specialist assessments to identify outcomes of BoNT-A therapy. The tools used are not necessarily mutually exclusive.

Baseline assessment: screening and selection for BoNT-A therapy

BoNT-A therapy targets reduction of muscle over-activity, predominantly spasticity and/or dystonia. Therefore, it is essential to quantify the presence of these motor disorders, to differentiate the spasticity from the other components of hypertonia and to select some sensitive measure of change to determine local responsiveness to BoNT-A. These assessments measure change at the impairment or 'body structures and functions' level [11]. This is the level at which BoNT-A may have a direct impact, with anticipated changes in gross motor function, goal attainment activities and participation being indirect and less predictable.

The GMFCS is clearly prognostic of long-term gross motor ability in CP and helps the family and multidisciplinary team identify clinically relevant, realistic goals. Clinically relevant goals can be broadly grouped and may include improving gait and function (GMFCS I–III), improving posture (GMFCS III–V), relieving pain and discomfort and/or reducing the burden of care (GMFCS V). As part of the initial assessment, the clinician should discuss with the family whether the types of goals they have identified can be met by BoNT-A therapy and, if not, what other options may be available.

Outcome assessment

The authors define high-quality outcome assessments as being consistent and free from error (reliable) and measuring what is intended to be measured (valid). The tool(s) also need to be responsive to change (able to detect minimal clinically important differences) as well as being tailored to the children involved and the purpose of measurement [12].

No single tool covers all domains of the International Classification of Function and Disability (ICF) [11]. To assess children with CP comprehensively, a range of tools are required, some of which are better suited to clinical use and others for research purposes. It is recommended that selection of outcome measures should include at least one measure of body function and structure (as this relates to local, technical response of injected BoNT-A) and at least one measure of function, activity or participation [as related to the goal(s) of, and satisfaction with, treatment]. Numerous outcome measures are available for use in children with CP, yet remarkably, a few published studies utilize an appropriate range of outcome measures.

Recommendation 1

The multidisciplinary team (MDT) providing the BoNT-A therapy should choose assessment tools that:
- Reliably differentiate the spasticity from fixed musculoskeletal contractures and other causes of hypertonia*
- Document the GMFCS and baseline function including, but not limited to, functional gross motor assessment; care needs; what the infant/child can/cannot do; analysis of movement; gait analysis; functional task analysis; and seating/sleeping positions*
- In ambulant children, describe gait and function using scales such as the Physician Rating Scale (PRS) or Observational Gait Scale (OGS) ± video recording*
- In non-ambulant children, describe abnormal postures and care needs in clinically relevant terms using valid and reliable tools*

*Expert opinion.

Tools for the assessment of spasticity in children with cerebral palsy: clinical versus research

A number of clinical tools have been described for the assessment of spasticity, dystonia and contracture in children with cerebral palsy. These scales include the Tardieu Scale, Modified Tardieu Scale (MTS), Ashworth Scale, Modified Ashworth Scale (MAS) and Australian Spasticity Assessment Scale (ASAS). These tools have been described, tested and widely reported. Their benefits and limitations are widely recognized. However, there are a number of methods for instrumented measurement of spasticity, both directly and indirectly, including var-

Table 2 Recommended assessments

Tool	ICF domain Body Structures	Activities	Participation	Domain of measurement (Spasticity / Function)	Valid	Reliable	Responsive	Clinical Practice	Research
Australian Spasticity Assessment Scale (ASAS) [36]	●			Quantifies the amount of muscle spasticity present via measurement of the 'spastic catch' on an ordinal scale	●	●	?	●	●
Modified Tardieu Scale (MTS) [18]	●			Quantifies the degree of muscle spasticity present via measurement of the 'spastic catch' to determine muscles for injection (continuous scale in degrees)	?	?	?	●	●
Muscle length as measured by range of joint motion (ROM)	●			Measure the muscle length to understand the degree of contracture present (represented in degrees of joint movement)	●	●	●	●	●
Goal Attainment Scaling (GAS) [45]	●	●	●	Measures intervention outcomes based on individualised goals	●	●	●	●	●
Video Gait Analysis (VGA or 2DGA)		●		Records sagittal and frontal gait parameters	?	●	●	●	●
3DGA	●	●		Primarily EMG — Kinetic and kinematic data	●	●	●	●	●
Physician Rating Scale (PRS) [38]		●		Ordinal criteria descriptors of gait quality	?	●	●	●	●
Functional Independence Measure for Children (WeeFIM®) [43]		●		Evaluation, self-care independence of children	●	●	?	●	●
Pediatric Evaluation of Disability Inventory (PEDI) [41]		●		Evaluation, self care, mobility and social function of children with physical disability	●	●	●		●
Gross Motor Function Measure (GMFM-66) [44]	●	●		Evaluation, determination of gross motor capacity	●	●	●		●

● Addresses this domain/possesses this property/fulfills this purpose; ?: may possess this property.

ious powered systems, resonant frequency and indirectly using gait analysis. Unfortunately, none of the instrumented measures fulfil the requirements for a useful tool in the clinical setting (Table 2). Both the clinical and instrumented measures have recently been reviewed by Johnson and Pandyan [13].

Measurements of body structure and function

Many clinical tools have been described for the assessment of spastic hypertonia in the literature [14–26], and a detailed discussion is beyond the scope of this document.

The Tardieu Scale and the Modified Tardieu Scale (MTS)

Despite the Tardieu Scale [26,27] being the most relevant uninstrumented clinical tool for the assessment of spasticity and being consistent with current definitions (in that it examines muscle response and resistance to passive movement at varying velocities, including rapid passive movement), it has been found by clinicians to have limited clinical utility in the paediatric setting as it is a lengthy procedure. The Modified Tardieu Scale (MTS) is a valid, reliable and sensitive abridged version [18,28–30]. It utilizes the most clinically useful parts of the Tardieu Scale: the angle of catch at the most rapid velocity (R1). R1 of the MTS can then be compared with R2, (joint angle when the muscle length is at its maximum, assessed by moving the limb through its entire range of movement (ROM) using slow passive movement) [31]. The relationship between the R1 and R2 estimates the relative contributions of spasticity compared to contracture [18]. Additional recommendations [32] include that R2 needs to be tested immediately preceding the R1, and the R1 needs to be tested three times in rapid succession. This procedure ensures identification of voluntary effort [32] and overcomes the inertia of the sliding muscle fibres [33,34], allowing the neural component to be isolated. It also ensures that the condition of the muscle prior to testing R1 can be replicated [32,35].

Modified Ashworth Scale (MAS)

The most commonly reported measure of 'spasticity' in the literature is the Modified Ashworth Scale (MAS) [15]. As the MAS is performed at a single velocity, it is not truly able to distinguish, describe, measure or rate spasticity. Rather, the MAS measures passive resistance to motion that may or may not be caused by an increased response to stretch. Despite its widespread use and its ability to identify general hypertonia, it is recommended that this tool no longer be used to describe spasticity because of its limited validity.

Australian Spasticity Assessment Scale (ASAS)

The Australian Spasticity Assessment Scale (ASAS) addresses the limitations of the MAS. The ASAS scores the muscle's response to slow and rapid passive movement on a 5-point ordinal scale without the subjectivity and wording ambiguities of the MAS. This tool provides clinicians with a user-friendly, quick to administer, valid and reliable alternative to other spasticity measures. Early research suggests this tool has excellent reliability and clinical utility and therefore offers a new, alternative spasticity assessment tool [36].

A clear profile of the spasticity is presented by the MTS and the ASAS together (Table 2).

Gait and function in ambulant children (GMFCS levels I–III)

The original and most common indication for the use of BoNT-A in children with CP is in the management of gait dysfunction, such as equinus gait or toe-walking. More recently, the management of gait dysfunction has been expanded by the injection of multiple muscles in the lower limbs; in order of frequency: the gastrocsoleus, hamstrings, hip adductors, tibialis posterior and iliopsoas.

In the clinical setting, the description of gait and function are highly relevant to not only the selection of the individual child who may benefit from BoNT-A therapy, but also for the identification of target muscles and prescription of concurrent therapies, including serial casting and choice of ankle-foot orthoses.

The gold standard for comprehensive assessment of gait function in ambulant children with CP is three-dimensional instrumented gait analysis (3DGA), including various combinations of temporo-spatial measurements, three-dimensional kinematics, kinetics, dynamic electromyography and physiological testing (Table 2). 3DGA is the cornerstone of outcome measurement in clinical research trials of BoNT-A therapy in ambulant children with CP, but it is limited in the clinical context by cost and availability. In addition, instrumented gait analysis is not feasible with many of the children who are identified in the literature as being the most responsive to BoNT-A therapy for gait dysfunction. This includes children aged one to four years, with limited walking abilities and with limitations in cooperation and physical size to complete an instrumented gait study. However, 3DGA has led to the identification of gait patterns, classifications and descriptors, which are useful in the clinical setting including the sagittal gait patterns identified by Rodda [37].

In the absence of 3DGA, clinicians in the multidisciplinary team should employ observational gait analysis when they assess children's walking. These

observations can be formalized by employing an observational gait scale as such as the Physician Rating Scale (PRS) (Table 2) [38].

The PRS is a qualitative, ordinal, observational scale with good repeatability [39] and excellent intra-rater reliability but limited inter-rater reliability, when used for evaluating gait in children with CP [40].

Video gait analysis (VGA) has been widely used in research studies investigating the use of BoNT-A for gait dysfunction in children with CP and is increasingly used in routine clinical management. The value of the VGA is greatly enhanced when combined with the PRS or one of several other observational gait scales.

Assessment of gross motor function, activities and activity limitation

Functional goal attainment
It is important to note that the measurement of gross motor function, activities and activity limitation in children with CP is time-consuming, requires expertise and is therefore expensive. This applies to the majority of measures with established reliability, validity and sensitivity, and as a result, they have limited use in routine clinical practice, although essential in research studies. The tension between measures with clinical relevance and practicality and those which are relevant only to research studies is not yet resolved in the literature. The literature is clear, however, that the gold standard measure of gross motor function in children with CP is the Gross Motor Function Measure (GMFM-66) [41,42] (Table 2). The GMFM-66 quantifies how much motor function the child is able to demonstrate. It is a criterion-referenced, observational measure for assessing change over time in gross motor function and was designed specifically for use in children with CP [41].

The Functional Independence Measure for Children (WeeFIM®) [43] (Table 2) and the Pediatric Evaluation of Disability Inventory (PEDI) [44] (Table 2) are also well established and useful in the research context for children with more severe involvement (GMFCS levels IV and V). The PEDI assesses a child's functional skills and behaviours including caregiver assistance in complex activities and can be useful for the child with more significant activity limitation (Table 2). The WeeFIM® assesses the impact of a disorder and the assistance required rather than the functional ability, and whilst it has a scoring system, which, in some instances, is not sensitive enough for short-term pre- and post-treatment comparisons, it has clinical utility for monitoring over time, particularly in GMFCS V.

The Goal Attainment Scaling (GAS) [45] (Table 2) helps to identify what types of changes are needed in order for any clinical change to be meaningful to the child and family. It also provides the family with a way to evaluate progress, make informed decisions about care and, where relevant, remain motivated to engage in rehabilitation programmes.

Recommendation 2

- Muscle length (R2), Modified Tardieu Score (R1) and Australian Spasticity Assessment Scale (ASAS) when presented together profile and quantify spasticity*
- Instrumented gait analysis is the most objective measure of gait and function in children with CP but its use is largely limited to the research context*
- VGA may be used both in research and clinical management*
- Observational gait analysis and the use of gait classifications and observational gait scales are recommended for routine clinical use*
- A valid measure of gross motor functional ability that is appropriate to the goal of treatment should be selected*

*Expert opinion.

Is there a role for Botulinum Neurotoxin type-A in the multidisciplinary management of children with cerebral palsy?

Animal studies relevant to the use of botulinum neurotoxin type-A in children

Research into consequences of spasticity in children with CP is hampered by the lack of a suitable animal model. A number of researchers have attempted to develop animal models of spasticity with little success. When a standardized brain injury is inflicted on the experimental animal, death or full recovery usually results. It is exceedingly difficult to produce a chronic neurological lesion with the phenotypical manifestations of CP. However, the hereditary spastic mouse is an animal model that displays some features that are similar to the problems of deficient muscle tendon growth, in relation to longitudinal bone growth, which occur in the limbs of children with CP [46]. The 'spastic equinus' leading to toe-walking and deficient gastrocsoleus growth was described by Ziv and Rang in 1984 [46].

Cosgrove and Graham [47] provided 'proof of concept' that development of contracture in the mouse was prevented by BoNT-A and paved the way for clinical trials in the use of BoNT-A in children with CP. However, in more recent studies, injections of BoNT-A in juvenile rats without spastic muscle alteration prevented maturational growth and induced progressive and persistent atrophy of muscle [48]. Chen *et al.* [49] found that injection of BoNT-A to the gastrocnemius reduced the wet mass by 50%, and this atrophy was not reversed by exercise.

In another study, the same group found that BoNT-A led to a reduction in gastrocnemius mass in juvenile animals, leading to an alteration in myosin heavy chain isoforms and reduction in titin content [50]. This may have adverse implications for muscle strength.

In summary, injection of BoNT-A into juvenile mice with hypertonia resulted in *improved* longitudinal growth of the gastrocsoleus, whereas injection of BoNT-A in a variety of experimental animals with *normal* muscles led to reduction in cross-sectional area and other changes that may have implications in respect of producing weakness in the long term. It remains to be seen which of these viewpoints and experimental animals most closely replicates muscle growth in children with CP.

By their nature, most randomized clinical human trials have ethical, clinical and practical limitations including relatively short duration of the period of control. Parents may agree to have their children randomized to either standard treatment or placebo injection for relatively short periods of time, greatly limiting the information that can be gleaned from RCTs evaluating BoNT-A therapy. However, additional information exists from cohort studies both prospective and retrospective as to the overall contribution of BoNT-A in the multidisciplinary management of children with CP. In a long-term cohort study, Molenaers *et al.* found that the introduction of BoNT-A and clinical gait analysis resulted in a significant number of improvements in the management of children with CP over a number of years [51]. These included the fact that children were older at age of first orthopaedic surgery, fewer repeat surgeries were required and functional outcomes were improved. Graham *et al.*, in unpublished observations, have found that the introduction of BoNT-A over a 15- year period at The Royal Children's Hospital in Melbourne resulted in the elimination of isolated gastrocsoleus lengthening surgery with a consequent dramatic reduction in the incidence of crouch gait at 5–10 year follow-up. In simple terms, the introduction of BoNT-A removed the pressure for surgeons to perform lengthening of the gastrocsoleus in younger children. Following one to five years of BoNT-A management, children proceeded to single-event multi-level surgery, which was preceded by instrumented gait analysis. At that time, severe crouch gait, which historically had been prevalent in the patient population, had been almost eliminated.

Far from repeated injections of BoNT-A causing weakness and increased gait dysfunction, the ability to provide targeted management of spastic equinus has resulted in greatly improved clinical outcomes [1,39,51, Vuillermin C: Unpublished observations]. However, concerns are sometimes expressed about the 'muscle weakening' effects of BoNT-A in children with CP. In the RCTs quoted in this consensus and in other non-randomized trials, gait parameters have usually been reported as improved. In one study, investigating changes in sagittal ankle kinetics, Boyd *et al.* reported relative normalization of ankle moments and increased ankle power generation following BoNT-A injection in children with CP. Whatever lessons are gleaned from animal studies or from injection of adult volunteers with normal muscles, the kinetic evidence from injection of BoNT-A in children with CP supports improvements in kinetic parameters of gait.

What is the optimal botulinum toxin treatment regimen?

A review of the RCTs of BoNT-A used in children with CP revealed 29 heterogeneous studies including dose-ranging studies in the management of spastic equinus and prevention of hip displacement and multilevel injections of lower limb muscles to improve gait and functioning (Appendix 1). In the interests of further analysis, the authors decided to group these heterogeneous studies into five principal groups, recognizing that some studies could have been included in more than one group.

Group 1 RCTs: dose-ranging and injection site technique studies. *N* = 7

Recommended doses of BoNT-A have been established by clinician-led dose-ranging studies combined with expert opinion derived from other classes of studies. It is important to note that dose-ranging studies have largely focused on injection of the gastrocsoleus for spastic equinus and that much less robust information is available to guide dose selection in other muscle groups and in multilevel injection protocols.

The authors found one Class I RCT [52] (Appendix 1) that reported a dose-dependent relationship and efficacy for Dysport®, supported by evidence from RCTs graded as Class III [53–58]. It is notable that there is no Class I RCT investigating the optimum dose of BOTOX® for spastic equinus in children with CP. Inadequate information in respect of concealed allocation and the lack of a power analysis affected the quality of most trials. One Class I study investigated three different doses of Dysport® to the gastrocsoleus in comparison to placebo and clearly identified an optimum dose, 20 Units/Kg [52]. Polak [54] compared two doses of Dysport® (8 Units/Kg versus 24 Units/Kg) and found that the higher dose was more effective without any increase in adverse events. Wissel, investigating two different doses of BOTOX®, found similar

results in reduction in spasticity and improved range of motion and gait parameters in the high-dose group, but with a slightly increased incidence of minor adverse events [53].

In a large study investigating three different doses of BOTOX® [57], dose-dependent improvements in dynamic deformities and gait patterns favoured the higher doses without significant differences in adverse events; however, this study had methodological weaknesses.

A small study utilizing single-site injection of the gastrocsoleus was compared with multiple-site injections, and no significant differences were found in outcomes [55].

Group 2 RCTs: BoNT-A versus placebo/control in spastic equinus. *N* = 7

The seven studies in this group were graded by the authors as two Class I and five Class II using the AAN criteria (Appendix 1). All seven studies are supportive of BoNT-A injection in the management of spastic equinus and constitute level I evidence and Grade A treatment recommendation for this indication. The outcome measures reported in these studies vary in complexity, reliability and ICF domain with earlier studies utilizing the PRS and 3DGA, and more recent studies including measures of gross motor function (GMFM) as well as adding psychometric refinements of the PRS to describe outcomes [59]. Class I evidence now exists to confirm significant benefits in terms of objective gait parameters when BOTOX® is used to manage spastic equinus [60]. Whilst the treatment size effect in terms of gait improvement is substantial, improvements in the GMFM are notably smaller and less consistent [61–63]. The Class I evidence rating refers to improvements in gait leading to a level A recommendation. However, improvements in gross motor function were found only in Class II studies, leading to a level B grading (that is to say, probably effective).

Group 3 RCTs: BoNT-A injection compared to serial casting for spastic equinus. *N* = 5

BoNT-A has historically been the most frequently used alternative to serial casting. Therefore, many studies have compared the outcomes of injection of BoNT-A with serial casting for the management of spastic equinus (Appendix 1) [39,64–67]. Collectively, these studies show inconclusive and conflicting differences between serial casting and BoNT-A. However, these studies were small, underpowered and some lacked objective outcome measures, with frequent failure to differentiate the goal of equinus contracture manage-ment from the goal of dynamic equinus management, thus making definitive conclusions difficult. Findings include (i) improvements in sagittal ankle kinematics at two weeks post serial casting and two weeks post injection of BoNT-A with the serial casting group relapsing to baseline levels at 12 weeks post-intervention, whereas the improvements in the BoNT-A group were sustained [39]; (ii) significant incidence of adverse effects from serial casting on gait resulting in a significant parental preference for injections [64]; (iii) reduction in spasticity, some improvements in gait and a small increase in GMFM walking scale favouring injection of BoNT-A combined with serial casting compared with BoNT-A alone [65]; (iv) no added improvements in outcomes from injection of BoNT-A combined with serial casting compared with serial casting alone [66]; and (v) no significant improvements in BoNT-A only group, but significant improvements in gait parameters and other outcome measures in the two groups that received serial casting ± BoNT-A [67]. The effects of serial casting seem to be at least as strong, and in some studies stronger, than the effects of injection of BoNT-A, but this must be balanced by the preferences of parents.

There appeared to be a trend supporting the effects of serial casting combined with injection of BoNT-A as shown by muscle length, spasticity measures and gait parameters, but with limited benefits on functional ability.

Group 4 RCTs: injection of the adductor and hamstring muscles. *N* = 4

Injection of the adductor and hamstring muscle groups in children with CP (GMFCS I-III) may be as part of multilevel injection protocols aiming to improve gait and functioning. They are also used in more severely involved children (GMFCS IV & V) in an attempt to improve other aspects of function and positioning or in the prevention of progressive hip displacement [68–71]. One Class I study investigating the outcome of adductor and hamstring injection to improve function in children with CP (Appendix 1) reported a significant reduction in adductor spasticity, no change in GMFM and a significant improvement in GAS for the intervention group [69]. Similarly, the Class III study [68] also reported no significant difference in GMFM between the treatment and control groups. In contrast, Hazneci [70] (Class III) compared BoNT-A injected into the adductor and hamstring muscles to a Johnstone pressure splint (JPS) and reported GMFM outcomes were better in the injection group.

Graham [71] (Class I) reported the outcome of a multicentre study using serial injections to the hip

adductors and hamstrings combined with use of the standing, walking and sitting hip (SWASH) brace compared with 'standard' management (Appendix 1). Whilst children in the treatment group progressed to surgery at a significantly lower rate than those in the control group (possibly influenced by the rate of progression of contractures), the authors concluded this was not an effective way to manage hip displacement in the long term. Moreover, a significant number of adverse events were reported in the BoNT-A group, and, in a previous subgroup analysis, no significant improvement in GMFM was found.

In summary, taking into consideration the class of the study and the direction of the change in outcome measure, there is a Grade A recommendation that BoNT-A injections to the adductors and hamstrings is *not effective* to improve gross motor function in children with CP, as determined by GMFM. There is a Grade A recommendation that BoNT-A injections *are effective* in delaying the need for surgery in the management of hip displacement in children with CP, but only in the short term. There is a level C recommendation that BoNT-A injections are possibly effective in children achieving intervention goals as determined by the GAS.

Group 5 RCTs: multilevel BoNT-A injections to improve gait and functioning. *N* = 6

The RCTs in this group were even more heterogeneous in terms of study populations, quality of RCT, injection protocols and outcome measures than the previously reported groups [72–77].

Of the six RCTs identified, the authors graded four as Class II and two as Class III, with no studies reaching a Class I grading (Appendix 1). The studies reported widely different outcome measures, with the study by Scholtes *et al.*, although included twice, presumably reports the same patient cohort. The 2006 study by Scholtes [74] reports gross motor outcomes, and the 2007 study [75] reports spasticity, muscle length and gait outcomes. In this group, only one study reports the following outcomes: Vulpe Assessment Battery (VAB) [72], GAS [4], 3DGA [75] and PEDI [77]. In contrast, four studies reported outcomes in terms of gross motor function, principally using the GMFM [72,74,76,77]. However, the changes in gross motor function were contradictory, with two studies [72,77] finding no significant improvement in gross motor function and two studies [74,76] reporting a small improvement. Therefore, the classification of recommendation for multilevel injections is graded as level U. That is to say, current data are inadequate or conflicting.

Comparisons of the studies reporting variable changes in gross motor function in children with CP show considerable variation in age and GMFCS levels. Studies reporting younger children at GMFCS levels I and II have found more consistent improvements in gross motor function. In those studies investigating changes in gross motor function in older children and at GMFCS levels III and IV, either less improvement or no improvement in gross motor function is generally reported. In older children with more physical limitations, there may be less potential to show improvement in gross motor function, and the presence of occult contractures may also be an important factor in decreasing the benefits of BoNT-A injection.

Recommendation 3

- BoNT-A is established as effective in the management of spastic equinus to improve gait. (level A)
- BoNT-A is probably effective to improve goal attainment and function in the management of spastic equinus (level B)
- BoNT-A is similar to serial casting in the management of spastic equinus with current data being inadequate or conflicting (level U)
- BoNT-A injections to the adductor muscles is probably effective in some specific areas of goal attainment (level B)
- BoNT-A injections to the adductor muscles do not improve gross motor function (level A)
- BoNT-A injections to the adductor (and hamstring) muscles may delay hip displacement, but does not affect long-term outcome (level A)
- BoNT-A injections to multiple lower limb muscles have inadequate and conflicting data in respect of gait, goal attainment and function (level U)

Injection protocols, dose, dilution and injection sites

Given the widespread use of BoNT-A therapy in children with CP, the multiple indications and heterogeneous groupings of target muscles, it is unsurprising that the evidence base for promoting safety and efficacy remains very limited, and much of the current clinical use of BoNT-A in children with CP remains 'off label'.

Two commercially available BoNT-A preparations are regularly used in children with CP: BOTOX® (Allergan Pty Ltd) and Dysport® (Ipsen). There is very little published information on the use the Xeomin® (Merz Pharmaceuticals) BoNT-A product, which was launched in 2005. Each preparation has a unique biological potency, and there are no firmly established conversion factors. It is important for clinicians to be aware that the doses for these products are *not* interchangeable. We strongly advise against the use of conversion factors between different preparations on BoNT-A.

Table 3 Products and doses

Product	Dose U/kg body weight		Maximum Total Dose
	Range in literature	Recommendation	
BOTOX®	6–24 U/Kg (up to 30 U/Kg used in occasional multilevel injections)	GMFCS I–IV without risk factors: 16–20 U/Kg GMFCS V with risk factors: 12–16 U/Kg*	< 300 U [53,57] < 400–600 U [79]
Dysport®	10–30 U/Kg	20 U/Kg [52] (level B recommendation)	200–500 U [54] (level U Recommendation) < 900 U [79]

Risk factors include symptoms and signs of pseudobulbar palsy, swallowing difficulties, history of aspiration and respiratory disease. When risk factors are present, evaluate the level of risk and either further reduce the total dose or avoid using BoNT-A.
*Expert opinion.

There are no dose-ranging studies that address the optimum dose of BOTOX®. Recommendations in previous studies, consensus statements and this document are 'expert opinion'; that is to say, no RCTs have been published. Given recent concerns about adverse events, the authors have chosen total doses in units per Kg body weight for BOTOX®, which are intermediate between the figures proposed in two previous consensus statements, and which err on the side of caution (Table 3). It is the responsibility of the treating physician to carefully choose the dose they consider appropriate for the individual case concerned.

In addition to the RCTs reviewed in detail by the authors, review of non-RCT literature confirms marked escalation in recommended doses of BOTOX®, both in relation to specific indications such as spastic equinus as well as in multilevel protocols. For example, in 2000, Graham [78] made the following recommendations: maximum dose at any one site 50 Units, maximum dose in any one injection session 300 Units or 12 Units per Kg. In 2006, Heinen [79] in a European consensus statement reported a published total dose range up to 20–24 Units per Kg for this preparation (Table 3). It should be noted that both of these suggested upper dose limits were determined by expert opinion, not supported by clinical trial.

One Class I study exists for the use of Dysport®, and this is only for the indication of spastic equinus [52]. (Table 3).

Although the incidence of adverse events following injection of BoNT-A in the RCTs reviewed in this paper and in other literature remains relatively low, systemic adverse events can include generalized weakness, diplopia, dysphagia, aspiration, pneumonia and death. This serves as a warning that systemic spread of BoNT-A may occur in children with CP and much further work is required before high-dose protocols can be accepted as safe. Given that the major risks of serious systemic adverse events reside in the child, it seems prudent to make recommendations based on

Table 4 Favourable Response to BoNT-A and physiotherapy

Aim	Expected Outcome	Indication	Grade of Recommendation
Reduction in body structures impairment	Reduction in spasticity and improved dynamic ROM	Decreased involuntary over-activity of injected muscles. Observed by a reduction in 'R1 R2' difference, measured on the ASAS [36] and MTS [18].	A
	Improved selective motor control	Improved ability to isolate and selectively control ankle movements. Selective motor control is measured via Selective Motor Control Scale [18].	U
	Improved strength	Greater strength in agonist and antagonist muscle groups, measured via a dynamometer or the Medical Research Council scale (graded 1–5).	U
	Improved passive ROM	BoNT-A in combination with casting is used to reduce contracture. Improved passive ROM is measured via goniometry.	B
Improved functional activity performance	Improved function and task performance	Improvements in individualized goal performance of functional tasks (e.g. walking, running, kicking a ball). Observed by an increase in GMFM scores [99] and /or measured by an increase in GAS [45].	B
Improved quality of life and personal factors	Reduction in pain	Decreased pain and spasm, measured on a Visual Analogue Scale (VAS), COPM [100], GAS [45] WeeFIM® [43] or PEDI [44].	U

GMFCS level and pre-existing medical co-morbidities. Additionally, dose calculation will be influenced by muscle size, muscle activity and experience from previous treatments with BoNT. Risk factors include symptoms and signs of pseudobulbar palsy, swallowing difficulties, history of aspiration and respiratory disease. When risk factors are present, evaluate the level of risk and either further reduce the total dose or avoid using BoNT-A.

Choice of the number and position of injection sites has been based on anatomical considerations more recently supported by anatomical studies investigating the location of neuromuscular junctions and motor end plates. However, there are no high-level clinical trials supporting injection site choice.

Traditionally, the localization of target muscle has been by using a combination of anatomical landmarks and palpation. Early protocols also suggested the use of moving distal joints through a range of motion to observe the motion of a needle placed in the target muscle. More recently, studies have confirmed that target muscle identification by palpation and anatomical landmarks alone is inaccurate, except for the gastro-csoleus [80].

Both electrical stimulation and real-time ultrasound improve the accuracy of injection; however, electrical stimulation is uncomfortable and usually requires mask anaesthesia. Ultrasound is emerging as the preferred modality to improve the accuracy of intramuscular injection of BoNT-A in children with CP. It is quick to perform and pain-free, and real-time visualization of the spread of BoNT-A within the targeted muscle can be used to document accurate intervention. Additional information concerning muscle size (atrophy) and degree of fibrosis can also be visualized using ultrasound and has the potential to add additional information for dose calculations prior to injection of the targeted muscle [81,82].

Although recent work using electrical stimulation and ultrasound in children with CP has demonstrated improved *accuracy* of delivery of BoNT-A to the target muscle, the *clinical relevance* of improved injection accuracy remains a matter for further study.

In the RCTs reported in this review, dilution of BoNT-A varies, and there is no high-level evidence to guide choice of dilution. In children with CP, the recommended dilution for the BOTOX® product varies from 100 Units reconstituted in between 1 to 4 mLs of normal saline. Evidence from the adult literature suggests that higher dilutions may be more effective for a given dose of toxin. It is not known in children with CP whether dose dilution has an impact on the rate of local spread and/or systemic adverse events.

Recommendations for delivery of BoNT-A

The onset of the therapeutic effect of BoNT-A occurs within the first few days, peaking approximately four weeks after injection. Duration of effect is approximately three to six months. The main clinical indicator for re-injection is the return of muscle spasticity. Other factors involved in decision-making about re-injection include prior clinical response/s (balancing the positive effects and adverse events) and length of time elapsed since last injection (frequent, repeat injections elevate the risk of developing an antibody response, which can result in non-response to treatment).

Conservative re-injection intervals of six months or more are recommended in children with CP. Where the treatment is acute and for short duration, such as traumatic brain injury, re-injection intervals may be as short as three months.

Recommendation 4

- Conversion factors between different preparations of BoNT-A can lead to life threatening miscalculations and their use is strongly discouraged. Rates and sizes of reactions may be different between preparations (level A).
- Determination of dose relates to severity of spasticity, goal of treatment, size of targeted muscle, distribution of neuromuscular junctions with that muscle and previous responses to BoNT-A (if known).
- Dose should be cautiously selected in patients of GMFCS level V and any patient with dysphagia or breathing problems.
- Injection interval for serial BoNT-A should generally be no less than six months.
- Precise localization of muscle injection sites helps to improve the safety profile of BoNT-A by reducing the likelihood of unwanted toxin migration (level U)*. Use injection techniques which allow the operator to accurately isolate the target muscle (ultrasound is the preferred method).

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*Expert opinion

What are the optimal adjunctive interventions?

During the past decade, there has been a switch in clinicians' thinking towards looking for adjunctive interventions to '*augment BoNT-A therapy*'. In fact, BoNT-A is the adjunctive intervention.

The therapeutic interventions aimed at improving function or reducing pain and care-giver burden have long been in place, and it was in the early 1990s that BoNT-A became available as an adjunctive clinical tool that assisted in achievement of these goals by directly reducing spasticity. The challenge of determining what and how interventions are best combined with lower limb BoNT-A to achieve optimal outcomes has been

recognized since the early use of BoNT-A in children with CP [60,68,71,83]. Despite this, there is a paucity of high-level evidence for specific adjunctive interventions [84–86]. The current practice of combining therapies with BoNT-A is based largely on the clinical reasoning that a 'window of opportunity' exists with BoNT-A that allows elongation of shortened muscles and improved motor control; that this period may be long enough for muscle growth, skill development and improvement in function or ease of care and that these gains are facilitated by adjunctive interventions.

The most commonly cited adjunctive interventions to lower limb BoNT-A are casting, orthotic management (ankle-foot orthoses) and physiotherapy (strengthening, stretching, targeted motor training). These interventions are generally considered essential components of post-BoNT-A care [18,74,75,87,88].

Appendix 2 provides a summary of high-level evidence for adjunctive interventions. Other physiotherapy approaches such as neurodevelopmental therapy (NDT) have been cited as an adjunct to BoNT-A [70,72,89] and appear to be more commonly used for non-ambulant children. Night-splinting [87] and use of adaptive devices or equipment for positioning [84,89] are considered by some authors as part of optimal orthotic management. Electrical stimulation and other electrotherapy modalities [56,89], along with a range of medically and surgically based interventions including oral medications, phenol injections, orthopaedic and neurosurgical interventions, have also been discussed in the literature; however, there are insufficient data in any of these areas to make recommendations.

Casting as an adjunctive intervention for management of spastic equinus:

Two Class II studies have compared the effect of casting plus BoNT-A with BoNT-A alone [65,67] or with casting alone [66,67]. Bottos [65] showed improvements in GMFM walking domain, Ashworth Scale (AS) and stride length for the BoNT-A plus casting group. Similarly, Ackman [67] reported significant improvements in ankle kinematics, spasticity, passive ROM and dorsiflexion strength in both the casting and the BoNT-A plus casting group, but no significant differences in the BoNT-A alone group. In contrast, Kay [66] reported no beneficial effect of BoNT-A plus casting over casting alone, noting a more rapid return of spasticity following BoNT-A plus casting. A comparison of casting-prior-to-BoNT-A with casting-following-BoNT-A [88] showed only minimal reduction in length of time of casting when applied following BoNT-A.

The existing studies provide neither strong nor consistent evidence that casting provides additional benefit to BoNT-A (level U recommendation) or that the order of casting (either prior to or following BoNT-A) affects outcome (level U recommendation).

Orthoses (AFOs) as an adjunctive intervention for BoNT-A in the management of spastic equinus:

The systematic review of Figueiredo [89] identified 20 studies addressing efficacy of ankle-foot orthoses (AFOs) in children with CP (in isolation from lower limb BoNT-A). All 20 studies were classed at low levels of evidence. Whilst many of the studies combined AFOs with lower limb BoNT-A and provided some information on efficacy of combined interventions, they did not provide evidence of AFOs as an adjunctive intervention. Only one small RCT [65] compared BoNT-A plus AFO plus physiotherapy (PT) with BoNT-A plus casting plus PT and reported the group receiving casting made greater improvements at four months post-BoNT-A as measured by AS, GMFM and gait analysis.

Physiotherapy as an adjunctive intervention

An ongoing challenge when reviewing the evidence is determining what is encompassed by the term 'physiotherapy'. There is often limited detail regarding programme content, the modalities used, dose and delivery model. This is the case for the studies included in this review. Physiotherapy programmes vary from detailed programmes including strengthening, stretching and targeted motor training delivered three times a week for 12 weeks, which may be combined with casting and orthotic or night splint use [74–76] or neurodevelopmental therapy (NDT) three times weekly for three months [70] to regular or usual physiotherapy. Lower limb BoNT-A and physiotherapy have been combined in the majority (24 of 29) of the RCTs in Appendix 1, which represents the highest quality of evidence available for lower limb BoNT-A (three Class I, 13 Class II and eight Class III studies). Despite the high proportion of RCTs combining physiotherapy plus BoNT-A in the experimental group of each trial, there is insufficient evidence to support or refute physiotherapy interventions as an adjunct to lower limb BoNT-A (level U recommendation) as no high-level studies have investigated these interventions specifically as adjunctive interventions. A number of specific physiotherapy interventions that are commonly used in clinical practice have been validated in isolation from BoNT-A. For example, there is high-level evidence that strengthening in children with CP is effective in isolation (level B recommendation). Other physiotherapy interventions have conflicting or limited evidence to support them, however, are established current practice in many

centres. Expert opinion supports combining physiotherapy and BoNT-A (Table 4).

Recommendation 5

- Serial casting should *follow* BoNT-A for management of fixed calf contracture (level U).*
- AFOs are an effective adjunctive intervention to improve gait and protect foot integrity (level U).*
- Prolonged stretching is an adjunctive intervention to BoNT-A to assist in management of muscle length (level U).*
- Strengthening is an essential adjunctive intervention to BoNT-A when goals to improve motor function are identified (level U).*
- Targeted motor training is as an essential adjunctive intervention when goals to improve motor function are identified (level U).*

*Expert opinion

Management algorithm
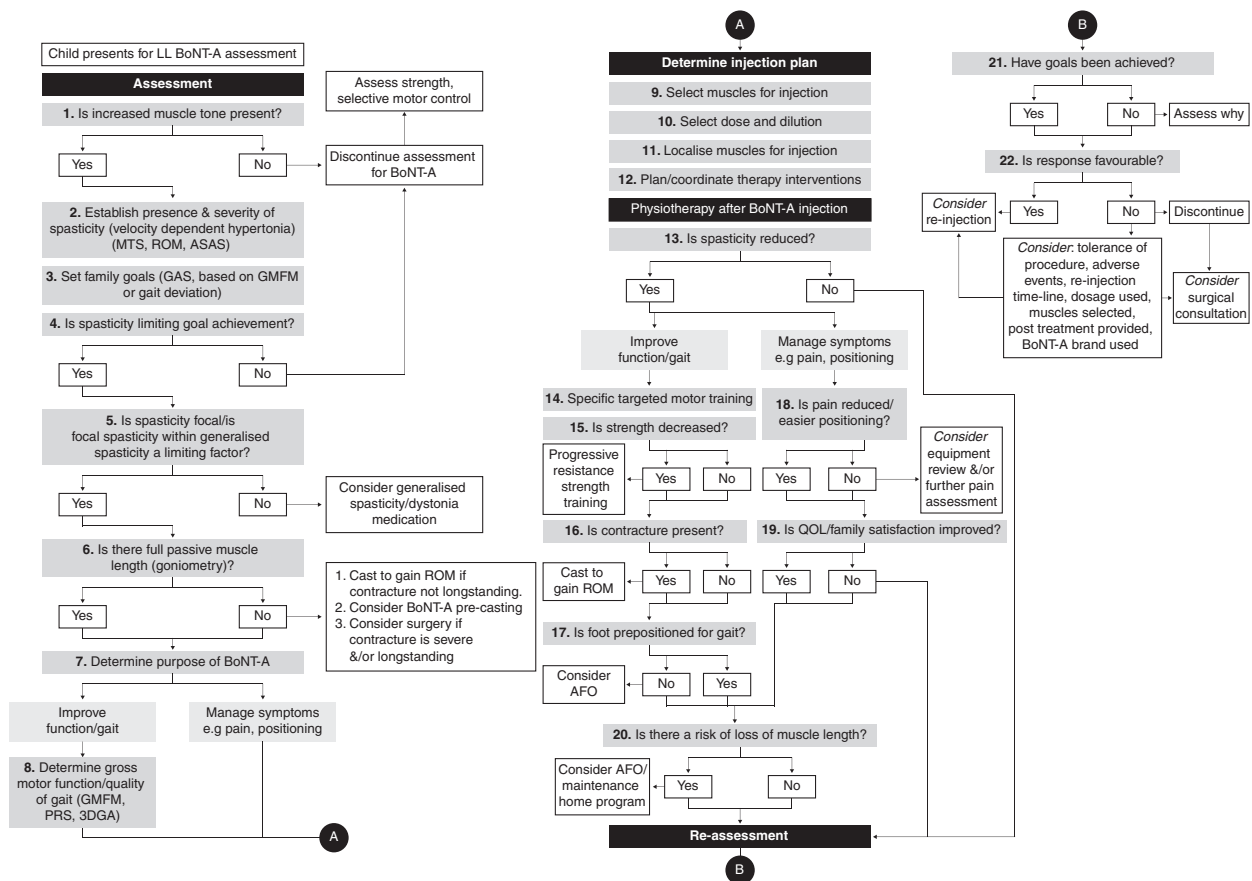
How should patients be monitored?

BoNT-A is safe and effective [90]. The focal, temporary and reversible nature of the drug contributes to its safety [90]. However, prior to commencement of BoNT-A intervention, children and parents should be informed about the potential risks, side effects and adverse events of the treatment, including, but not limited to, procedural risks. Appropriate consent should be obtained. BoNT-A is usually well tolerated by children with lower limb spasticity caused by CP; however, side effects and adverse events can occur (rates of adverse events in clinical trials are: 25% for those treated with BoNT-A and 15% for untreated controls) [90]. Children injected with higher total doses experience more adverse events [91].

Efforts should be made to appropriately monitor and reduce or prevent side effects and adverse events. The goal of review is to monitor not only the immediate effects of the BoNT-A injection, but to inform ongoing management decisions including, but not limited to, future injections. Post-injection review should occur within six weeks of BoNT-A injection. Where resources do not allow clinical review for all treated children, those who are receiving the treatment for the first time and those considered to be at higher risk of experiencing an adverse event or side affect

should be prioritized. Telephone review can sometimes replace clinical review for children receiving unchanging serial BoNT-A treatment and who have no previous history of an adverse event. Families must be taught how to monitor adverse events to maximize safety.

Adverse events arising from BoNT-A injections are categorized as either local or generalized. Local adverse events are common (range 0–30%) but are usually mild and self-limiting. They include pain, swelling and bruising [92]. The most commonly reported events after lower limb BoNT-A include excessive localized weakness in the lower limb resulting in falls and clumsiness (which is not unexpected given the intended clinical action of BoNT-A is to dampen hyperactivity of injected muscles). Children who experience trauma from the injections or excessive local weakening, affecting their balance and increasing the number of falls, are more likely to discontinue BoNT-A intervention [93]. Local reactions can also occur if the BoNT-A migrates into adjacent muscles [90].

Generalized adverse events, or systemic reactions, are very rare in this population [94–96]. Systemic adverse reactions following BoNT-A injection include nausea, fatigue, malaise bladder incontinence or disturbance, flu-like symptoms and rash [90]. Children with more severe motor involvement (GMFCS IV–V) and pre-existing laryngeal and pharyngeal dysfunction are thought to be most at risk [96]. The time to onset of systemic reactions can vary, from immediately post-injection to weeks after injection. Respiratory complications may be related to both procedural factors as well as the BoNT-A. For example, multilevel injection protocols involving the use of electrical stimulation for target muscle identification frequently require the use of anaesthesia. General anaesthesia in its own right is a risk factor for aspiration and chest infection, and it can be difficult to separate the risk of the procedure from the risk of injection. However, incontinence of bladder and bowel is clearly a systemic response to BoNT-A injection and has been reported in many studies at varying BoNT-A doses. Incontinence is clearly a systemic pharmacologic adverse event and is not related to procedural issues.

In rare cases, hospitalization and death have been reported [97]. There are two published reports of fatalities, both thought to be not related to the injection. There are no reports of increased seizures relative to controls.

Non-response can also occur with BoNT-A and is thought to be caused by antibody formation [93,98]. The likelihood of non-response increases with repeated injections [99].

Recommendation 6

- Lower doses coupled with careful monitoring, especially of oral feeding, are recommended for patients with known risk factors (level U)*.
- Verbal and written explanation of both potential benefits and possible adverse events should be given to parents or carers before the first injection. Parents should be taught how to identify the signs and symptoms of an adverse event (such as dysphagia, dysphonia, dyspnoea, respiratory distress, generalized weakness or incontinence) and instructed to seek medical attention immediately if the child experiences difficulty swallowing, talking, breathing, or muscle weakness.
- Clinical review should occur 26 weeks following BoNT-A injection.
- Structured review of functional outcomes should occur four–six months following BoNT-A injection.

What are the expected outcomes of botulinum toxin and therapy?

A favourable response to BoNT-A is reduction in spasticity (which is the primary aim of the treatment) and improvement in the pre-set individualized goals.

Level A evidence supports the effectiveness of BoNT-A for reducing muscle spasticity in children with lower limb spasticity. Secondary aims and potential favourable responses of BoNT-A combined with physiotherapy are to create a 'window of opportunity' for increasing functional activity, reducing caregiver burden and improving symptom management. Whilst the presented RCTs have shown the functional and gait outcomes of BoNT-A, more rigorous research is needed into desired outcomes relating to caregiver burden and symptom management such as pain control.

Failure to respond to BoNT-A, or an unfavourable response, is characterized by the following:

1 no or insufficient reduction in muscle spasticity (dose, needle placement and antibody response factors may be responsible);
2 no translation to desired gains in function or symptom management from the reduction in spasticity; and
3 adverse events that outweigh the benefits experienced.

Future directions

There are many unresolved issues. The literature does not yet define the ideal time to start BoNT-A therapy, the ideal frequency of injection, nor when to definitively cease BoNT-A therapy. There is a need for longer term studies, which include multiple treatment cycles. Clearer knowledge of the incidence of background morbidity in the CP population is needed to enable clinicians to distinguish what are true BoNT-A adverse effects.

There is a paucity of evidence related to the effects of BoNT-A on muscle strength and muscle morphology, and further studies in this area should consider the outcome measures of cross-sectional anatomy using ultrasound, MRI and, if possible, fine-structural analysis.

Most of the literature reviewed in this paper focused on measures of body function and structure (good evidence of local technical response of BoNT-A), but little in the domains of activity or participation, and this needs to be addressed in future studies with objective, gold standard outcome measures across all domains of the ICF.

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Conflicts of interest

References

1. Koman AL, Mooney JF, Smith BP, Goodman A, Mulvaney T. Management of spasticity in cerebral palsy with botulinum toxin A: preliminary investigation. *J Pediatr Orthop* 1993; **13:** 489–495.

2. Cosgrove AP, Corry IS, Graham HK. Botulinum toxin in the management of the lower limb in cerebral palsy. *Dev Med Child Neurol* 1994; **36:** 386–396.

3. American Academy of Neurology. AAN classification of evidence for therapeutic intervention. 2004. Available online: http://www.neurology.org (accessed 23/January/2009).

4. Stanley F, Blair E, Alberman E. *Cerebral Palsies: Epidemiology and Causal Pathways*. London: MacKeith Press, 2000.

5. Sanger TD, Delgado MR, Gaebler-Spira D, Hallett M, Mink JW. Classification and definition of disorders causing hypertonia in childhood. *Pediatrics* 2003; **111:** e89–e97.

6. Watson L, Blair E, Stanley FJ. *Report of the Western Australian Cerebral Palsy Reister to Birth year 1999*. Perth: Telethon Institute for Child Health Research, 2006. Available online: http://www.ichr.uwa.edu.au/files/user1/WACR_Report_A4.pdf

7. Hutchinson R, Graham HK. Management of spasticity in children. Chapter 12. In: Barnes MP, Johnson GR eds. *Upper Motor Neurone Syndrome and Spasticity*. 2nd edn. Cambridge: Cambridge University Press, 2008: 2.

8. Rodda JM, Graham HK, Galea MP, Baker R, Nattrass GR, Wolfe R. Correction of severe crouch gait in spastic diplegia by multilevel orthopaedic surgery: Outcome at one and five years. *J Bone Joint Surg* 2006; **88-A:** 2653–2664.

9. Stout JL, Gage JR, Schwartz MH, Novacheck TF. Distal femoral extension osteotomy and patellar tendon advancement to treat persistent crouch gait in cerebral palsy. *J Bone Joint Surg* 2008; **90-A:** 2470–2484.

10. Palisano RJ, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997; **45:** 113–120.

11. World Health Organization. *International Classification of Functioning, Disability and Health (ICF)*. Geneva: World Health Organization, 2001.

12. Guyatt G, Walter S, Norman G. Measuring change over time: assessing the usefulness of evaluative instruments. *J Chronic Dis* 1987; **40:** 171–178.

13. Johnson GR, Pandyan AD. The Measurement of Spasticity. In: Barnes MP, Johnson GR eds. *Upper Motor Neurone Syndrome and Spasticity*, 2nd edn. Cambridge University Press: Cambridge, 2008: 2.

14. Ashworth B. Preliminary trial of carisoprodal in multiple sclerosis. *Practitioner* 1964; **192:** 540–542.

15. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther* 1987; **67:** 206–207.

16. Peacock WJ, Staudt LA. Functional outcomes following selective posterior rhizotomy in children with cerebral palsy. *J Neurosurg* 1991; **74:** 380–385.

17. Johann-Murphy M. New York University Rhizotomy Program: physical Therapy Rhizotomy Evaluation. *Pediatr Phys Ther* 1990; **2:** 103–106.

18. Boyd RN, Graham HK. Objective measures of clinical findings in the use of botulinum toxin type A for the management of children with cerebral palsy. *Eur J Neurol* 1999; **6**(Suppl. 4.): 523–535.

19. Bleck EE, ed. *Orthopeadic Management in Cerebral Palsy*. Clinics in Developmental Medicine No. 100. London: Mac Keith Press, 1987.

20. Sindou M, Jeanmonod D. Microsurgical dorsal rhizotomy for the treatment of spasticity and pain in the lower limbs. *Neurosurgery* 1989; **24:** 655–670.

21. Jobin A, Levin MF. Regulation of stretch reflex threshold in elbow flexors in children with cerebral palsy: a new measure of spasticity. *Dev Med Child Neurol* 2000; **42:** 531–540.

22. Trombly CAed. *Occupational Therapy for Physical Dysfunction*. Baltimore: Williams and Wilkins, 1983.

23. Peacock WJ, Arens LJ, Berman B. Cerebral palsy spasticity. Selective posterior rhizotomy. *Pediatr Neurosci* 1987; **13:** 61–66.

24. Levin MF, Hui-Chan CW. Relief of hemiparetic spasticity by TENS is associated with improvement in reflex and voluntary motor functions. *Electroencephalogr Clin Neurophysiol* 1992; **85:** 131–142.

25. Roques CF, Felez A, Marque P, Chatain M, Condouret J, Tuffery RA. A motor scale for the hemiplegic patients' motor function assessment. *Rehabilitation and Physical Medicine* 1997; **40:** 147–158.

26. Tardieu G, Shentoub S, Delarue R. A la recherche d'une technique de mesure de la spasticite imprime avec le periodique. *Neurologique* 1954; **91:** 143–144.

27. Held J, Peierrot-Deseilligny E. *Reeducation Motrice des Affections Neurologique*. Paris: Bailliere, 1969: 31–42.

28. Boyd RN, Barwood SA, Baillieu CE, Graham HK. Validity of a clinical measure of spasticity in children with cerebral palsy in a randomized clinical trial. *Dev Med Child Neurol* 1998; **40**(Suppl. 78): 7 (Abstract).

29. Fosang AL, Galea MP, McCoy AT, *et al*. Measures of muscle and joint performance in the lower limb of children with cerebral palsy. *Dev Med Child Neurol* 2003; **45:** 664–670.

30. Gracies JM, Marosszeky JE, Renton R, Sananam J, Gandevia SC, Burke D. Short-term effects of dynamic lycra splints on upper limb in hemiplegic patients. *Arch Phys Med Rehabil* 2000; **81:** 1547–1555.

31. Gibson N, Laird K, Mori R, Shillington T, Price C. *Paediatric Biomechanical Assessment: Significance to the Interpretation of Gait*. Perth WA: CD ROM Princess Margaret Hospital for Children, 2002.

32. Shircore L, Love SC, Gibson N, Price C. Do you R1 before you R2? (Abstract). Australian Physiotherapy Conference, Perth, Western Australia. 2003.

33. Lakie M, Robson LG. Thixotrophy: the effect of stimulation in frog muscle. *Journal of Exercise Physiology* 1988; **73:** 627–630.

34. Walsh EG. Measure of muscle tone. *Paraplegia* 1992; **30:** 507–508.

35. Morris S. Ashworth and Tardieu Scales: their clinical relevance for measuring spasticity in adult and paediatric neurological populations. *Phys Ther Rev* 2002; **7:** 53–62.

36. Love SC, Gibson N, Cole J, Williams N, Blair E. The reliability of the Australian Spasticity Assessment Scale.

(Abstract). Proceedings of the Australasian Academy of Cerebral Palsy and Developmental Medicine Conference, April 2008, Brisbane, Australia.

37. Rodda JM, Graham HK, Carson L, Galea MP, Wolfe R. Sagittal gait patterns in spastic diplegia. *J Bone Joint Surg. British Volume* 2004; **86:** 253–258.

38. Koman LA, Mooney JF 3rd, Smith BP, Goodman A, Mulvaney T. Management of spasticity in cerebral palsy with botulinum-A toxin: report of a preliminary, randomized, double-blind trial. *Journal of Pediatric Orthopaedics* 1994; **14:** 299–303.

39. Corry IS, Cosgrove AP, Duffy CM, McNeill S, Taylor TC, Graham HK. Botulinum toxin A compared with stretching casts in the treatment of spastic equinus: a randomised prospective trial. *Journal of Pediatric Orthopaedics* 1998; **18:** 304–311.

40. Maathuis KG, van der Schans CP, van Iperen A, Rietman HS, Geertzen JH. Gait in children with cerebral palsy: observer reliability of Physician Rating Scale and Edinburgh Visual Gait Analysis Interval Testing scale. *Journal of Pediatric Orthopaedics* 2005; **25:** 268–272.

41. Avery LM, Russell DJ, Raina PS, Walter SD, Rosenbaum PL. Rasch analysis of the Gross Motor Function Measure: validating the assumptions of the Rasch model to create an interval-level measure. *Arch Phys Med Rehabil* 2003; **84:** 697–705.

42. Russell DJ, Rosenbaum PL, Gowland C, *et al. Gross Motor Function Measure Manual*, 2nd edn. Hamilton, Ontario, Canada: Chedoke-McMaster Hospitals, 1993.

43. Msall ME, DiGaudio K, Duffy LC, *et al*. Normative sample of an instrument for tracking functional independence in children. *Clin Pediatr* 1994; **33:** 431–438.

44. Haley SM, Coster WJ, Ludlow LH, Haltiwanger JT, Andrellos PJ. *The Pediatric Evaluation of Disability Inventory: Development, Standardisation and Administration Manual*. Boston: New England Medical Center Publications, 1992.

45. Kiresuk TJ, Smith A, Cardillo JE (eds). *Goal Attainment Scaling: Applications, Theory and Measurement*. Hillsdale, NJ: L Erlbaum Associates, 1994.

46. Ziv I, Blackburn N, Rang M, Koreska J. Muscle growth in normal and spastic mice. *Dev Med Child Neurol* 1984; **26:** 941–984.

47. Cosgrove AP, Graham HK. Botulinum toxin A prevents the development of contractures in the hereditary spastic mouse. *Dev Med Child Neurol* 1994; **36:** 379–385.

48. Velders M, Legerlotz K, Falconer SJ, Stott NS, McMahon CD, Smith HK. Effect of botulinum toxin-A induced paralysis and exercise training on mechanosensing-signalling gene expression in juvenile rat gastrocnemius muscle. *Exp Physiol* 2008; **93:** 1273–1283.

49. Chen J, Stott NS, Smith HK. Effects of botulinum toxin A injection and exercise on the growth of juvenile rat gastrocnemius muscle. *J Appl Physiol* 2002; **93:** 1437–1447.

50. Legerlotz K, Matthews KG, McMahon CD, Smith HK. Botulinum toxin-induced paralysis leads to slower myosin heavy chain isoform composition and reduced titin content in juvenile rat gastrocnemius muscle. *Muscle Nerve* 2009; **39:** 472–479.

51. Molenaers G, Desloovere K, Fabry G, De Cock P. The effects of quantitative gait assessment and Botulinum toxin A on musculoskeletal surgery in children with cerebral palsy. *J Bone Joint Surg* 2006; **88-A:** 161–170.

52. Baker R, Jasinski M, Maciag-Tymecka I, *et al*. Botulinum toxin treatment of spasticity in diplegic cerebral palsy: a randomized, double-blind, placebo-controlled, dose-ranging study. *Dev Med Child Neurol* 2002; **44:** 666–675.

53. Wissel J, Heinen F, Schenkel A, *et al*. Botulinum toxin A in the management of spastic gait disorders in children and young adults with cerebral palsy: a randomized, double-blind study of "high-dose" versus "low-dose" treatment. *Neuropediatrics* 1999; **30:** 120–124.

54. Polak F, Morton R, Ward C, Wallace WA, Doderlein L, Siebel A. Double-blind comparison study of two doses of botulinum toxin A injected into calf muscles in children with hemiplegic cerebral palsy. *Dev Med Child Neurol* 2002; **44:** 551–555.

55. Detrembleur C, Lejeune TM, Renders A, Van den Bergh PYK. Botulinum toxin and short-term electrical stimulation in the treatment of equinus in cerebral palsy. *Mov Disord* 2002; **17:** 162–169.

56. Sätilä H, Pietikäinen T, Iisalo T, *et al*. Botulinum toxin type A injections into the calf muscles for treatment of spastic equinus in cerebral palsy: a randomized trial comparing single and multiple injection sites. *Am J Phys Med Rehabil* 2008; **87:** 386–394.

57. Wang Y, Gao B. A dose-response relationship research on botulinum toxin type A intramuscular injections of lower extremity spasticity in children with cerebral palsy. *Childs Nerv Syst* 2008; **24:** 545–547.

58. Sätilä H, Iisalo T, Pietikäinen T, *et al*. Botulinum toxin treatment of spastic equinus in cerebral palsy – A randomized trial comparing two injection sites. *Am J Phys Med Rehabil* 2005; **84:** 355–365.

59. Koman LA, Mooney JF, Smith BP, Walker F, Leon JM, BOTOX Study Group. Botulinum toxin type A neuromuscular blockade in the treatment of lower extremity spasticity in cerebral palsy: a randomized, double-blind, placebo-controlled trial. *J Pediatr Orthop* 2000; **20:** 108–115.

60. Sutherland DH, Kaufman KR, Wyatt MP, Chambers HG, Mubarak SJ. Double-blind study of botulinum toxin injections into the gastrocnemius muscle in patients with cerebral palsy. *Gait and Posture* 1999; **10:** 1–9.

61. Ubhi T, Bhakta BB, Ives HL, Allgar V, Roussounis SH. Randomised double blind placebo controlled trial of the effect of botulinum toxin on walking in cerebral palsy. *Arch Dis Child* 2000; **83:** 481–487.

62. Love SC, Valentine JP, Blair EM, Price CJ, Cole JH, Chauvel PJ. The effect of botulinum toxin type A on the functional ability of the child with spastic hemiplegia a randomized controlled trial. *Eur J Neurol* 2001; **8**(Suppl. 5)**:** 50–58.

63. Bjornson K, Hays R, Graubert C, *et al*. Botulinum toxin for spasticity with cerebral palsy: a comprehensive evaluation. *Pediatrics* 2007; **120:** 49–58.

64. Flett PH, Stern LM, Waddy H, Connell TM, Seeger JD, Gibson SK. Botulinum toxin A versus fixed cast stretching for dynamic calf tightness in cerebral palsy. *J Paediatr Child Health* 1999; **35:** 71–77.

65. Bottos M, Giannini S, Benedetti MG. Botulinum toxin with and without casting in ambulant children with spastic diplegia: a clinical and functional assessment. *Dev Med Child Neurol* 2003; **45:** 758–762.

66. Kay RM, Rethlefsen SA, Fern-Buneo A, Wren TAL, Skaggs DL. Botulinum toxin as an adjunct to serial casting treatment in children with cerebral palsy. *Journal of Bone and Joint Surgery* 2004; **86:** 2377–2384.

67. Ackman JD, Russman BS, Thomas S, *et al*. Comparing botulinum toxin A with casting for treatment of dynamic equinus in children with cerebral palsy. *Dev Med Child Neurol* 2005; **47:** 620–627.

68. Boyd RN, Dobson F, Parrott J, *et al*. The effect of botulinum toxin type A and a variable hip abduction orthosis on gross motor function: a randomized controlled trial. *Eur J Neurol* 2001; **8**(Suppl. 5)**:** 109–119.

69. Mall V, Heinen F, Siebel A, *et al*. Treatment of adductor spasticity with BTX-A in children with CP: a randomized, double-blind, placebo-controlled study. *Dev Med Child Neurol* 2006; **48:** 10–13.

70. Hazneci B, Tan AK, Guncikan MN, Dincer K, Kalyon TA. Comparison of the efficacies of botulinum toxin A and Johnstone pressure splints against hip adductor spasticity among patients with cerebral palsy: a randomized trial. *Mil Med* 2006; **171:** 653–656.

71. Graham HK, Boyd R, Carlin JB, *et al*. Does botulinum toxin A combined with bracing prevent hip displacement in children with cerebral palsy and "hips at risk"? *J Bone Joint Surg* 2008; **90:** 23–33.

72. Reddihough DS, King JA, Coleman GJ, *et al*. Functional outcome of botulinum toxin A injections to the lower limbs in cerebral palsy. *Dev Med Child Neurol* 2002; **44:** 820–827.

73. Steenbeek D, Meester-Delver A, Becher JG, Lankhorst GJ. The effect of botulinum toxin type A treatment of the lower extremity on the level of functional abilities in children with cerebral palsy: evaluation with goal attainment scaling. *Clin Rehab* 2005; **19:** 274–282.

74. Scholtes VA, Dallmeijer AJ, Knol DL, *et al*. The combined effect of lower-limb multilevel botulinum toxin type A and comprehensive rehabilitation on mobility in children with cerebral palsy: a randomized clinical trial. *Arch Phys Med Rehabil* 2006; **87:** 1551–1558.

75. Scholtes VA, Dallmeijer AJ, Knol DL, *et al*. Effect of multilevel botulinum toxin A and comprehensive rehabilitation on gait in cerebral palsy. *Pediatr Neurol* 2007; **36:** 30–39.

76. Hawamdeh ZM, Ibrahim AI, Al-Qudah AA. Long-term effect of botulinum toxin (A) in the management of calf spasticity in children with diplegic cerebral palsy. *Europa Medicophysica* 2007; **43:** 311–318.

77. Moore AP, Ade-Hall RA, Tudur Smith C, *et al*. Two-year placebo-controlled trial of botulinum toxin A for leg spasticity in cerebral palsy. *Neurology* 2008; **71:** 122–128.

78. Graham HK, Aoki KR, Autti-Ramo I, *et al*. Recommendations for the use of botulinum toxin type A in the management of cerebral palsy. *Gait and Posture* 2000; **11:** 67–79.

79. Heinen F, Moleanaers G, Fairhurst C, *et al*. European consensus table 2006 on botulinum toxin for children with cerebral palsy. *European Journal of paediatric Neurology* 2006; **10:** 215–225.

80. Chin TY, Nattrass GR, Selber P, Graham HK. Accuracy of intramuscular injection of botulinum toxin A in juvenile cerebral palsy: a comparison between manual needle placement and placement guided by electrical stimulation. *J Pediatr Orthop* 2005; **25:** 286–291.

81. Berweck S, Schroeder AS, Fietzek UM, Heinen F. Sonography-guided injection of botulinum toxin in children with cerebral palsy. *Lancet* 2004; **363:** 249–250.

82. Schroeder AS, Berweck S, Lee SH, Heinen F. Botulinum toxin treatment of children with cerebral palsy – a short review of different injection techniques. *Neurotox Res* 2006; **9:** 189–196.

83. Boyd RN, Hays RM. Current evidence for the use of botulinum toxin type A in the management of children with cerebral palsy: a systematic review. *Eur J Neurol* 2001; **8**(Suppl. 5)**:** 1–20.

84. Dumas HM, O'Neil ME, Fragala MA. Expert consensus on physical therapist intervention after botulinum toxin A injection for children with cerebral palsy. *Pediatr Phys Ther* 2001; **13:** 122–132.

85. Lannin N, Scheinberg A, Clark K. AACPDM systematic review of the effectiveness of therapy for children with cerebral palsy after botulinum toxin A injections. *Dev Med Child Neurol* 2006; **48:** 533–539.

86. Blackmore AM, Boettcher-Hunt EJordanM, Chan MD. A systematic review of the effects of casting on equinus in children with cerebral palsy: an evidence report of the AACPDM. *Dev Med Child Neurol* 2007; **49:** 781–790.

87. Molenaers G, Desloovere K, Eyssen M, *et al*. Botulinum toxin type A treatment of cerebral palsy: an integrated approach. *Eur J Neurol* 1999; **6**(Suppl. 4)**:** S51–S57.

88. Desloovere K, Molenaers G, Jonkers I, *et al*. A randomized study of combined botulinum toxin type A and casting in the ambulant child with cerebral palsy using objective outcome measures. *Eur J Neurol* 2001; **8**(Suppl. 5)**:** 75–87.

89. Figueiredo EM, Ferreira GB, Moreira RCM, Kirkwood RN, Fetters L. Efficacy of ankle-foot orthoses on gait of children with cerebral palsy: Systematic review of literature. *Pediatr Phys Ther* 2008; **20:** 207–223.

90. Nauman M, Albanese A, Heinen F, Molenaers G, Relja M. Safety and efficacy of toxin type A following long-term use. *Eur J Neurol* 2006; **13**(Suppl. 4)**:** 35–40.

91. Bakheit AM, Severa S, Cosgrove A, *et al*. Safety profile and efficacy of botulinum toxin A (Dysport) in children with muscle spasticity. *Dev Med Child Neurol*, 2001; **43:** 234–238.

92. Boyd RN, Graham JEA, Nattrass GR, Graham HK. Medium-term response characterisation and risk factor analysis of botulinum toxin type A in the management of spasticity in children with cerebral palsy. *Eur J Neurol*, 1999; **6**(Suppl. 4)**:** S37–S45.

93. Linder-Lucht M, Kirschner J, Herrmann J. Why do children with cerebral palsy discontinue therapy with botulinum toxin A? : Letter to the editor *Dev Med Child Neurol* 2006; **48:** 319–320.

94. Bakheit AM, Ward CD, McLellan DLI. Generalised botulism-like syndrome after intramuscular injections of botulinum toxin type A: a report of 2 cases. *Journal of Neurology and Neurosurgical Psychiatry* 1997; **62:** 198.

95. Bhatia KP, Münchau A, Thompson PD. Generalised muscular weakness after botulinum toxin injections for dystonia: a report of three cases. *Journal of Neurology and Neurosurgical Psychiatry* 1999; **67:** 90–93.

96. Howell K, Selber P, Graham HK, Reddihough D. Botulinum neurotoxin A: An unusual systemic effect. *J Paediatr Child Health* 2007; **43:** 499–501.

97. U.S. Food and Drug Administration (FDA) Follow-up to the February 8, 2008, Early Communication about an Ongoing Safety Review of Botox and Botox Cosmetic (Botulinum toxin Type A) and Myobloc (Botulinum

toxin Type B). Last updated: 06/18/2009. Available online: http://www.fda.gov Accessed: 02/07/2009.

98. Herrmann J, Geth K, Mall V, *et al*. Clinical impact of antibody formation to botulinum toxin A in children. *Ann Neurol* 2004; **55:** 732–735.

99. Russell D, Rosenbaum P, Cadman D, Gowland C, Hardy S, Jarvis S. The gross motor function measure: a means to evaluate the effects of physical therapy. *Dev Med Child Neurol* 1989; **31:** 341–352.

100. Law M, Baptiste S, McColl MA, Opzoomer A, Polatajko H, Pollock N. The Canadian Occupational Performance Measure: an outcome measure for occupational therapy. *Canadian Journal of Occupational Therapy* 1990; **57:** 82–87.

101. El-Etribi MA, Salem ME, El-Shakankiry HM, El-Khaky AM, El-Mahboub SM. The effect of botulinum toxin – type A injection on spasticity, range of motion and gait patterns in children with spastic diplegic cerebral palsy: an Egyptian study. *The International Journal of Rehabilitation Research* 2004; **27:** 275–281.

102. Mackey A, Walt S, Stott NS. Botulinum toxin type A in ambulant children with cerebral palsy. *Physiotherapy* 2003; **89:** 219–232.

103. Lukban MB, Rosales RL, Dressler D. Effectiveness of botulinum toxin A for upper and lower limb spasticity in children with cerebral palsy: a summary of evidence. *J Neural Transm* 2009; **116:** 319–331.

104. Simpson DM, Gracies JM, Graham HK, *et al*. Assessment: botulinum neurotoxin for the treatment of spasticity (an evidence-based review). *Neurology* 2008; **70:** 1691–1698.

105. Bertoti DB. Effect of short leg casting on ambulation in children with cerebral palsy. *Phys Ther* 1986; **66:** 1522–1529.

106. Leach J. Children undergoing treatment with botulinum toxin: the role of the physical therapist. *Muscle Nerve* 1997; **20**(Suppl. 6)**:** S194–S207.

107. Romkes J, Brunner R. Comparison of a dynamic and a hinged ankle-foot orthosis by gait analysis in patients with hemiplegic cerebral palsy. *Gait Posture* 2002; **15:** 18–24.

108. Buckon CE, Thomas SS, Jakobson-Huston S, Moor M, Sussman M, Aiona M. Comparison of three ankle-foot orthosis configurations for children with spastic diplegia. *Dev Med Child Neurol* 2004; **46:** 590–598.

109. Radtka SA, Skinner SR, Johanson ME. A comparison of gait with solid and hinged ankle-foot orthoses in children with spastic diplegic cerebral palsy. *Gait Posture*. 2005; **21:** 303–310.

110. Lam WK, Leong JC, Li YH, Hu Y, Lu WW. Biomechanical and electromyographic evaluation of ankle foot orthosis and dynamic ankle foot orthosis in spastic cerebral palsy. *Gait Posture* 2005; **22:** 189–197.

111. Goldstein EM. Spasticity management: an overview. *J Child Neurol* 2001; **16:** 16–23.

112. Gaebler-Sira D, Revivo G. The use of botulinum toxin in pediatric disorders. *Phys Med Rehabil Clin N Am* 2003; **14:** 703–725.

113. Pin T, Dyke P, Chan M. The effectiveness of passive stretching in children with cerebral palsy. *Dev Med Child Neurol* 2006; **48:** 855–862.

114. Pin TW. Effectiveness of static weight-bearing exercises in children with cerebral palsy. *Pediatr Phys Ther* 2007; **19:** 62–73.

115. Tardieu C, Lespargot A, Tabary C, Bret MD. For how long must the soleus muscle be stretched each day to prevent contracture? *Dev Med Child Neurol* 1988; **30:** 3–10.

116. Tremblay F, Malouin F, Richards CL, Dumas F. Effects of prolonged muscle stretch on reflex and voluntary muscle activations in children with spastic cerebral palsy. *Scand J Rehabil Med* 1990; **22:** 171–180.

117. Richards CL, Malouin F, Dumas F. Effects of a single session of prolonged plantarflexor stretch on muscle activations during gait in spastic cerebral palsy. *Scand J Rehabil Med* 1991; **23:** 103–111.

118. Dodd KJ, Taylor NF, Damian DL. A systematic review of the effectiveness of strength-training programs for people with cerebral palsy. *Arch Phys Med Rehabil* 2002; **83:** 1157–1164.

119. Verschuren O, Ketelaar M, Takken T, Helders PJM, Gorter JW. Exercise programs for children with cerebral palsy: a systematic review of the literature. *Arch Phys Med Rehabil* 2008; **87:** 404–417.

120. Dodd KJ, Taylor NF, Graham HK. A randomized clinical trial of strength training in young people with cerebral palsy. *Dev Med Child Neurol* 2003; **45:** 652–657.

121. Unger M, Faure M, Frieg A. Strength training in adolescent learners with Cerebral Palsy: a randomised control trial. *Clin Rehab* 2006; **20:** 469–477.

122. Liao HF, Liu YC, Lin WY. Effectiveness of loaded sit-to-stand resistance exercise for children with mild spastic diplegia: a Randomized Clinical Trial. *Arch Phys Med Rehabil* 2007; **88:** 25–31.

123. Verschuren O, Ketelaar M, Gorter JW, Helders PJM, Uiterwaal CS, Takken T. Exercise training in children and adolescents with cerebral palsy. *Arch Pediatr Adolesc Med* 2007; **161:** 1075–1081.

124. Bower E, McLellan DL, Arney J, Campbell MJ. A randomised controlled trial of different intensities of physiotherapy and different goal-setting procedures in 44 children with cerebral palsy. *Dev Med Child Neurol* 1996; **38:** 226–237.

125. Ketelaar M, Vermeer A, Hart H, van Petegem-van-BeekE, Helders PJM. Effects of a functional therapy program on motor abilities of children with cerebral palsy. *Phys Ther* 2001; **81:** 1534–1545.

126. Bower E, Michell D, Burnett M, Campbell MJ, McLellan DL. Randomized controlled trial of physiotherapy in 56 children with cerebral palsy followed for 18 months. *Dev Med Child Neurol* 2001; **43:** 4–15.

Appendix 1: paediatric lower limb botulinum toxin evidence table

Technical papers/injection techniques

Citation	Design	Participants	Intervention	Outcomes	Total	Systemic	Local	Level of evidence	Mask/obj outcome	Representative pop	Baseline equivalent	Concealed allocation	Primary outcome	Ex/inclusion criteria	Adequate power
Wissel; 1999 [53]	RCT double-blind	$N = 33$ CP, hemi/diplegia 3–21 years Spastic gait pattern	2 groups: 1. High dose = 200 U BOTOX®/dilution 200 U/ml 2. Low dose = 100 U BOTOX®/dilution 100 U/ml; 2 level injections: 1st level: 2–3 muscle bellies of triceps surae (gastrocs ± soleus) 0.2 ml (40 U vs. 20 U) injected 2nd level: semitendinous or gracilis ± rectus femoris; 0.2 to 0.4 ml (40–80 U vs. 20–40 U) injected	Body structures: • Increased ROM with high dose (& equal safety). Active DF greater in high dose $P < 0.05$. No difference for knee ROM • Decrease tone both doses (AS at knee) at 6–8 weeks. Greater tone $P < 0.05$ reduction with high dose • Greater improved stride length $P < 0.01$ & velocity $P < 0.01$ with high dose	$n = 3$ low dose $n = 5$ high dose	No systemic AE in either group	Gait abnormality $n = 1$ Transient unwillingness to walk $n = 5$ Pain $n = 2$ Local haematoma $n = 1$	Class II	✓	✓	✓	×	✓	✓ ✓	×
Baker; 2002 [52]	RCT double-blind, placebo-controlled	$N = 125$ CP, diplegia 2–9 years Dynamic equinus	4 groups: 1. 10 U/kg Dysport® 2. 20 U/kg Dysport® 3. 30 U/kg Dysport® 4. placebo	Body structures: • Decreased tone for all 3 doses compared with placebo • Improved ROM (Electro-goniometry) for all 3 doses compared with placebo. Activities: • Gross motor (GMFM) improved for all doses. Improvement most pronounced with 20 U/kg, increased DF with knee extended; response over 16 weeks	$n = 58$ ($n = 21$ 10 U; $n = 10$ 20 U; $n = 17$ 30 U; $n = 10$ placebo). No difference in AE rate between groups	• Fever, viral infection, vomiting, diarrhoea $n = 14$ • URTI $n = 6$ • Seizure $n = 6$	Pain $n = 10$ Falls $n = 7$	Class I	✓	✓	✓	✓	✓	✓ ✓	✓
Polak; 2002 [54]	RCT double-blind, multi-centre	$N = 48$ CP, hemiplegia 3–15 years Ambulant, spastic equinus	2 groups: 1. Low dose: ($n = 23$) 8 U/kg Dysport® 2. High dose: ($n = 25$) 24 U/kg Dysport®	Body Structures: • Maximum gastrocnemius length during gait cycle (gait analysis) improved at both doses at 4 weeks. Better gastrocs length only maintained with high dose at 12 weeks. • Maximum DF measured during stance and swing phase better with high dose (swing $P < 0.05$; stance $P < 0.01$). Maintained improvement in DF in stance at 12 weeks 24 U more effective than 8 U and lasted longer Dose response was not linear Optimal dose between 200–500 U	$n = 12$ ($n = 6$ high dose; $n = 6$ low dose). No difference in AE rate between groups	Generalized weakness lasting 4 weeks $n = 1$	• Pain $n = 12$	Class III	✓	✓	?	?	✓	✓	?

Appendix 1: *(Continued)*

Citation	Design	Participants	Intervention	Outcomes	Adverse events — Total	Adverse events — Systemic	Adverse events — Local	Level of evidence	Mask/obj outcome	Representative pop	Baseline equivalent	Concealed allocation	Primary outcome	Ex/inclusion criteria	Adequate power
Detrembleur; 2002 [55]	RCT, single-blinded	N = 12 CP, hemi-/diplegia Dynamic foot equinus Ambulant	2 groups: 1. BOTOX® + E stim (n = 6) 2. BOTOX® only (n = 6) Injections to soleus, & gastrocnemius under EMG guidance using local anaesthetic cream. Dose per muscle 2–5 U/kg	Body structures: • Improved PRS scores 1 & 3 months both groups • Improved DTRs 1 month both groups • Improved segmental kinematics with reduced foot equinus at 1 & 3 months both groups. Short-term E stim did not enhance the effect of BOTOX® on clinical measures, gait variables or ankle stiffness.	Not described	Not described	Not described	Class II	✔	✔	✔	✗	✔	✔	✗
Sätilä; 2008 [56]	RCT, atypical randomization	N = 17 (25 limbs) CP, GMFCS I–IV Ambulant	2 groups: 1. Multiple-site injections 2. Single-site injections, gastrocnemius Dose 4 U/kg BOTOX® per med and lat gastrocs	Body structures: • No difference between groups	n = 8	No systemic AEs	• Calf tenderness n = 5 • Calf spasm n = 1 • Clumsiness n = 2	Class III	✔	✔	?	?	✔	✔	✗
Wang; 2008 [57]	RCT single-blinded	N = 150 CP, di/hemi/quad mono/paraplegia 2–12 years	3 groups: 1. Low dose 1 U/kg 2. Middle-dose 3 U/kg 3. High dose 5 U/kg Max dose 300 U (brand unspecified) 3–5 injection sites per muscle	Body structures: • Decreased tone all doses P < 0.01 • Improved PRS scores all doses P < 0.01 Activities: • Dose-dependent functional improvements in dynamic deformities and spastic gait pattern favouring higher dose	n = 23 (n = 5 low dose; n = 8 middle-dose; n = 10 high dose). No difference between groups	No systemic AEs	• Local pain n = 21 • Weakness n = 1 • Unsteady gait n = 1	Class III	?	✔	?	?	?	✔	?
Sätilä; 2005 [58]	RCT	N = 19 CP 18 month–7 years GMFCS I–IV Ambulant Spastic equinus gait	Total dose 12 U/kg diplegia & 6 U/kg hemiplegia 2 groups: Proximal injections: (n = 9, 12 legs) BOTOX® 3 U/kg per site into proximal gastrocnemius ± hamstring (n = 3) Distal injections: (n = 10, 13 legs) BOTOX® into mid-belly gastrocnemius ± hamstring injections (n = 2)	Body structures: • Increased active & passive DF with knee extended & flexed in both groups • Decreased tone (MAS) both groups • Slightly better improvement in equinus gait at 8 weeks for distal group, not maintained at 16 weeks (VGA).	n = 19 (n = 9 proximal; n = 10 distal). No difference between groups	• Tiredness n = 3 • Fever, flu-like illness n = 2	• Calf tenderness n = 9 • Clumsiness n = 3 • Irritability n = 2	Class III	✔	✔	?	✗	✔	✔	✗
Injection of the calf for spastic equinus versus placebo															
Koman; 1994 [38]	RCT double-blind, placebo-controlled	N = 12 CP, hemi/diplegia 4–11 years	2 groups: 1. BOTOX® injections 1–2 UKg 2. Placebo	Body structures: No differences between groups (BioDex) Activities: Subjectively gait was better with BOTOX®	n = 3	No systemic AEs	Pain n = 3 Unsteadiness n = 3 Headache n = 1	Class II	✔	✔	✔	✔	✔	✔	✗

Appendix 1: *(Continued)*

Citation	Design	Participants	Intervention	Outcomes	Adverse events — Total	Adverse events — Systemic	Adverse events — Local	Level of evidence	Quality — Mask/obj outcome	Quality — Representative pop	Quality — Baseline equivalent	Quality — Concealed allocation	Quality — Primary outcome	Quality — Ex/inclusion criteria	Quality — Adequate power
Sutherland; 1999 [60]	RCT double-blind, placebo-controlled	N = 20 (1 drop out) CP 2–16 years Ambulatory Dynamic equinus	2 groups: 1. Injections of BOTOX® 4 U/kg a wk 0 & 4 weeks (n = 10). Hemiplegia & diplegia received the same total dose 2. Injections of saline at wk 0 & 4 weeks (n = 9)	Body structures: Improved dynamic DF (f3° or more) after BOTOX® (3DGA): • At 10% of gait cycle (P = 0.02) • Peak DF in stance phase (0.006) • Peak DF in swing phase (0.006) No differences in step length, stride length, cadence or walking velocity. No significant differences in EMG data, passive DF	Not described	Not described	Not described	Class I	✓	✓	✓	✓	✓	✓	✓
Koman; 2000 [59]	RCT double-blind, placebo-controlled	N = 145 CP 2–16 years	2 groups: 1. BOTOX® 4 U/kg, 1 ml dilution. Max dose 200 U 2. Placebo	Body structures: Improved PRS composite score significantly greater in the BOTOX® group P < 0.05 Improvements in gait pattern lasted a minimum of 8 weeks No difference seen between diplegia versus hemiplegia, even though the hemiplegia received twice the dose. Perhaps the smaller dose was sufficient	Adverse events not itemized in the paper. n = 0 serious, severe, or irreversible adverse events were experienced. Majority of AEs were mild. n = unknown			Class I	✓	✓	✓	✓	✓	✓	✓
Ubhi; 2000 [61]	RCT double-blind placebo-controlled	N = 40 CP, di/hemiplegia 2–16 years Ambulant Dynamic equinus	2 groups: 1. Dysport® to med/lat gastroc & soleus ± hamstring (n = 22). Dose 24 U/kg diplegia. 15 U/kg hemiplegia. Dilution 200 U/ml of 0.9% saline 2. Placebo	• Activities: Improved GMF at 12 weeks (GMFM), (37% Dysport®, 7% placebo, P = 0.04) • Improved initial foot contact (VGA) at 6 weeks (48% subjects, P = 0.02) and 12 weeks (50% subjects, P = 0.003) • No change in walking efficiency (PCI)	n = 7 (n = 6 BoNT-A; n = 1 placebo)	Vomiting n = 1 (placebo) Wheezing n = 1 Seizure n = 1	• Pain n = 2 Falls n = 2	Class II	✓	?	?	×	×	✓	✓
Love; 2001 [62]	RCT matched pairs	N = 24 CP hemiplegia 3–13 years GMFCS I	2 groups: 1. BOTOX® + physiotherapy 2. Physiotherapy	Activities: Improved GMF with BOTOX® at 3 months (P < 0.02) with even greater differences at 6 months (P < 0.004). Decreased tone (MAS) from BOTOX® at 3 months (P < 0.002) & 6 months (P < 0.016).	n = 0	No AEs		Class II	?	✓	✓	?	✓	✓	?
El-Etribi; 2004 [101]	RCT	N = 40 CP diplegia 2–6 years Ambulant equinus deformity	2 groups: 1. Injections of BOTOX® + physiotherapy. 3–6 U/kg, 2 ml dilution, maximum dose 200 U/ injection to gastrocnemius ±hip adductors or hamstrings 2. Physiotherapy	Body Structures: Reduced (P = 0.001) with BOTOX® Increased passive DF with the knee flexed (P = 0.001), extended (P = 0.001) and active DF (P = 0.001) (Improvement in PRS composite score (P = 0.001)	Not described	Not described		Class II	?	✓	?	?	✓	✓	?

Appendix 1: *(Continued)*

Citation	Design	Participants	Intervention	Outcomes	Adverse events Total	Systemic	Local	Level of evidence	Quality Mask/obj outcome	Representative pop	Baseline equivalent	Concealed allocation	Primary outcome	Ex/inclusion criteria	Adequate power
Bjornson; 2007 [63]	RCT double-blind, placebo-controlled	N = 33 CP diplegia 3–12 years GMFCS I–III	2 groups: 1. 12 U/kg BOTOX® to bilateral gastrocnemius 2. Placebo saline	Body structures: • Decrease spasticity BOTOX® (3 & 8 weeks) • Increased DF BOTOX® (12 weeks) • Improved voluntary torque BOTOX® (12 weeks) Activities: • Improved goal performance BOTOX® (12 weeks) • Improved gross motor function BOTOX® (24 weeks) No differences between groups in satisfaction with performance goals, energy expenditure, Ashworth scores.	n = 56 No difference between groups	No systemic AEs	• Soreness n = 6 • Decreased activity n = 3	Class II	✔	✔	✔	✔	✗	✔	✗

Injection of the calf with casting as the comparator

Citation	Design	Participants	Intervention	Outcomes	Total	Systemic	Local	Level of evidence	Mask/obj outcome	Representative pop	Baseline equivalent	Concealed allocation	Primary outcome	Ex/inclusion criteria	Adequate power
Corry; 1998 [39]	RCT single-blind	N = 20 CP 2–9 years Ambulant Dynamic equinus	2 groups: 1. BoNT-A + physiotherapy: (n = 10 – 17 calves) to gastroc and soleus (4 sites per calf) max of 0.4 ml injected BOTOX® (n = 8) 80–200 U, 6–8 U/kg. Dysport® (n = 2) 240–320 U, 15 U/kg 2. Serial Casting + physiotherapy: (n = 10, 15 legs) walking casts at plantargrade	Body structures: • Increased passive DF (knee flexed) both groups 2 weeks, with effect not significant at 12 weeks after casting; no between group difference • Decreased calf tone (Ashworth) at 2 weeks with BoNT-A (P = 0.0001) but not casting. Relapse in both groups 12 weeks, with casting relapse greater than BoNT-A • Improved PRS scores; no difference between groups • Effect from BoNT-A maintained at 12 weeks compared with casting (3DGA)	n = 7 (n = 1 BoNT-A; n = 6 casting)	No systemic AEs	• Pain n = 5 • Inflammation n = 2	Class II	✔	✔	✔	?	✔	✔	✔
Flett; 1999 [64]	RCT single-blind	N = 20 CP, di/quad/hemi/ triplegia 2–8 years Ambulatory	2 groups: 1. BOTOX®. 4–8 U/kg max 20 u/site + night plasters (4–8 weeks post injection) 2. Serial Casting: Casting using fixed plaster (2 × 2 weeks) + night plasters (8 weeks from casting)	Body structures: • Improved dynamic calf both groups • Parents favoured BOTOX® and highlighted the inconvenience of serial casting	Not described			Class II	✔	✔	✔	✔	✔	✔	?

Appendix 1: (*Continued*)

Citation	Design	Participants	Intervention	Outcomes	Total	Systemic	Local	Level of evidence	Mask/obj outcome	Representative pop	Baseline equivalent	Concealed allocation	Primary outcome	Ex/inclusion criteria	Adequate power
Bottos; 2003 [65]	RCT	$N = 10$ CP diplegia 4–11 years Ambulatory Equinus	2 groups: 1. Dysport® ($n = 5$) 15–20 U 2. Dysport® & cast: ($n = 5$) 15–20 U + inhibitory cast after injection for 3 weeks	Body structures: • Reduced spasticity (Ashworth) from Dysport® + casting at 4 months ($P < 0.006$) Activities: • Improved walking (GMFM) from Dysport® + casting at 4 months ($P = 0.007$) • Increased walking speed (gait analysis) at 4 months from Dysport® + casting ($P = 0.028$)	Not described	Class II			✓	✓	✓	×	✓	✓	?
Kay; 2004 [66]	RCT	$N = 23$ CP hemi/di/quadriplegia 4–13 years Ambulatory Equinus contracture	2 groups: 1. Casting: ($n = 12$, limbs = 20) 2. BOTOX® + casting: ($n = 11$, limbs = 16) 8 U/kg, max dose 400 U + serial casting 1–3 weeks post injection	Body structures: • Contractures reduced at same rate in both groups • Spasticity decreased (Ashworth) in both groups but returned faster in BOTOX® + casting	Not itemized	Class II			✓	✓	✓	✓	?	✓	?
Ackman; 2005 [67]	RCT double-blind placebo-controlled	$N = 39$ CP 3–9 years GMFCS I–II	3 groups: 1. BoNT-A only (brand not specified) 2. Placebo injection + Casting 3. BoNT-A + casting	Body structures: • No change in dynamic equinus from BoNT-A (1 year) but BoNT-A + casting & casting alone showed medium and long-term benefits • No change in gait velocity and stride length from any treatment	$n = 2$ ($n = 1$ BoNT-A; $n = 1$ BoNT-A + casting)	No systemic AEs	Falls $n = 2$	Class II	✓	✓	&	✓	✓	✓	×
Adductor injections Boyd; 2001 [68]	RCT, multi-centre	$N = 39$ Bilateral CP 1–4 years GMFCS I–V	2 groups: 1. BOTOX®: ($n = 19$) repeated 6 months 4 U total 16 U/kg/ + SWASH brace. 2. Control: ($n = 20$) No hip bracing & no injections	Activities: • Improved gross motor (GMFM) no difference between groups • Children GMFCS II and III achieved greater improvement in gross motor function	$n = 3$ ($n = 2$ BOTOX®; $n = 1$ SWASH brace refit)	$n = 2$ resp infections	$n = 1$ swash brace re-fit	Class II	✓	✓	×	✓	?	✓	?
Mall; 2006 [69]	RCT double-blind, placebo-controlled	$N = 61$ CP bilateral adductor spasticity MP < 50% 18 months–10 years GMFCS I–V	2 groups: 1. Dysport®: 30 U Dysport®/kg to max dose 1500 U 2/3 adductors, 1/3 medial hamstrings 2. Placebo	Body Structures: • Reduced spasticity (Fast-catch & Ashworth) ($P = 0.01$) Dysport® group • Improved goal attainment Dysport® group (GAS) ($P = 0.04$)	$n = 12$ ($n = 9$ Dysport®; $n = 3$ placebo)	• Urinary incontinence $n = 1$ • Pollakiuria $n = 1$ • Swallowing problem $n = 3$	Weakness $n = 7$	Class I	✓	?	?	✓	✓	✓	✓

Appendix 1: (*Continued*)

Citation	Design	Participants	Intervention	Outcomes	Adverse events — Total	Adverse events — Systemic	Adverse events — Local	Level of evidence	Quality — Mask/obj outcome	Quality — Representative pop	Quality — Baseline equivalent	Quality — Concealed allocation	Quality — Primary outcome	Quality — Ex/inclusion criteria	Quality — Adequate power
Haznedi; B 2006 [70]	RCT	N = 43 CP diplegia	2 groups: BoNT-A(brand not specified): 300 U into adductors & med hamstrings + 3×/ week NDT (i = 22) Splints: Johnstone pressure splints (JPS) – 3 days/week in 30 min sessions + 3×/ week NDT (n = 21)	Body Structures: • Improved passive hip abduction (ROM) from BoNT-A P = 0.01 • Reduced tone from BoNT-A (Ashworth) P = 0.002 • Improved distance between knees from BoNT-A P = 0.02 Activities: • Improved gross motor function from BoNT-A (GMFM) P = 0.034	Not described	Class III			×	✓	✓	×	✓	?	×
Graham; 2008 [71]	RCT single-blind, multi-centre	N = 90 CP bilateral spasticity 1–5 years	2 groups: BOTOX®: 6 monthly to adductor & hamstring muscles + hip abduction Control: No hip bracing & no injections	Body Structures: • Small benefit from BOTOX® + brace but debatable clinical relevance • Progressive hip displacement continued in both groups • Rate of hip displacement (MP change/ year) was slightly reduced from BOTOX® + brace, • Progression to surgery slower from BOTOX® + brace	n = 45	• Death n = 2 unrelated to injection • Incontinence n = 3 • Generalized weakness n = 2 • Flu-like illness n = 1 • Fever n = 6 • Vomiting n = 2 • Diarrhoea n = 2 • Vomiting & diarrhoea n = 1	• Bruising n = 3 • Pain n = 3 • Weakness n = 3	Class I	?	✓	✓	✓	✓	✓	✓
Multilevel injections Reddihough; 2002 [72]	RCT cross-over	N = 61 CP, di/ quadriplegia	2 groups: 1. BoNT-A(brand not specified) + PT (12 months): (n = 22) Injected in 2–6 muscle groups. 8–20 U/kg body wt. Max dose 300 U 2. PT only (6 months): then BoNT-A + PT for subsequent 6 months (n = 27)	Body structures: • Reduced tone (MAS) at 6 months from BoNT-A • Improved right DF with knee extended at 3 months from BoNT-A • Improved right DF with knee flexed at 6 months from BoNT-A Activities: • No difference in GMF between treatments Parental perception: • BoNT-A more positive response 3 & 6 months	n = 22	• Incontinence n = 4 • Out of sorts n = 2	• Pain n = 11 • Weakness n = 5	Class III	✓	✓	×	×	✓	✓	?

Appendix 1: (*Continued*)

Citation	Design	Participants	Intervention	Outcomes	Adverse events — Total	Adverse events — Systemic	Adverse events — Local	Level of evidence	Quality — Mask/obj outcome	Representative pop	Baseline equivalent	Concealed allocation	Primary outcome	Ex/inclusion criteria	Adequate power
Steenbeek; 2005 [73]	RCT multiple baseline. Randomized to 2 time points for injection	N = 11 CP 3–12 years GMFCS I–IV	2 groups, both received the same treatment at different time points: 1. Group 1: (n = 5) the baseline phase lasted 8 weeks, Tx phase lasted 6 weeks 2. Group 2: (n = 6) the baseline phase lasted 6 weeks, Tx phase lasted 8 weeks BOTOX® 4–6 U/kg max 50 U per site	Activities: • Improved functional ability after BOTOX® • Improved goal achievement (n = 33) (P < 0.001) (GAS)	Not described			Class III	✓	✓	?	✓	✓	✓	×
Scholtes; 2006 [74]	RCT using Multiple baseline, multi-centre	N = 46 CP 4–11 years Ambulant	2 groups: • Multilevel BOTOX® (n = 23): 4–6 U/kg, max total does 600 U) + intense physiotherapy • Physiotherapy (n = 24)	Body structures: • No difference in energy cost. Activities: • Improved GMF (GMFM) at 12 & 24 weeks from multilevel BOTOX® + PT. • Before-after analysis of the total group (n = 46) showed a significant long-term improvement (48 weeks)	Not described			Class III	×	✓	✓	✓	?	✓	?
Scholtes; 2007 [75]	RCT multi-centre single-blind	N = 46 CP 4–11 years Ambulant	2 groups: Multilevel BOTOX®: (n = 23) 4–6 U/kg, max total dose 600 U + Intensive Physiotherapy ± casting Control: (n = 24) with multilevel BOTOX® injections after control period	Body structures: • Improved knee angle mid stance (P < 0.01) from multilevel BOTOX® + PT • Improved knee angle terminal swing (P < 0.01) from multilevel BOTOX® + PT • Improved hip rotation terminal swing (P < 0.01) from multilevel BOTOX® + PT • Decreased spasticity hamstrings & gastrocs (P < 0.01) from multilevel BOTOX® + PT • Gains not maintained at 24 weeks	Not described systematically	• Gait deterioration 6 weeks post injection n = 2		Class II	✓	✓	✓	?	✓	✓	?
Hawamdeh; 2007 [76]	RCT single-blind	N = 60 CP diplegia 3–15 years	2 groups: 1. BoNT-A: (n = 40) 3 successive injections BOTOX® (6–12 U/kg total 200 U) or Dysport® (calculated at 5:1 U Dysport®: BOTOX®) + Intensive Physiotherapy 2. Physiotherapy: (n = 20)	Body structures: • Decreased spasticity (MAS) from multilevel BOTOX® +PT • Increased PROM ankle from multilevel BOTOX® + PT • Increased GMF from multilevel BOTOX® + PT	Not described			Class II							

Appendix 1: (*Continued*)

Citation	Design	Participants	Intervention	Outcomes	Adverse events — Total	Adverse events — Systemic	Adverse events — Local	Level of evidence	Quality — Mask/obj outcome	Representative pop	Baseline equivalent	Concealed allocation	Primary outcome	Ex/inclusion criteria	Adequate power
Moore, 2008 [77]	RCT double-blind placebo-controlled, parallel group	N = 64 (240 injection sessions) CP, spasticity in 1–2 legs 2–6 years	2 groups: 1. Dysport®: (n = 32) 3 monthly cycles (max 8 cycles)/2 years + PT, casting, orthopaedic surgery. Dose 15 U/kg increased over 3 cycles to max 30 mu/kg. 2. Placebo: (n = 32) normal saline in 3 monthly cycles (max 8 cycles)/2 years + PT, casting, orthopaedic surgery	Activities: • No cumulative difference in function (PEDI & GMFM) at 1–2 years	n = 408 (n = 29 Dysport®, n = 27 placebo). No difference between groups	• Incontinence n = 9 • UTI n = 3 • Systemic n = 31 • Respiratory n = 49 • Seizure n = 4	• Local swelling n = 2 • Pain n = 8 • Cramps n = 1 • Mobility disturbance n = 30 • Bad behaviour n = 8	Class II	✓	✓	✓	✗	✓	✓	✗

3DGA, Three-dimensional gait analysis; AE, Adverse event(s); AS, Ashworth Scale; CP, Cerebral palsy; DF, Dorsiflexion; EMG, Electromyography; E stim, Electrical stimulation; GMF, Gross motor function; GMFCS, Gross Motor Function Classification System; GMFM, Gross Motor Function Measure; MAS, Modified Ashworth Scale; n, Number of cases; PEDI, Pediatric Evaluation of Disability Index®; PRS, Physician Rating Scale; PT, physiotherapist; RCT, Randomized Controlled Trial; ROM, Range of movement; SWASH, Standing, Walking and Sitting Hip Orthosis®; Tx, treatment; U, Units; URT, Upper respiratory tract infection; VGA, Video gait analysis.

Appendix 2: paediatric lower limb botulinum toxin evidence table for adjunctive interventions (with recommendations for management of equinus and/or multilevel injections to improve gait and function)

Intervention Option	Indications for Use	Intensity of intervention	Selected Reviews & Expert Opinion: AAN level of evidence Class IV	Selected Clinical Studies: AAN level of evidence for intervention Summary of Evidence Classification of Recommendations	
				Standard Intervention (in isolation)*	Adjunctive intervention to BoNT-A
Casting Single cast application Serial casting	Equinus with reduced ROM of DF; Gait training; poor AFO tolerance	Casts applied for 4–14 days; repeat application of casts with/without break until desired passive ROM achieved. Monitor AEs	Molenaers 1999 [87] Mackey 2003 [102] Lannin 2006 [85] Heinen 2006 [79] Blackmore 2007 [86] Lukban 2008 [103] Simpson 2008 [104]	Bertoti 1986: III* [105] Data inadequate though trend towards support for casting Recommendation U*	• BoNT-A + casting versus BoNT-A + AFO Bottos 2003: II [65] Ackman 2005: II [67] Recommendation B • BoNT-A + casting versus casting Kay 2004: II [66] Ackman 2005: II [67] (conflicting results) Recommendation U • Trend towards support for BoNT-A + casting however neither strong nor consistent evidence that casting provides additional benefit to BoNT-A. Recommendation U • Casting pre-BoNT-A versus casting post BoNT-A Desloovere 2001:IV [88] Insufficient evidence to support or refute that the order of casting + BoNT-A affects outcome despite trend towards support for casting to follow BoNT-A rather than precede it. Recommendation U
Orthotic management Ankle-foot orthoses (AFOs)	Dynamic equinus; poor selective motor control of DF; improve foot/ankle/knee biomechanics; improve biomechanics of gait	Worn during day for functional activities, dependent on identified goals	Leach 1997 [106] Graham 2000 [78] Boyd 2001 [68] Mackey 2003 [101] Heinen 2006 [79] Figueiredo 2008* [89]	Romkes 2002 III* [107] Buckon 2004: III* [108] Radtka 2005: III* [109] Lam 2005: III* [110] Possibly effective Recommendation C*	• BoNT-A + casting versus BoNT-A + AFO Bottos *et al.* 2003: II [65] • Insufficient evidence despite widespread use. Recommendation U

Appendix 2: (Continued)

Intervention Option	Indications for Use	Intensity of intervention	Selected Reviews & Expert Opinion: AAN level of evidence Class IV	Selected Clinical Studies: AAN level of evidence for intervention Summary of Evidence Classification of Recommendations: Standard Intervention (in isolation)*	Adjunctive intervention to BoNT-A
Stretching (Physiotherapy) Sustained stretch – splinting Static weight bearing exercises	Reduced muscle activity in lengthened position; reduced extensibility/ROM; risk of contracture	Maintain at 'threshold length' for significant time; optimal intensity unknown	Leach 1997 [106] Molenaers 1999 [87] Goldstein 2001 [111] Dumas 2001 [84] Gaebler-Spira & Revivo 2003 [112] Lannin 2006 [85] Pin 2006* [113] Pin 2007* [114]	Tardieu 1988:III* [115] Tremblay 1990: III [116] Richards 1991: III* [117] Data inadequate Recommendation U*	• No higher level studies were located, data inadequate Recommendation U
Strengthening (Physiotherapy) Functional strength training Progressive resistance strength training Assisted active & active exercise Endurance training	Muscle weakness and reduced endurance	3× week; minimum 6 weeks; 3 sets of 8–12 repetitions at max load maintaining good form; rest between sets; increase load by 10%. High repetition, low load for increasing endurance	Leach 1997 [106] Dodd 2002* [118] Dumas 2001 [84] Verschuren 2008* [119]	Dodd 2003: II* [120] Unger 2006 II* [121] Liao 2007: II* [122] Verschuren 2007: II* [123] Probably effective Recommendation B*	• No high-level studies were located, data inadequate Recommendation U
Targeted motor training (Physiotherapy) Motor function training ADL training Gait training	Goal activity or function	2 – 3 times a week, 8 – 12 weeks, repetition & practice specific tasks/activities; contextualized learning incorporated into daily activity optimal	Leach 1997 [106] Graham 2000 [78] Dumas 2001 [84] Mackey 2003 [102] Heinen 2006 [79]	Bower 1996: II* [124] Ketelaar 2001: II* [125] Bower 2001: II* [126] Possibly effective Recommendation C*	• No high-level studies were located, data inadequate Recommendation U

AE, Adverse event(s); ROM, Range of movement; AFO, Ankle-foot orthoses; DF, dorsiflexion.