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REVIEW ARTICLE

Botulinum Toxin in the Management of Children with Cerebral Palsy

Iqbal Multani[1,2] · Jamil Manji[1,2] · Tandy Hastings-Ison[1,3] · Abhay Khot[1,2,3] · Kerr Graham[1,2,3,4]

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Abstract

During the past 25 years, botulinum toxin type A (BoNT-A) has become the most widely used medical intervention in children with cerebral palsy. In this review we consider the gaps in our knowledge in the use of BoNT-A and reasons why muscle morphology and function in children with cerebral palsy are impaired. We review limitations in our knowledge regarding the mechanisms underlying the development of contractures and the difficulty in preventing them. It is clear from this review that injection of BoNT-A in the large muscles of both the upper and lower limbs of children with cerebral palsy will result in a predictable decrease in muscle activity, which is usually reported as a reduction in spasticity, for between 3 and 6 months. These changes are noted by the use of clinical tools such as the Modified Ashworth Scale and the Modified Tardieu Scale. Decreased muscle over-activity usually results in improved range of motion in distal joints. Injection of the gastrocnemius muscle for toe-walking in a child with hemiplegia or diplegia usually has the effect of increasing the passive range of dorsiflexion at the ankle. In our review, we found that this may result in a measurable improvement in gait by the use of observational gait scales or gait analysis, in some children. However, improvements in gait function are not always achieved and are small in magnitude and short lived. We found that some of the differences in outcomes in clinical trials may relate to the use of adjunctive interventions such as serial casting, orthoses, night splints and intensive therapy. We note that the majority of clinical trials of the use of BoNT-A in children with cerebral palsy have focussed on a single injection cycle and this is insufficient to understand the balance between benefit and harm. Most outcomes were reported in terms of changes in muscle tone and there were fewer studies with robust methodology that reported improvements in function. Changes in the domains of activities and participation have rarely been reported in studies to date. There were no clinical reviews to date that consider the findings of studies in human volunteers and in experimental animals and their relevance to clinical protocols. In this review we found that studies in human volunteers and in experimental animals show muscle atrophy after an injection of BoNT-A for at least 12 months. Muscle atrophy was accompanied by loss of contractile elements in muscle and replacement with fat and connective tissue. It is not currently known if these changes, mediated at a molecular level, are reversible. We conclude that there is a need to revise clinical protocols by using BoNT-A more thoughtfully, less frequently and with greatly enhanced monitoring of the effects on injected muscle for both short-term and long-term benefits and harms.

1 Introduction

In this review, we are aware of the complexity of cerebral palsy, our lack of knowledge about pathophysiology and the mechanisms that lead from hypertonia to contractures and how little is known about the long-term effects of one of the most frequently used interventions, botulinum toxin type A (BoNT-A). The quotation attributed to Voltaire may be appropriate:

> "Doctors prescribe medicines of which they know little, to cure diseases of which they know less in human beings of whom they know nothing."

The first publications reporting the use of BoNT-A in children with cerebral palsy (CP) were by Koman et al. in

✉ Kerr Graham
kerr.graham@rch.org.au

1 Royal Children's Hospital, 50 Flemington Road, Parkville, VIC 3052, Australia

2 Orthopaedic Department, Royal Children's Hospital, 50 Flemington Road, Parkville, VIC 3052, Australia

3 Hugh Williamson Gait Laboratory, Royal Children's Hospital, 50 Flemington Road, Parkville, VIC 3052, Australia

4 University of Melbourne, Parkville, Australia

Key Points

Injection of botulinum toxin type A (BoNT-A) is effective for reducing over-activity in muscles in children with cerebral palsy. This results in a reduction in muscle strength and muscle tone with small, short-lived gains in aspects of gait and function, in some children with cerebral palsy.

This is achieved at the cost of muscle atrophy, which may not be completely reversible. The harmful effects of muscle atrophy may be related to the function of the target muscle.

Injections of BoNT-A are generally safe for the child but there are local risks to the injected muscle in the ambulant child and there are increased risks of systemic adverse events in non-ambulant children.

There are grounds for modification of existing injection protocols and further research is required to evaluate the long-term effects and risk versus benefit of BoNT-A injections in skeletal muscle, in children with cerebral palsy.

The timing of progression from BoNT-A therapy to definitive muscle–tendon lengthening should be carefully considered by the multidisciplinary team.

the United States in 1993 and by Graham et al. in the United Kingdom in 1994 [1, 2]. Since then, the use of BoNT-A has become a 'standard of care' for children with CP in many countries, leading to widespread clinical use and the publication and dissemination of consensus statements [3–6]. There is a need for a review of the recent literature with a view to modifying existing BoNT-A protocols, in the light of recent animal and clinical studies that have raised concerns regarding harm to the injected muscle [7]. Gough et al. were the first to raise concerns regarding the use of BoNT-A in children with CP [8]. They questioned the use of an agent whose mechanism of action is to *cause* weakness, in order to manage a condition *characterised by weakness*. They also raised the issue of the potential for long-term effects before much of the recent experimental work in animal models [7, 8].

The most frequent indication for BoNT-A therapy in CP is to treat focal muscle over-activity to improve gait and function in children who can walk [1, 2]. Injection of the upper limb to improve posture and function is the second most frequent indication for BoNT-A therapy in children with CP [9, 10]. The use of BoNT-A in non-ambulant children with CP also merits discussion, given the heterogeneous indications and the risk of systemic adverse events [11, 12]. Injections of BoNT-A may also be used as an analgesic agent, particularly when pain is related to muscle spasm [3].

In recent years, there has been a proliferation of basic science animal studies reporting the effects of BoNT-A using invasive techniques that would not be possible in children [7]. These studies may be relevant to BoNT-A protocols and will also be discussed.

1.1 Muscle Imaging

The use of ultrasound in BoNT-A management is important for two reasons. Firstly, 2-Dimensional Ultrasound (2DUS) has emerged as the preferred technique for imaging muscles during the injection procedure [13]. Secondly, 3-Dimensional Ultrasound (3DUS) has yielded substantial new information regarding the natural history of muscle development in children with CP, as well as changes following injection of BoNT-A [14, 15].

1.2 Botulinum Toxin Preparations and Warning/Disclaimer

New preparations of botulinum neurotoxins are being developed and released on the market on a regular basis. Extensive clinical data exists for only two type A preparations, onabotulinum toxin A (Botox®, Allergan) and abobotulinum toxin A (Dysport®, Ipsen, UK), for children with CP [1–6, 9, 11, 12, 16, 17]. Information is growing with respect to the use of Xeomin®, from Merz Pharmaceuticals, Germany and for several preparations from Korea and China (Table 1) [18]. The new preparations that are being developed are type A toxins with different formulations in terms of additional proteins and other excipients [18]. The clinical effects may be similar to existing formulations but there will almost certainly be differences that will require further research and clinical trials. There is limited clinical information relating to the use of the more recently released toxins and the following warning/disclaimer is relevant.

Botulinum neurotoxins are the most potent biological toxins known in the natural world. Deaths from ingested botulinum toxin, in the form of food poisoning, still occur as well as deaths from botulinum toxin injected for medical and therapeutic purposes. The licencing and registration of preparations of botulinum toxins, vary from country to country and labelling may be specific for indications within each jurisdiction [18, 19]. Within countries where the preparations have been approved, many current clinical indications are 'off-label' [18–20].

Table 1 Botulinum neurotoxin preparations

Generic name	Onabotulinum Toxin A	Abobotulinum Toxin A	Incobotulinum Toxin A	Rimabotulinum Toxin B
Brand name	Botox®	Dysport®	Xeomin®	Myobloc/Neurobloc®
Manufacturer	Allergan Inc. (USA)	Ipsen (UK)	Merz Pharmaceuticals (Germany)	Solstice Neurosciences (USA)
Units/vial	100	500	100	2500, 5000 or 10,000
Constituents and excipients	Haemaglutinin, human albumin, saccharose, sodium chloride	Haemaglutinin, human albumin, 20% solution lactose	Human albumin, saccharose	Haemaglutinin, human albumin solution, 0.05% sodium chloride, sodium succinate
pH	7.4	7.4	7.4	5.6
Preparation	Vacuum dried	Lyophilised	Lyophilised	Solution

2 Definition of Cerebral Palsy (CP)

The internationally agreed definition of CP, devised in 2005, is as follows:

> "A group of permanent disorders of development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing foetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour, by epilepsy and by secondary musculoskeletal problems" [21].

CP is an umbrella term covering a wide range of cerebral disorders, with the common finding of a motor disorder, originating from early childhood [22] (Fig. 1). Although the brain insult is static, the effects of the neurological involvement are dynamic and change with time and growth of the child [22, 23] (Fig. 2). CP can be defined as a "static encephalopathy, with progressive musculoskeletal pathology" [23, 24]. The progression of dynamic contracture to fixed contracture is a fundamental issue underpinning effective use of BoNT-A [22, 23] (Figs. 1 and 2). The mechanisms by which the CNS lesions are expressed as a movement disorder are complex, as are the mechanisms underlying progression to fixed musculoskeletal deformity [19, 25]. The majority of muscles in children with CP have a combination of muscle overactivity (dynamic contracture) with some element of fixed shortening. Muscle deformity may be related more to impaired muscle growth and altered adaptation than to spasticity [25]. However, at this time we have interventions that address muscle over-activity (BoNT-A) and interventions for fixed contracture, which include muscle–tendon lengthening, hence the simplified scheme illustrated in Fig. 2. For a fuller discussion please see the hypotheses discussed by Gough and Shortland and the review of muscle morphology in CP by Barrett and Lichtwark [25, 26].

3 Classification of CP

3.1 Topographical Distribution

The most common types of CP are hemiplegia (one side of the body is affected), diplegia (both lower limbs are affected with fine motor problems restricted to the upper limbs) and quadriplegia, in which all four limbs are affected [19]. Topographical classification is useful because it identifies the limb segments in which there may be hypertonia requiring intervention. It is not very reliable and precise classification is not always possible. This has led colleagues in Europe to simplify the topographical distribution into 'unilateral' and 'bilateral' [27].

3.2 Gross Motor Function

The Gross Motor Function Classification System (GMFCS) is a five-level ordinal grading system based on the assessment of self-initiated movement with emphasis on function during sitting, standing and walking [28]. It has been shown to be valid, reliable, stable and a clinically relevant method for the classification and prediction of motor function in children with CP, between the ages of 2 and 18 years. GMFCS is important when using BoNT-A therapy because the indications and adverse event profile are different according to GMFCS level [19].

3.3 Movement Disorder

Much work has been done in recent years to standardise the definitions of movement disorders and the reader is referred to these monographs for further information [29, 30]. The majority of children with CP develop hypertonia, as one feature of spasticity [19, 30]. *Spastic CP* is the most common type of movement disorder, accounting for approximately 60–85% of all CP in developed countries [27, 31]. A widely used definition of spasticity is "a velocity-dependent resistance to passive movement of a joint and its associated

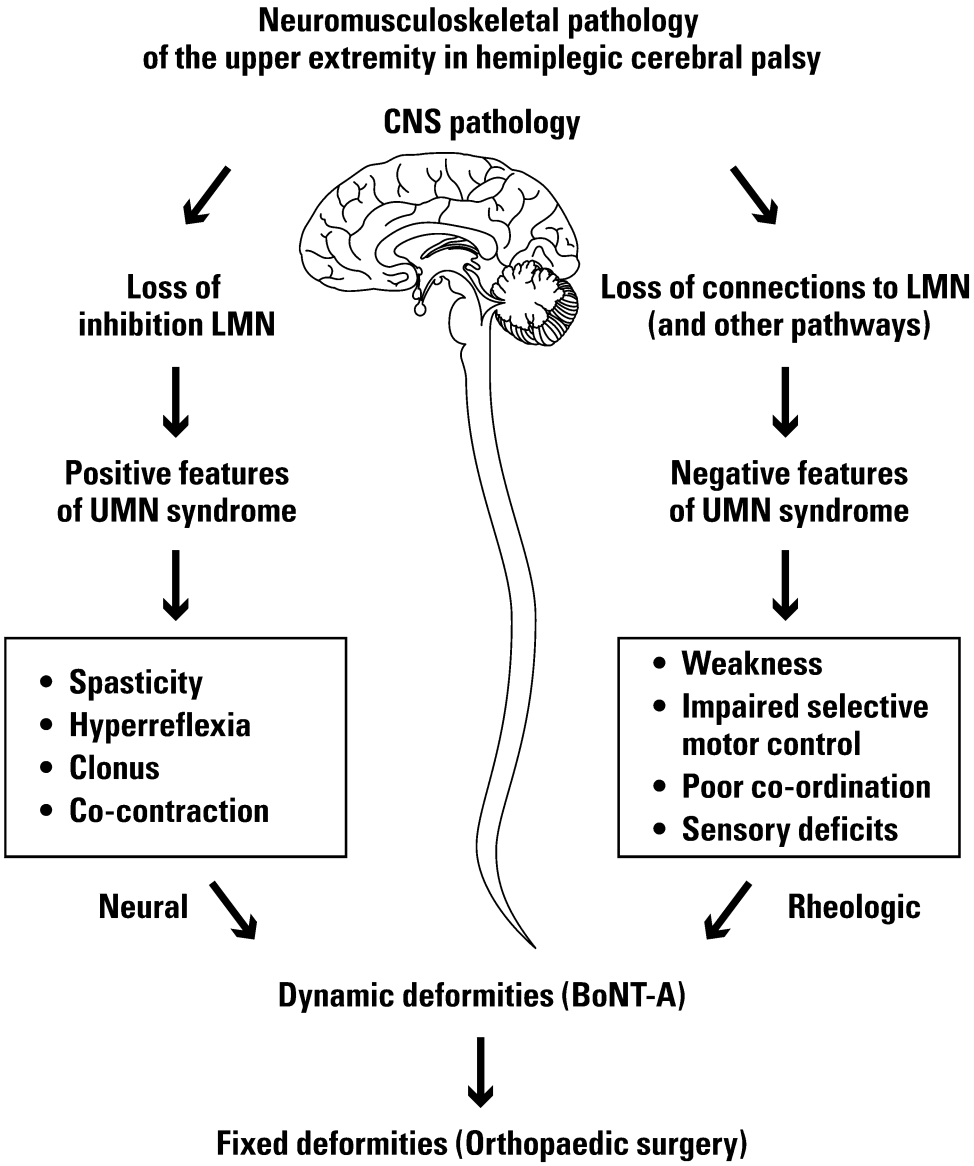

Fig. 1 Schematic of the interaction between the positive and negative features of the upper motor neuron (UMN) syndrome, leading to spasticity with dynamic contractures and fixed muscle–tendon contractures. Dynamic or flexible contractures are often treated by injection of botulinum toxin type A (BoNT-A). Fixed contractures are usually treated by orthopaedic surgery. *LMN* lower motor neuron

musculature". Historically, the term encompassed many of the components of the whole upper motor neuron (UMN) syndrome [29, 30, 32]. Spasticity, along with other features of the UMN syndrome, leads to a loss of the ability of a muscle to stretch in a relaxed state, which may in turn impair longitudinal growth of the muscle [33]. *Dyskinetic CP* affects between 10 and 25% of children and is characterised by involuntary movements, fluctuating muscle tone and inability to execute and co-ordinate simple tasks with accuracy. Dyskinetic movement disorders may be athetoid, dystonic or choreiform [30]. *Ataxic CP* is relatively uncommon, accounting for < 5% of children with CP [19, 31].

3.4 International Classification of Functioning

The World Health Organisation's (WHO) International Classification of Functioning (ICF) describes health conditions in several domains, including body structure and function, activity and participation, modified by both environmental and personal factors as noted in Fig. 3 [34]. A number of tools exist to measure parameters in children with CP within ICF domains and new measurement tools are under development. Many of the traditional measures of body structure and function predate the development of ICF and clinicians and researchers are not always in agreement as to which measure belongs to which domain. Recent tools for measuring activities and participation have been designed for task appropriateness [22, 34].

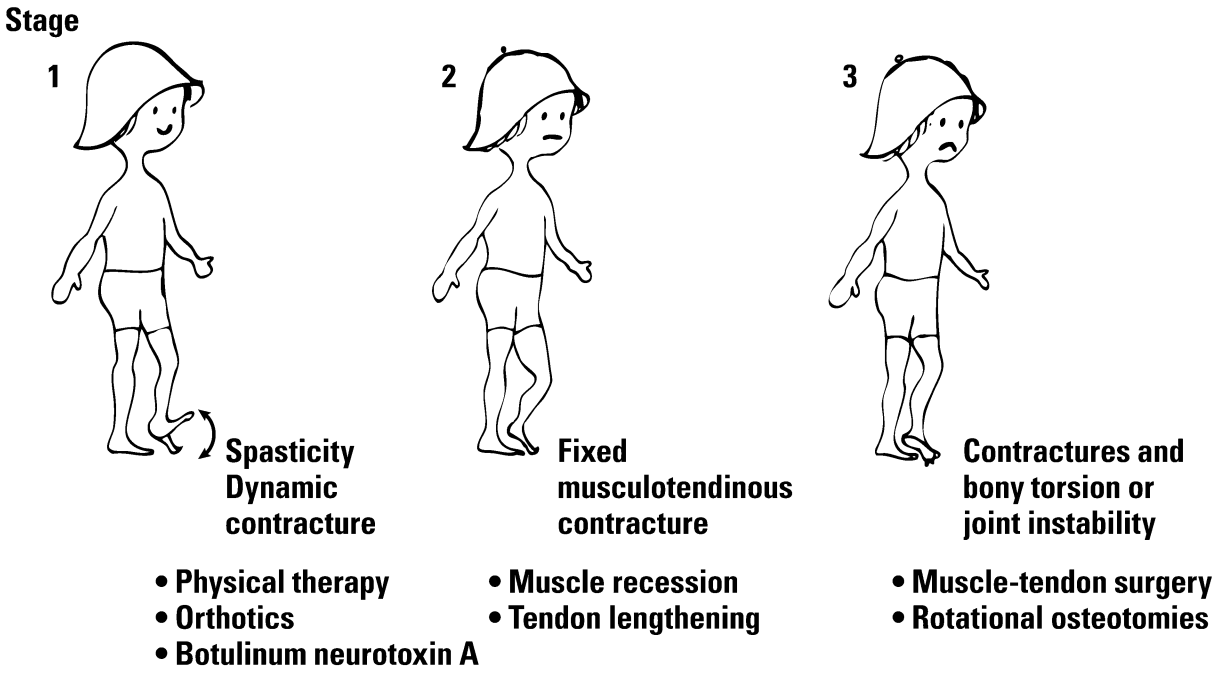

Fig. 2 Staging the musculoskeletal pathology in children with cerebral palsy. Younger children have spasticity which is dynamic and which reduces at rest and disappears under the relaxation of a general anaesthetic. This is the stage when injections of botulinum toxin type A (BoNT-A) or neurosurgical procedures such as selective dorsal rhizotomy (SDR) may be helpful. At Stage 2 and 3, the musculoskeletal pathology is fixed and correction requires orthopaedic surgery

3.5 Progressive Musculoskeletal Pathology

Children with CP do not have contractures, hip dislocation or spinal deformity at birth [22]. Fixed musculoskeletal pathology usually develops during childhood [19, 23, 24]. There are many statements in the literature linking contractures to spasticity, but the pathogenesis of muscle contracture is more complicated than the presence of spasticity [25, 26]. Frequent stretching of relaxed skeletal muscle is a prerequisite for normal muscle growth [23]. In children with CP, skeletal muscles are often hypertonic and do not readily relax. They are less frequently stretched due to reduced physical activity and because of antagonist co-contraction [19, 26]. The limb pathology can be considered in

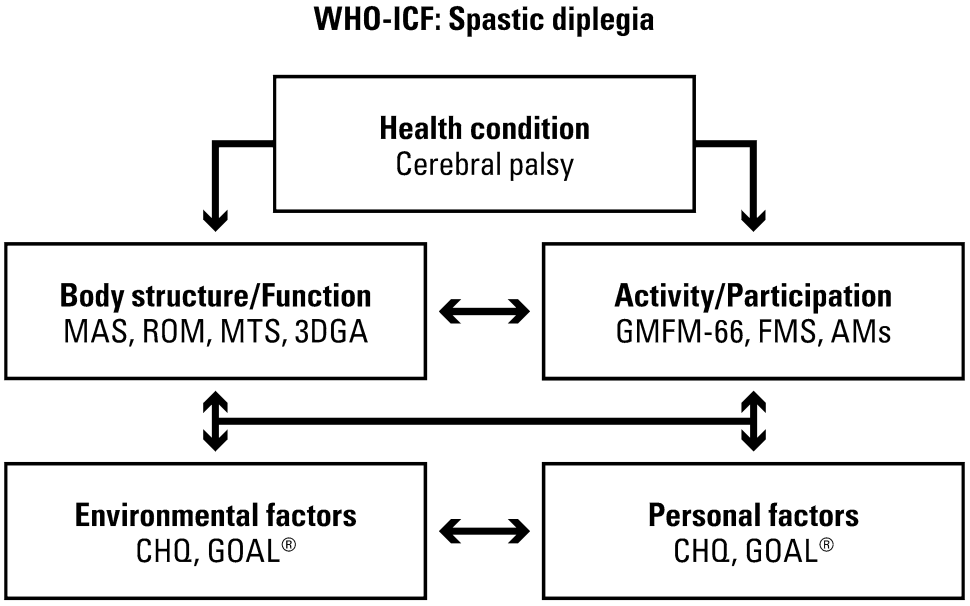

Fig. 3 Schematic of the World Health Organisation's (WHO) International Classification of Functioning (ICF) and potential outcome measures. *AM* activity monitor, *CHQ* Child Health Questionnaire, *FMS* Functional Mobility Scale, *GMFM66* Gross Motor Function Measure, *GOAL*® Gait Outcomes Assessment List, *MAS* Modified Ashworth Scale, *MTS* Modified Tardieu Scale, *ROM* range of motion (goniometry), *3DGA* 3-dimensional gait analysis

three stages for simplicity but, in reality, these stages overlap and are a complex continuum (Fig. 2).

4 Measurement Scales and Outcome Measures

4.1 Measurement of Spasticity: Modified Ashworth and Modified Tardieu Scales

The Modified Ashworth Scale (MAS) is the most widely used scale to measure spasticity in the child with CP, despite problems with validity and reliability [35, 36]. It is necessary to consider both its utility and limitations in the clinic and in the understanding of outcome studies [19, 35, 36].

The Modified Tardieu Scale (MTS) grades the quality of muscle reaction to passive stretch and measures the dynamic component of muscle spasticity. To measure the dynamic component, the joint is moved as fast as possible through its full range of movement. The angle when the muscles first 'catch', that is, when the stretch reflex is activated, is measured as R1. The angle of full passive range of motion (ROM) is R2. The difference between these angles (R2–R1) reflects the potential ROM available to the child if spasticity could be eliminated (dynamic component).

The MTS is considered to be a substantial improvement and of greater utility than the MAS [37, 38]. Nevertheless, both MAS and MTS have limitations, in the domains of both validity and reliability [35–38]. For this reason, several research groups have pursued efforts to measure spasticity and joint ROM objectively, using biomechanical approaches [39, 40].

Ordinal scales such as MAS are prone to bias. In our first double-blind, randomised, placebo-controlled trial (RCT) of the use of BoNT-A in the upper limb of children with hemiplegia, we included a question to physiotherapists and the parents of children enrolled in the trial. We asked, "Do you think your child was injected with Botox or placebo?" [9]. The majority of therapists and parents correctly identified whether their child had been injected with active drug or placebo, despite careful measures to ensure that injections were administered in a double-blind fashion. This experience was repeated in a second RCT investigating the potential role of BoNT-A injection as an analgesic agent, with the same result [41]. Therefore, although many clinical trials are described as single-blind or double-blind, both clinicians and parents (who frequently complete questionnaires) are able to determine from examination and observation of their child as to whether the child has been injected with the active drug or placebo. This renders blinding ineffective and also means that the risk of bias and a placebo effect, when using MAS, pain scales or quality-of-life (QoL) measures, is high [11, 41].

4.2 Passive Range of Motion by Goniometry

Measurement of joint ROM is a widely used proxy measure for muscle tendon length. Joint ROM using a goniometer is used in clinical practice and outcomes research in the use of BoNT-A [42]. Accuracy and reliability are improved by training and by two clinicians working together, one to stabilise the joint and the second to apply the goniometer to recognised anatomical landmarks and read the appropriate angle. Reliability of goniometric measurements can be improved by standardising the applied force and by using digital photography of anatomic landmarks as described by Hastings-Ison et al. [43].

4.3 Canadian Occupational Performance Measure and Goal Attainment Scales

Injections of BoNT-A are used to achieve functional goals that are meaningful to children with CP and their parents. For these reasons various forms of Goal Attainment Scaling (GAS) as well as the Canadian Occupational Performance Measure (COPM) have been used in an effort to add a patient-reported outcome measure (PROM) to MAS and MTS [44]. The COPM is an individualised measure designed to detect change in occupational performance over time [44]. GAS is also used as an individualised outcome measure, especially for attributes where no standardised measure exists [45]. Ideally, the COPM is used first to identify functional goals for the GAS. Between three and five goals for intervention are selected and scaled by applying a numerical score. Both COPM and GAS are subjective, but they give a voice to the child and parent or carer. However, given the *subjective* nature of these scales, they should be combined with *objective* outcome measures. Without the combination of subjective and objective outcome measures, interpretation of change is more difficult.

4.4 Gait Assessment for Ambulant Children

The most common indication for the use of BoNT-A therapy for children with cerebral palsy is to improve walking [1–6]. In younger children, the most common gait abnormalities are toe-walking, secondary to spastic equinus [19]. In older children, flexed knee gait (crouch) and stiffness around the knee are the most commonly reported gait problems [46, 47]. The gold standard assessment is 3-Dimensional Gait Analysis (3DGA), which provides accurate, valid and reliable information regarding a child's gait pattern [19]. It is capable of identifying both gait deviations and the response to BoNT-A therapy [19, 48]. However, 3DGA has limited availability and is not easy to use in children under the age of 3–4 years or below one meter in height. Given that BoNT-A

therapy is frequently used in children from age 2–4 years, alternatives to 3-DGA are needed [1, 2].

A number of scales to rate gait in children with CP have been devised, commencing with the Physician Rating Scale (PRS) by Koman et al. in 1994 [49]. However, we found the PRS to have poor reliability, necessitating modifications in clinical trials [50]. Since then, the Observational Gait Scale (OGS) and the Edinburgh Visual Gait Scale (EVGS) have been widely use and reported in the literature [51–53]. Observational scales are best conducted using good quality 2-dimensional video recording with the option for archiving data and video replay with slow-motion capability [51–53]. The EVGS is currently the best available observational tool for gait assessment when 3-dimensional gait analysis is not available [53]. All observational gait scales are limited in sensitivity to detect small changes following injection of BoNT-A and have limitations in both reliability and validity. Recent studies were able to detect change in EVGS following BoNT-A therapy but failed to confirm clinically significant improvements [52].

Three-dimensional gait analysis provides objective, valid and reliable documentation of gait in children with CP [19, 45]. Earlier studies utilised isolated kinematic measures at the ankle and knee and were able to detect improvements following injection of BoNT-A [54]. More recently, dynamic electromyography, kinetics and summary statistics of gait such as the Gait Profile Score (GPS) have also been reported [55, 56]. A combination of kinematic parameters and a summary statistic of overall gait pattern (GPS) are recommended as the highest level for objective documentation of changes in gait in children with CP [55, 56].

4.5 Gross Motor Function

The gold standard for the measurement of Gross Motor Function is the Gross Motor Function Measure (GMFM), which has been shown to be valid, reliable and responsive to clinically meaningful change [57]. The GMFM requires approximately 1 h to perform and is conducted by experienced, trained physiotherapists. In children who can walk, dimensions D and E are most relevant. When GMFM is used as the primary outcome measure in trials of BoNT-A therapy, the outcomes have been mixed [58, 59].

GMFCS is valid (based on GMFM), reliable and stable in children with cerebral palsy [60]. It is the definitive tool to *classify* a child's current function and to predict future function [60]. It was not intended to be used as an *outcome measure* and it does not have the psychometric properties to be used as such [19].

4.6 Outcome Measures for Non-Ambulant Children

BoNT-A therapy in non-ambulant children with CP has been less well studied and BoNT-A is less suitable in non-ambulant children than in ambulant children. Children at GMFCS Level IV and V generally have a mixed movement disorder with generalised hypertonia, which is often severe and affects all four limbs as well as the trunk [19, 22]. MAS, MTS, goniometry and radiology can be combined to assess issues related to hypertonia in the ICF domains of body structure [22, 34]. Many non-ambulant children have complex medical comorbidities [19, 22]. Injecting multiple muscle groups on a recurrent basis poses a risk of serious adverse events including severe respiratory events and mortality [61]. For the majority of non-ambulant children, generalised tone management may require oral medications or a neurosurgical procedure such as insertion of an intrathecal baclofen pump (ITB) [62]. In children at GMFCS IV and V, the musculoskeletal pathology becomes fixed with a very high prevalence of muscle tendon contractures, joint contractures, hip dislocation and spinal deformity [19, 24]. BoNT-A is not ideal as standard therapy for hypertonia in the non-ambulant child because only a few of the many hypertonic muscles can be treated due to limitations in total BoNT-A dose [1–6]. The most useful outcome measures at GMFCS IV and V may not be measures of body structure and function, in isolation. Health status, health-related quality of life (HRQoL) and caregiver burden can be reliably ascertained using the CPCHILD© questionnaire [63].

4.7 Outcome Measures for the Upper Limb

Upper-limb function is more complex than gait function and is impacted to a greater degree by impairments of sensation, proprioception and selective motor control [22]. The equivalent classification system to the GMFCS for classification of gross motor function in the upper limb is the Manual Ability Classification System (MACS) [64]. More complex classification systems that can also be used as outcome measures include the House classification [65]. Generic measures of hypertonia and spasticity such as the MAS and MTS are widely used in the upper limb in children with CP [35–37]. The COPM and GAS are also applicable as they can be individualised to the child and family goals and are not specific to lower-limb function [44, 48]. Specific outcome measures with good to excellent psychometric properties for the upper limb in children with CP include the ABILHANDS-Kids, the Assisting Hand Assessment (AHA), the Melbourne Assessment of Unilateral Upper Limb Function (MUUL) and the Shriners Hospitals for Children Upper Extremity Evaluation (SHUEE). Upper-limb outcome measures have been reviewed in detail elsewhere [66, 67].

5 Interventions for Spasticity and Dystonia

The choice of interventions for the management of the movement disorders associated with CP in children is extensive [19]. It can be difficult at first sight to determine on what criteria the choice should be made between the many options. Some have observed that the choice is determined "more by luck than judgement" [68]. Oral medications are increasingly used as first-line management for spasticity and dystonia in children with CP. Medications include baclofen, diazepam, tizanidine and less commonly dantrolene [69, 70]. Artane and L-dopa are being trialled in dystonia [70]. Most oral medications are limited by a combination of limited benefit and a high prevalence of side effects [19, 69, 71]. Medications for both spasticity and dystonia management have been reviewed extensively elsewhere and will not be considered further here [69–72]. Some studies have examined the benefits of using a background of oral spasticity management using either tizanidine or baclofen, combined with focal neurolytic injections of hypertonic muscles with BoNT-A [73, 74]. Others have investigated combining injections of BoNT-A and phenol [75].

Neurosurgical procedures for hypertonia include selective dorsal rhizotomy (SDR) for spasticity, the insertion of an ITB or insertion of electrodes for deep brain stimulation (DBS) for various forms of hypertonia [19, 76, 77].

Chemo-denervation by the injection of neurolytic agents has a long history in the management of focal and regional spasticity. Neurolysis by injection of phenol and alcohol was widely used before the introduction of BoNT-A [75, 78, 79].

6 Pharmacology and Mechanism of Action of Botulinum Neurotoxins (BoNT)

Botulinum neurotoxins (BoNT) are large proteins of approximately 150 kilodaltons (kDa) that are produced by bacteria from the *Clostridia Botulinum* family. The effects of BoNT at the molecular level are so precise that BoNT has been described as a "marvel of protein design" and a "molecular nano-machine" [80]. BoNT consists of an N-terminal light chain (LC, 50 kDa), which is a metalloprotease, connected to a C-terminal heavy chain (HC, 100 kDa) [18]. The heavy chain consists of two principal domains, the N terminal portion, which is the translocation domain that is involved in the release of the light chain into the cytosol of the motor neuron, and the C-terminal part that is the receptor binding domain, critical for the binding and endocytosis of BoNT-A into the presynaptic neuron [18].

Although there are seven major serotypes of BoNT (BoNT-A to BoNT-G), there are more than 40 BoNT subtypes including several hybrid or mosaic types, and new variations continue to be identified using immunological techniques [18].

BoNT primarily acts to inhibit the release of acetylcholine from the presynaptic terminal. The regulation of fusion of the synaptic vesicle with the plasma membrane involves a complex of proteins collectively referred to as SNAREs (Soluble-N Ethylmaleimide, Sensitive Factor Attachment Protein Receptor) or SNAP receptors. The principle SNARE proteins include VAMP/synaptobrevin, the pre-synaptic plasma membrane protein, syntaxin, and the synaptosomal protein, SNAP25. BoNT interferes with normal vesicle-membrane fusion by a multi-step process, illustrated in Fig. 4. The overall effect can be described as a neuro-paralysis or chemical denervation of muscle [80–82]. BoNT does not cross the blood–brain barrier and although retrograde transfer to the CNS from peripheral injection sites occurs to a limited degree, there is little evidence for direct central effects. The explanation for central effects is that peripheral chemo-denervation may lead to central reorganisation as a result of neuroplasticity [18].

7 BoNT in CP

Of the seven major BoNT serotypes, only types A and B have been used in children with CP. BoNT type B (BoNT-B) has a shorter duration of action than BoNT-A and a less satisfactory adverse event profile in children with CP [82].

The only indication for BoNT-B is resistance to BoNT-A caused by the presence of neutralising antibodies. The vast majority of clinical studies in children with CP have been with the various preparations of BoNT-A, principally onabotulinum toxin A (Botox®) and abobotulinum toxin A (Dysport®) [1–5]. Injection of BoNT-A produces a dose-dependent, partially reversible chemo-denervation of injected muscle by blocking pre-synaptic release of acetylcholine at the neuromuscular junction [18, 80, 81]. Because of rapid and high-affinity binding to receptors at the neuromuscular junction of the target muscle, little systemic spread of toxin occurs. However, it is important to note that some systemic spread occurs following every injection and this can be detected at remote sites by specialised techniques [18]. The diffusion of BoNT-A may be altered by alterations in muscle morphology such as reduced muscle volume and increased connective tissue [7, 25, 26].

Neurotransmission is restored initially by the sprouting of new nerve endings, but these are eliminated after about 3 months when the original nerve endings regain their ability to release acetylcholine [83]. Muscle strength is reduced because of acute muscle atrophy with the secondary effect of a reduction in muscle spasticity [7]. The clinical effects last from 3 to 6 months. Some biomechanical and imaging studies have shown effects lasting for > 12 months after a single

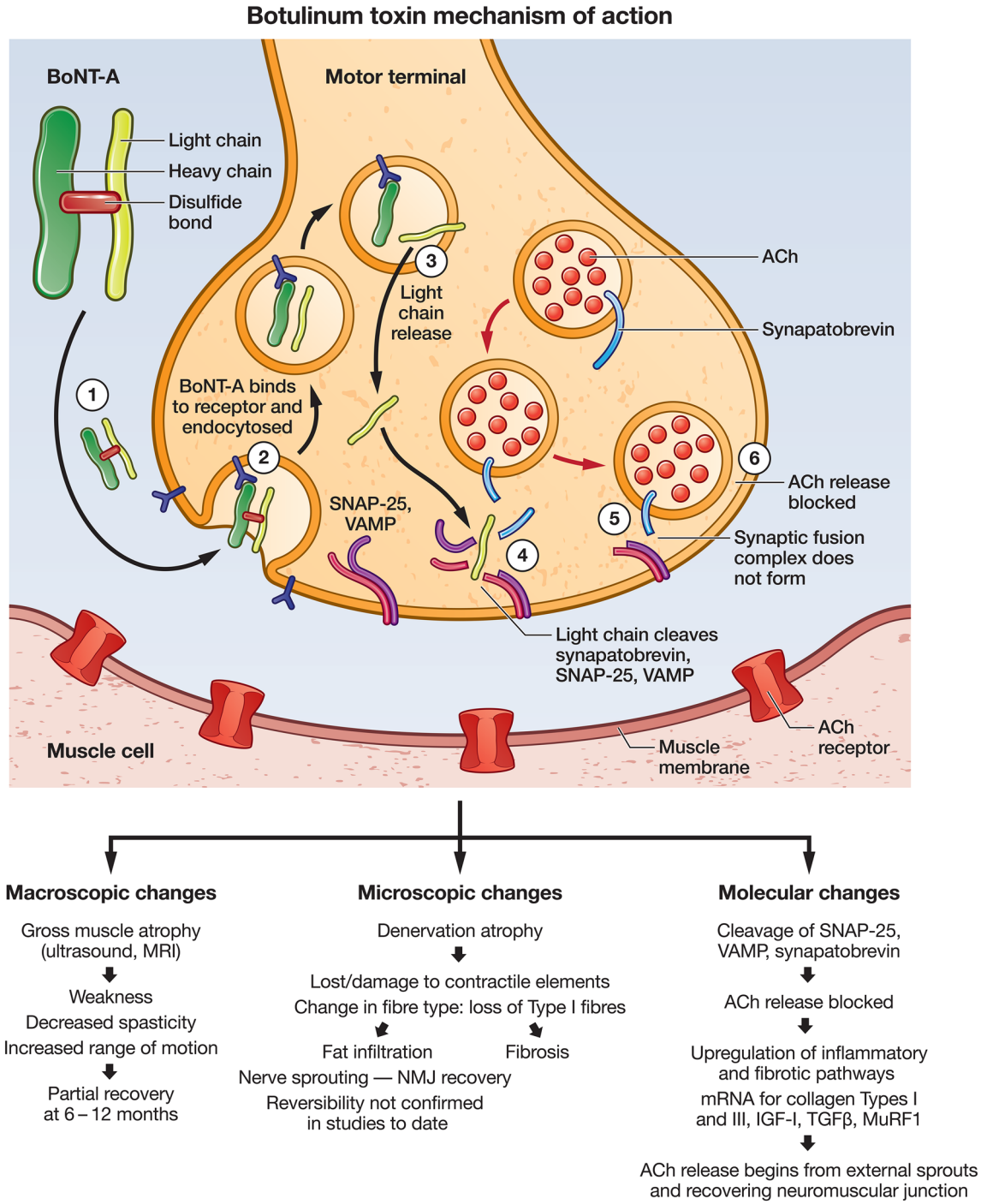

Fig. 4 Botulinum toxin type A (BoNT-A) mechanism of action. The BoNT-A heavy chain is shown in green and the light chain in yellow, linked by a disulphide bond. Acetylcholine (Ach), the neurotransmitter which is blocked by BoNT-A, is shown as red dots within a cellular vesicle in the nerve terminal. The effects of chemodenervation by injection of BoNT-A are summarised at macroscopic, microscopic and molecular levels. *SNAP 25* soluble *N*-ethylmaleimide fusion protein, attachment protein, *VAMP* vesicle associated membrane protein

injection of BoNT-A [84, 85]. The duration of action therefore should be considered not just in clinical terms but also in terms of muscle biomechanics and the effects on skeletal muscle at the macroscopic, microscopic and molecular levels [7]. It is particularly concerning that the adverse effects such as muscle atrophy last longer than the clinical effects, such as muscular relaxation [7, 84].

The predictable movement patterns and postures that are characteristic of spasticity enable a systematic rationale to be developed to identify the role of BoNT-A to manage muscle

overactivity [1–6]. The management of dystonia with BoNT-A is more complex and spasticity and dystonia frequently occur in combination as in mixed movement disorders [19, 22, 30]. Although the principle of BoNT-A therapy in children with CP is remarkably simple, the application is challenging in the presence of complex changing movement disorders and the insidious development of fixed contractures [22] (Fig. 5).

7.1 BoNT in the Ambulant Child with Equinus

The most common dynamic deformity in children with CP is equinus, which affects between 60 and 80% of children in early childhood [1, 2, 19]. Injection of the gastrocnemius or the gastrosoleus is the most common indication for BoNT-A therapy in children with CP [1–6]. This is for two main reasons. Injection of the gastrosoleus is moderately effective in the younger child with dynamic equinus and the alternative, muscle–tendon lengthening surgery, is unpredictable and frequently harmful [86]. However, the reverse is true as the child becomes older. The response to BoNT-A is barely detectable and surgical lengthening of the gastrocsoleus is effective and reliable [87, 88].

To assess the evidence for the use of BoNT-A in equinus, we reviewed numerous publications, which were mainly cohort studies, in combination with the higher quality studies previously reviewed in systematic reviews and evidence statements [6, 82]. The majority of studies were cohort studies, and more were described as prospective then retrospective. However, the majority were uncontrolled, which has little impact on the evidence for change in scales in the domain of body structure such as MAS or MTS. The lack of controls undermine many claims for improvements or changes in gross motor function. The majority of studies reported had a single injection cycle and the mean follow-up was usually about 6 months.

In terms of outcome tools, the most frequent were MAS and MTS, which were used in about three quarters of studies, followed by ankle ROM in about half of the studies. Observational gait scales (PRS, OGS, EVGS) were used with or without video in about a third of studies and some form of instrumented gait analysis was used in almost half of the studies, but the equipment used and the reliability were poorly described.

When MAS or MTS was the primary outcome measure, the majority reported a statistically significant improvement, that is, a reduction in spasticity. The majority of studies utilising observational gait scales reported an improvement, as did those utilising instrumented gait analysis [6, 82]. The majority of studies that reported GMFM reported improved gross motor function, but the majority of these studies were uncontrolled, making gains in GMFM as the result of natural history difficult to disentangle from gains as a result of injection of BoNT-A [22]. There was a trend for better study designs to report smaller or no improvements in GMFM [58]. Of concern was the observation that change in GMFCS was reported as an outcome measure in a number of studies.

Study designs were variable, the numbers of participants were generally small and mean follow up was short. Outcome measures were often poorly described and reliability was not reported. Some measures were used incorrectly (e.g. GMFCS). The majority of studies reported outcomes in the ICF domain of body structure, fewer reported valid measures of function and very few reported outcomes in the domains of activities and participation [34].

It was concluded that there is strong evidence for a reduction in spasticity in the plantar flexors of the ankle after injection of BoNT-A; there was moderate evidence for small improvements in gait with the caveat that observational gait

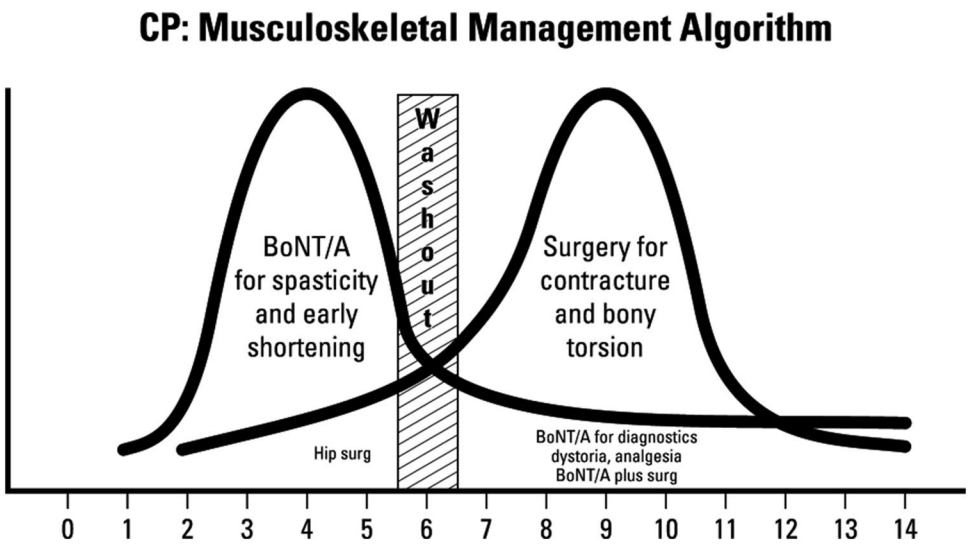

Fig. 5 Algorithm as to the timing of the use of botulinum toxin type A (BoNT-A) and orthopaedic surgery for ambulant children with cerebral palsy (CP). The peak age for the use of BoNT-A is between 2 and 6 years. The peak age for the use of orthopaedic surgery is between 6 and 12 years. It is desirable to have a 'washout' period with no injections when the response of the target muscle is limited

scales have limitations [51, 52, 89]. There was weak evidence for improvements in gross motor function, related to lack of controls and incorrect use of GMFCS [6, 82].

7.1.1 Systematic Reviews and Evidence Summaries

There are several good quality RCTs investigating the outcome of injection of BoNT-A for equinus with positive results utilising objective outcome measures such as 3-DGA as well lower quality outcome measures such as PRS, OGS, EVGS, MTS and MAS. These studies have been reviewed and graded by Simpson et al. and more recently, by Love et al. [6, 82].

It is important to note that the higher the quality of the study design and the more objective the outcome measure in terms of validity and reliability, the smaller and less predictable the response to BoNT-A therapy is reported. Even with 3-DGA, earlier studies focused on outcome measures of interest such as the range of equinus in stance and swing phases of gait [50, 54]. When newer, more global measures of gait function such as the GPS have been utilised, improvements in overall gait function have been noted to be much smaller, or absent [56].

One of the reasons for the paradox is that injection of BoNT-A to the gastrosoleus in children with spastic diplegia (bilateral CP) is in the context of generalised spasticity affecting proximal muscle groups including the hamstrings and iliopsoas [19]. Improvements in ankle dorsiflexion may be offset by deterioration in knee extension or hip extension, resulting in the paradox of improvement at the ankle level with deterioration at proximal levels [56]. Most clinicians are aware that in the long term, crouch gait (increased hip and knee flexion) is a more insidious and intractable gait disorder than equinus, which is easy to correct surgically, when a child is older, as a definitive procedure with a low rate of recurrence [87].

Most studies have shown that the improvements following BoNT-A therapy in children for spastic equinus are small and short-lived. In addition, children become unresponsive to injection of BoNT-A at a younger age than previously thought [52, 56]. Most clinically significant improvements are seen under the age of 4 years for equinus in spastic hemiplegia [6]. The response reduces between the ages of 4 and 6 years, and after the age of 6 years recent studies including both EVGS and 3DGA confirm little or no benefit from continued use of BoNT-A therapy [52, 56].

7.1.2 Dose and Frequency of Administration

Doses and dilutions of BoNT-A for the management of equinus depend on the preparation used and have been published and discussed extensively elsewhere [1–6]. There is one comprehensive *dose ranging study* for spastic equinus which clearly shows a dose response curve [90]. There are two RCTs that investigated and reported *frequency of injection* for spastic equinus. Both studies compare an injection schedule of three times per year (every 4 months) to once per year. Both studies reported that the once-per-year injection schedule was as effective with fewer adverse events than three times per year [91, 92]. Despite this Level I evidence, many clinicians inject at more frequent intervals. The once-per-year schedule is also aligned to experimental work in small mammal models, in which more frequent injections were reported to cause cumulative harm in terms of muscle atrophy, weakness and loss of contractile elements and fibrosis [7, 93, 94].

7.1.3 Muscle Targeting

Identification of the target muscle has traditionally been based on anatomical landmarks and palpation [1, 2]. The accuracy of injection based on palpation is poor except for the gastrocsoleus [95]. Electromyography, electrical stimulation and real-time ultrasound have improved the accuracy of injection of target muscles in children with CP [13, 95]. It has been more difficult to determine if improved accuracy of injection has improved clinical outcomes. Extensive literature and atlases now exist to enhance the understanding of 3-dimensional topographical anatomy based on real-time, high-quality ultrasound. The use of ultrasound is strongly recommended and requires specific training and equipment [13].

7.1.4 Conclusions

In younger children with no fixed contracture, injection of BoNT-A for equinus increases the dynamic length of the gastrocsoleus and results in improvements in selected gait parameters [96]. There is also evidence that appropriate use of BoNT-A in younger children may delay the onset of fixed equinus to a small but important degree, permitting later utilisation of orthopaedic surgery at optimum age [19, 56]. In general, this means a more predictable outcome for surgical treatment for equinus and less need for repeat surgery [87, 88]. However, almost 100% of children who need injections of BoNT-A for spastic equinus will also need surgical lengthening of the gastrocsoleus.

The optimism regarding prevention of contractures generated by the spastic mouse study has never been translated to the clinical situation [33]. In fact, there is mounting evidence that injection of BoNT-A might cause loss of contractile elements and increased fibrosis, which might lead to increases in contracture [7, 93, 94]; hence the need for constant dialogue between clinicians in the multidisciplinary team who practice both non-operative and operative management for children with CP [6]. Short-term gains in

achieving 'foot-flat' might be offset by longer-term harm to a muscle complex, which is a key to long-term gait function and independence [7, 17, 22–24]. Hence the urgent need for long-term studies, over multiple injection cycles (Fig. 6).

7.2 Injection of Proximal Muscles in the Lower Limb

The indications, techniques and outcomes for injecting the hamstrings and adductor muscles were first described by Cosgrove et al., Corry et al. and subsequently by others [97, 98]. Muscle hyper-activity in the hamstring and adductor muscles is more prevalent in the more severely involved child with bilateral involvement. This may result in scissoring postures and flexed, stiff-knee gait. Injection of the hamstrings can be combined with injection of the gastrocnemius in high-functioning children with diplegia [96, 97]. Most experienced clinicians consider that injection of up to four large muscle groups at a single session may be appropriate and is generally safe, if dose limitations and appropriate techniques are used [3–6]. Injection of more than four large muscle groups increases the risk of systemic spread, and local and systemic adverse events [19, 61].

7.3 Multi-Level Lower-Limb Injections

Molenaers et al. in Leuven, Belgium have pioneered integrated, multilevel BoNT-A spasticity management in the child with CP similar to the concept of single-event multilevel surgery [45, 99]. Gait deviations are identified using 3DGA, muscle overactivity is identified using a combination of 3DGA, electromyography and instrumented measures for spasticity. A tailored programme is then developed for each child consisting of targeted injections to the spastic muscles, serial casting, orthoses for daytime use, night splinting and intensive post-injection physiotherapy.

The Leuven Group has reported improvements in gait and function in several studies, of a degree and level that have rarely been matched in other centres [45, 56, 99]. Perhaps the integration of all of the components of their approach is required for optimum outcome [45]. However, the combination of so many medical, physical and therapy components to the programme makes it very difficult to isolate the contribution of each of the components to the overall outcome [45].

In contrast to the Leuven philosophy, Bakheit argues that BoNT-A injections can be effective as a stand-alone intervention when ancillary management is not available [100]. The evidence base for or against ancillary interventions is weak because it is very difficult to isolate component parts of the multimodal intervention strategy and subject them to adequately powered RCTs.

7.4 BoNT in the Non-Ambulant Child

Hip displacement may affect up to 90% of children at GMFCS Level V [19]. In the past, spastic adduction was considered to be the primary cause of hip displacement and the management of adductor spasticity and contracture received much attention [19]. It is now known that hip displacement in the non-ambulant child is much more related to limited function in hip abductors than spasticity in the hip adductors.

Graham et al. conducted a 3-year RCT investigating the outcomes of 6-monthly BoNT-A injections of the adductors

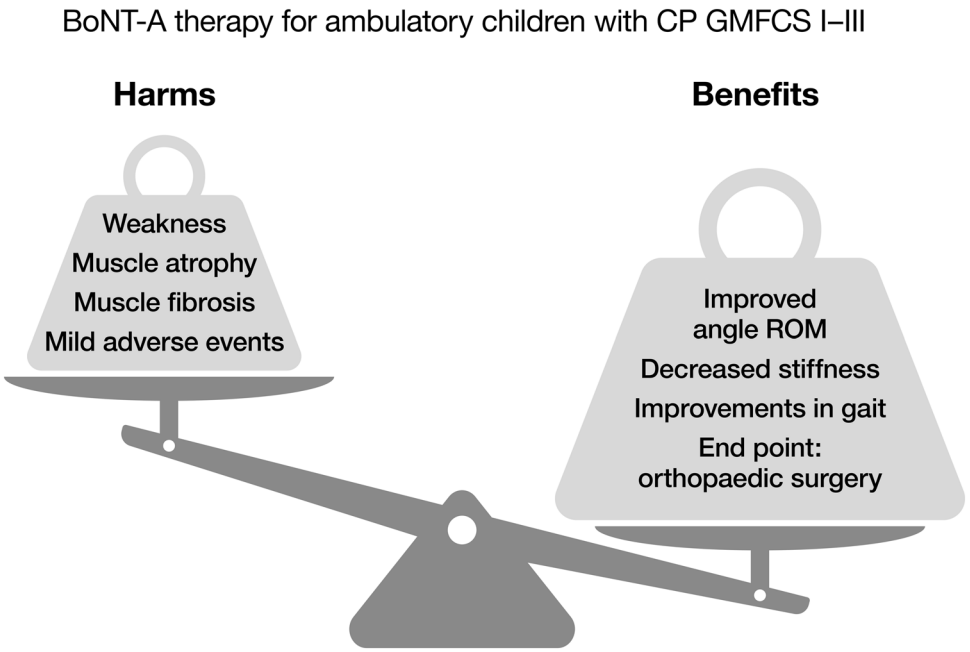

Fig. 6 Risk versus benefit for injection of botulinum toxin type A (BoNT-A) in the ambulant child with cerebral palsy (CP). The benefits (decreased spasticity, increased range of motion and improvements in gait *may* outweigh the harms (weakness, muscle atrophy and fibrosis). The understanding of risk to benefit may change with further studies, both clinical and in animal models. The endpoint is orthopaedic surgery for gait improvement. *GMFCS* Gross Motor Function Classification System

and hamstrings in children with CP, combined with a hip abduction brace. The outcomes of this study were negative. Gross motor function as determined by GMFM did not improve in the treatment group compared with the control group [101]. Hip displacement was not prevented and children in both groups required the same number of orthopaedic operations for hip displacement with the same outcomes in terms of hip morphology and pain at 10-year follow-up [102, 103].

Although smaller studies with short-term follow-up have suggested more optimistic outcomes, the weight of evidence suggests that gross motor function is not improved, and hip displacement and the need for orthopaedic surgery is not avoided by injection of the hip adductors in non-ambulant children with CP [101–103].

Copeland et al. reported the outcomes of an RCT of the use of BoNT-A in 41 non-ambulant children with CP for a range of heterogeneous indications, described as "care and comfort" [11]. They described the use of sham injections as controls and reported significant benefits in the COPM as the primary outcome measure. This trial was methodologically weak because blinding was not maintained with 77% of parents correctly identifying group allocation at 4 weeks after injection [11]. The combination of imperfect blinding and subjective outcome measures undermines the validity of the conclusions. Although there was no increase in serious adverse events in the treatment group compared with the control group, this may not be the case when BoNT-A is used in non-ambulant children in non-RCT conditions, when serious adverse events and deaths have been reported [61, 104]. In addition, those who advocate injections of BoNT-A in non-ambulant children rarely discuss an exit or termination strategy for the use of BoNT-A. In the ambulant child, the logical endpoint of BoNT-A therapy, for the majority of children, is orthopaedic surgery for fixed contracture [87, 88]. In the non-ambulant child, the endpoint is not clear and each injection cycle exposes the child to a greater risk of serious adverse events than is the case in the ambulant child [19, 104, 105] (Fig. 7). Hip adductor spasticity is more effectively treated by phenolisation of the obturator nerve than by injection of BoNT-A, especially when combined with adductor release surgery [78].

There is a small role for focal management of spastic-dystonia in the non-ambulant child for specific functional goals [11, 22]. In the upper limb, these include improvement of reach and grasp to facilitate control of a powered wheelchair. In the lower limb, a very useful indication is palliation of painful hip dislocation in a child who is too fragile to consider orthopaedic surgery [106]. However, prevention of hip displacement by hip surveillance and early surgery is clearly a better option.

7.4.1 Risks of BoNT in the Non-Ambulant Child

In non-ambulant children, global spasticity management using oral medications and when appropriate an intrathecal baclofen pump are both more effective and safer than injecting multiple muscles on a recurring basis with large doses of BoNT-A [76]. It is in the group of non-ambulant children with medical comorbidities that most of the fatalities have occurred after injection of BoNT-A leading the FDA in the United States to insist on a 'black box warning' for all botulinum toxin products [18]. Despite the limited benefits and poor evidence base, BoNT-A therapy continues to be widely

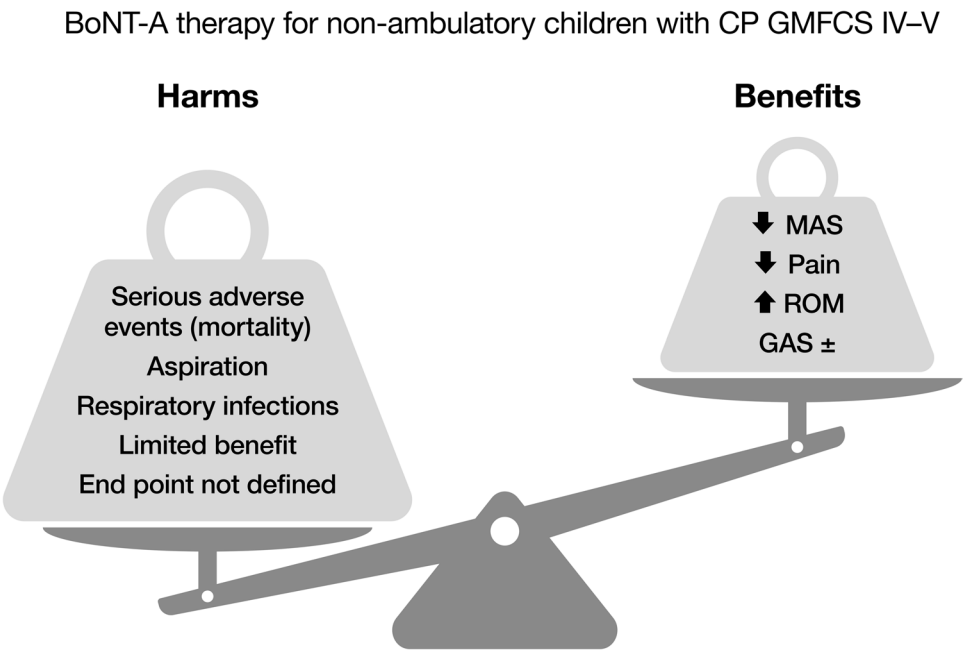

Fig. 7 Risk versus benefit for injection of botulinum toxin type A (BoNT-A) in the non-ambulant child with cerebral palsy (CP). The harms are the risk of serious/fatal adverse events and the benefits are modest. There may not be a defined endpoint and intermittent, lifelong injections are not an ideal proposition. *GMFCS* Gross Motor Function Classification System

used in non-ambulant children. In Australia, there have been four deaths in recent years attributed to the use of BoNT-A therapy in non-ambulant children with CP and the risk-to-benefit profile is poor [102, 107]. One exception may be the use of BoNT-A for pain relief, which is so prevalent in this population [106, 108].

7.5 Upper-Limb Injections: Impairments and Interventions

Upper-limb dysfunction is a common functional and cosmetic consequence of CP, particularly in children with hemiplegia [22]. A wide variety of management strategies have been adopted and the evidence base has been reviewed by Boyd et al. and more recently by Sakzewski et al. [109, 110].

Conventional therapeutic management of upper-limb hyperactivity in children with CP has involved the use of splinting and casting, and passive stretching, the facilitation of posture and movement, medication and sometimes orthopaedic or plastic surgery [109]. In a recent high-quality meta-analysis, Sakzewski et al. reported moderate to strong effects for BoNT-A and occupational therapy to improve outcomes compared with occupational therapy alone. Constraint-induced movement therapy achieved modest to strong treatment effects on improving movement quality and efficiency of the impaired upper limb compared with usual care [110].

Impairment of upper-limb function can impact on self-care abilities, activities of daily living, education, leisure activities and vocational outcomes (participation) [22]. Children may not be able to reach for objects, manipulate toys, feed themselves efficiently or use assistive communication devices [22, 109, 110]. A modest improvement in reaching function can be beneficial. Different muscles develop fixed contracture at different speeds. The pronator teres is invariably the first muscle in the hemiplegic upper limb to develop a contracture [22].

7.5.1 BoNT-A in the Upper Limb: Overview

The use of BoNT-A in the lower limb of children with CP is well established and RCTs have also been conducted in the upper limb, soon after the introduction of BoNT-A to clinical practice [9, 10]. The principal goal of treatment using BoNT-A in the upper limb of children with CP is to enhance function by allowing children to employ their treated arm and conduct daily activities more efficiently and effectively [9, 10, 22]. Additional aims are to decrease tone and increase ROM to prevent contracture and delay the need for surgery [9, 10, 22, 110, 111]. It is invariably the non-dominant arm that requires treatment, except in children with quadriplegia, when the dominant arm may benefit from intervention to improve grasp and release in activities such as steering a power wheelchair [111]. In the upper limb, it is even more important that BoNT-A therapy be goal-directed in the context of a multidisciplinary programme including splinting and occupational therapy [22, 110].

Additional problems in the upper limb will relate to a higher prevalence of dystonia, weakness, sensory impairment and impairment of selective motor control [19, 22]. These negative features may overshadow any benefit gained from BoNT-A injection and lead to more limited results of shorter duration [9]. The suitable candidate for BoNT-A therapy in the upper limb should be able to initiate active finger movements and activate and strengthen antagonist muscles to take advantage of temporary BoNT-A paresis of the agonists [10]. Children should have good grip strength because good grip strength may be reduced by BoNT-A injection [9, 10, 111]. Family-identified limitations, problems and goals should be analysed in great detail [112, 113].

In typical hemiplegic posturing, the most common target muscles are the biceps, brachialis, pronator teres, flexor carpi ulnaris, flexor carpi radialis and the adductor pollicis [22, 111]. Injection of the long finger flexors should be minimised to avoid weakening of grip strength [9, 10]. However, in non-ambulant children with severe spastic dystonia, and in some children with hemiplegia, if the aim is to improve palmar hygiene, injection of the long finger flexors is required in combination with serial casting [111]. The larger muscles are injected in one or two sites with the smaller muscles injected in a single site. Small-volume, high-concentration injections are advised, using ultrasound control, to avoid injection of unwanted muscles and diffusion into other muscle groups [112, 114].

7.5.2 BoNT-A in the Upper Limb: Evidence

Corry et al. conducted the first double-blind, placebo-controlled study involving multiple injections in the spastic upper extremity in children with CP [9]. As with many studies, a reduction in measures of spasticity were demonstrated but improvements in function were much more difficult to achieve [9]. Fehlings et al. conducted a single-blind, randomised study in 30 children with hemiplegia [10]. There were significant improvements in function in the BoNT-A group as measured by the Quality of Upper Extremities Skills Test (QUEST) at 1 month but the gains were not significant at longer term follow up.

Wallen et al. demonstrated that the dynamic joint ranges in the upper limb respond to BoNT-A injection and that there was a significant improvement in activities and participation at 3 and 6 months following injection [112]. Olesch et al. demonstrated the safety of repeated injections to the upper limb [113].

In 2005, Speth et al. reported a high-quality RCT investigating the addition of injections of BoNT-A, with intensive

therapy, to intensive therapy alone [114]. As in the first upper-limb RCT by Corry et al. in 1997, Speth et al. found a reduction in muscle overactivity, with some gains in ROM but very limited evidence for changes in function or participation [9, 114].

Objective evaluation of upper-limb function using a standardised, validated instrument is strongly recommended to document baseline function and also to assess changes following treatment. There are a variety of established instruments that can be used as outcome measures for upper-limb assessments, including QUEST, Melbourne Assessment of Unilateral Upper Limb Function (Melbourne Assessment) and the Assisting Hand Assessment (AHA). In studies utilising these valid, reliable and objective measures, sustained improvements in function have been difficult to identify [115]. As in the lower limb, the use of adjunctive interventions makes interpretation of treatment effects problematic [115]. As in the lower limb, children with upper-limb involvement should be considered for definitive orthopaedic surgery, when the response to injections of BoNT-A plateau, especially when fixed contractures progress and impair function [110]. In the first RCT in which injections of BoNT-A, tendon transfer surgery and usual therapy were compared, the surgical group had superior outcomes [116].

7.6 BoNT-A as an Analgesic Agent

The analgesic role of BoNT-A is complex and under continued evaluation both in animal models and in clinical trials [41, 117]. One of the most recent evidence-based reviews concluded that there was Level B evidence to support the use of BoNT-A in various neuralgias [117]. Musculoskeletal pain is a major clinical problem for many children with CP and appears to increase in the second decade and is very common in young adults [118]. Hypertonia amplifies pain and there is frequently a 'vicious cycle' of pain and spasm, in which pain provokes muscle spasm, which further increases pain [41]. The pain–spasm cycle may sometimes be broken by injection of BoNT-A.

In one small RCT, injection of BoNT-A reduced the requirements for opiates and resulted in a shorter hospital stay in children having adductor releases than in a control group [41]. However, in a recent, larger and higher quality trial, these findings were not replicated in children having bony reconstructive hip surgery [119]. This suggests that BoNT-A is more effective for painful spasms than for musculoskeletal pain [41, 119].

7.7 Adverse Events of BoNT-A

Injection of BoNT-A in ambulant children with cerebral palsy, who are physically well and have few medical comorbidities, is generally safe [1–6]. Minor adverse events including pain at the site of injection, weakness in the injected muscle or nearby muscles, falling, tripping, flu-like illness and short-term functional deterioration have all been reported, in studies ranging from small cohort studies and RCTs to evidence-based reviews [1–6, 9, 16, 82].

Systemic adverse events occur in ambulant children at a rate of between 1 and 5% [1–6]. Such events include transient incontinence of bowel, bladder or both [3, 6]. This is because cholinergic sphincter function is mediated by acetylcholine and therefore can be affected by systemic spread of BoNT-A [3]. The laryngeal and lower oesophageal sphincter are also controlled by smooth muscle with cholinergic innervation. The most serious adverse event, resulting in mortality, is paralysis of the pharyngeal or lower oesophageal sphincter, allowing aspiration of gastric contents into the respiratory tract with hypoxia, pneumonia, and in extreme cases, cardiac arrest and death [3].

Paradoxically, RCTs may not be the optimum source for determining the true prevalence of adverse events, especially serious adverse events. RCTs are conducted by experienced clinicians, with the dose, dilution and muscle targeting carefully prescribed and approved by an ethics committee. Patients enrolled in RCTs and prospective cohort studies are monitored closely and have frequent contact with clinicians [9, 16, 45, 96–98].

Adverse events in general clinical practice reflect the wider variety of techniques, dosing, dilution, targeting techniques and experience of clinicians in a wide range of practice settings [105, 120–122]. Naidu et al. conducted a retrospective study of a large number of injection episodes in children with CP, GMFCS I–V. They reported a strong association between serious adverse events requiring hospitalisation and GMFCS level [104]. They made a recommendation not to offer injections to non-ambulant children at GMFCS levels IV and V [104]. In a study with more robust methodology, using a prospective injection database, O'Flaherty et al. reported a similar prevalence of adverse events in non-ambulant children with CP in the month before injection as the month after injection [122]. In the O'Flaherty study, there were a limited number of experienced injectors, with high levels of training and experience [122].

7.7.1 Clinical Adverse Events and Pharmacovigilance Studies

Given the importance of experience and oversight, pharmacovigilance studies may be an important source of information on the prevalence of serious adverse events in community settings [105]. In 2016, a study was published from data using the WHO Global Individual Case Safety Report (ICSR) database, VigiBase®. Between 1995 and 2015, 162 ICSR were registered in VigiBase®. The most frequent adverse event was dysphagia, ($n = 27$, 17%) followed by

weakness ($n = 25$, 16%). There were 19 deaths recorded following injection of BoNT-A and mortality was more common in children than in adults [105]. Death and serious adverse events have rarely been reported in RCTs and indicate the need for ongoing recording and monitoring of serious adverse events in community settings [102, 105].

We consider that the risk-to-benefit ratio for the use of BoNT-A injections in large muscle groups, in non-ambulant children with CP, may not be acceptable (Fig. 7). There have been at least four deaths in Australia in non-ambulant children with cerebral palsy following injection of BoNT-A, with other events going unreported or underreported [102, 105, 107].

7.7.2 Adverse Events of BoNT-A in the Injected Muscle

The literature addressing the safety of BoNT-A has rightly focussed on the safety of the child with CP and the prevalence of adverse events [61, 121, 122]. However, during the past 15 years there has been a growing body of literature describing harmful effects of injection of BoNT-A at the level of the injected muscle [7, 93, 94]. These bodies of literature rarely intersect and the majority of reviews of BoNT-A make no mention of the risks of muscle atrophy and fibrosis [3, 7, 81]. In earlier literature, injection of BoNT-A was thought to be completely reversible and if the injection failed to improve gait and function, at least it would do no harm (Fig. 8) [83].

Injection of BoNT-A causes a chemo-denervation of skeletal muscle and denervation is followed by acute muscle atrophy [7, 84, 85, 106, 123]. The reduction in spasticity is not a primary effect but secondary to muscle atrophy [7] (Fig. 9). During the period of muscle atrophy, contractile muscle elements are partially replaced by fat and connective tissue [7, 85, 123]. When the effects of injection wear off, there is a partial recovery of muscle morphology and function, but the evidence in human volunteers and in experimental animals suggests that recovery is incomplete at 12 months after injection [7, 85, 123]. To date, there are no studies that extend for more than 12 months [7, 84, 85]. At this time, the degree of muscle recovery is not known nor is it known if skeletal muscle ever recovers fully after a single injection of BoNT-A. If there is even a small deficit at 6–12 months after the first injection, it is possible the deficits in skeletal muscle morphology and function may accumulate over time, with each injection cycle [94]. The implications will vary according to the muscle injected and its function. Muscle fibrosis is unlikely to help muscle function in any area of the body but might have more serious implications in antigravity, lower-limb muscles in ambulant children than in upper-limb muscles or perhaps in the muscles on non-ambulant children. These ideas all remain to be investigated and tested.

The Leuven and Perth groups have led the way in measuring changes in muscle volumes and morphology after injection of BoNT-A, using serial MRI or 3DUS [124, 125]. They have reported smaller reductions in muscle volumes than

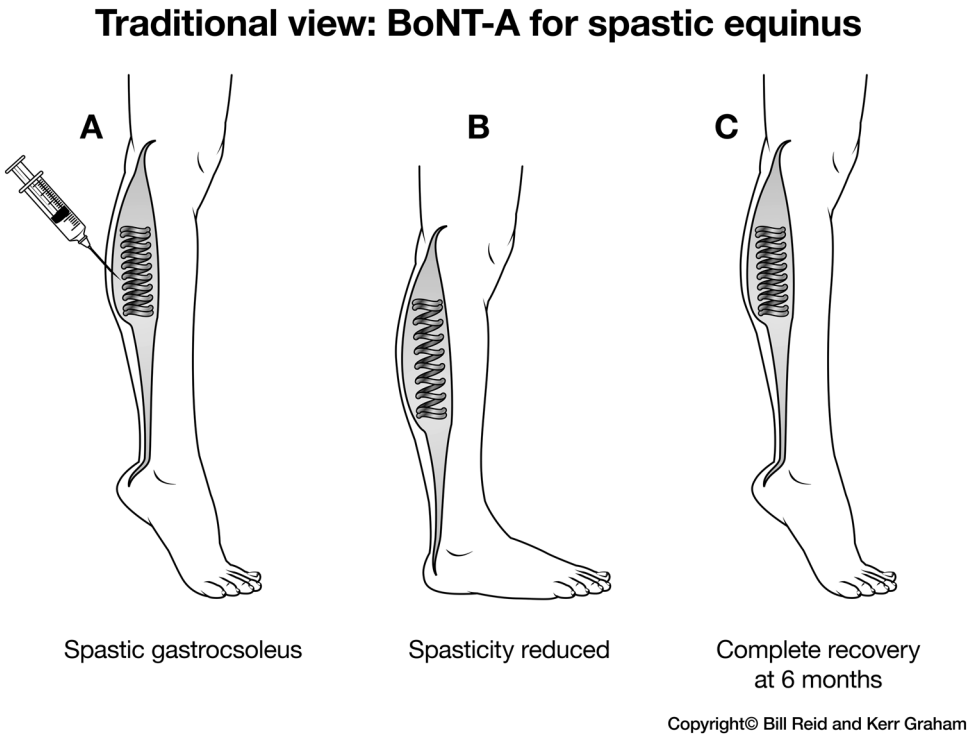

Fig. 8 Historical view of changes in the gastrocnemius muscle after injection of botulinum toxin type A (BoNT-A) for equinus gait. The spastic gastrocsoleus muscle is shown as a tightly coiled spring, causing the child to walk on their toes. After injection the spring (spasticity) is relaxed and the child achieves foot-flat. After 3–6 months, the effects of injection wear off and the equinus returns

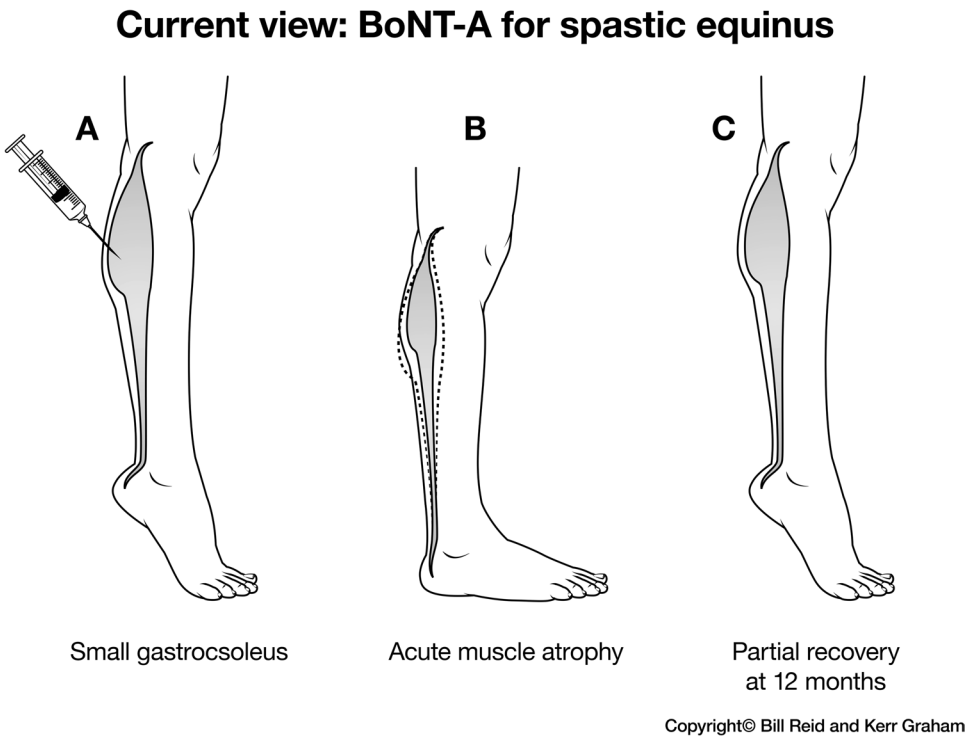

Fig. 9 Contemporary view of changes in the gastrocnemius muscle after injection of botulinum toxin type A (BoNT-A) for equinus gait. The gastrocnemius is small before injection with dynamic shortening and equinus at the ankle. After injection of BoNT-A there is acute atrophy, a decrease in spasticity and foot-flat. After 6–12 months there is partial recovery of the muscle and the equinus returns

reported in animal studies, which is encouraging [124, 125]. Changes in muscle volume may be related to the status of the muscle prior to injection. Muscle atrophy and recovery would be expected to differ in children with CP, typically developing volunteers and experimental animals. Changes in echo intensity in the muscles of children with CP at baseline and after injection of BoNT-A have recently been reported [25, 26, 124, 126]. The quality of the muscle as well as the volume needs to be considered, specifically the effects of BoNT-A injections on both contractile elements and non-contractile elements of the skeletal muscle [93, 94]. Decreases in muscle volume combined with increases in echo intensity might signal the double insult of muscle atrophy and muscle fibrosis [126]. There is pressing need for non-invasive monitoring of muscle structure and function throughout treatment with BoNT-A.

8 Conclusions

Given that two RCTs suggest that injection once every 12 months is as effective as injection every 4 months, we suggest decreasing the frequency of injection of BoNT-A to match this evidence. This would also align with evidence from studies in animal models [91–94]. We propose that measurement of muscle volume be performed before injection of BoNT-A and at regular intervals during the treatment phase to reduce as much as possible iatrogenic muscle atrophy and fibrosis.

We suggest that objective evaluation of each injection cycle be performed in the knowledge that there is a "law of diminishing returns" for repeat injections, especially in the gastrocsoleus (Fig. 5). It is not only acceptable but good medicine to stop injecting when muscle stops responding, even if the child and family are not ready for definitive surgery (Fig. 5). Knowing when to stop depends critically on recognition of the progression from dynamic to fixed contracture (Fig. 3). Better communication between BoNT-A injectors and surgeons would facilitate this process.

There is much more work to be done to improve the safety of BoNT-A injection by altering injection protocols and by using ancillary measures such as muscle strengthening to mitigate the effects of BoNT-A-induced atrophy [22, 124–126].

Compliance with Ethical Standards

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Conflict of interest Iqbal Multani declares no conflict of interest. Jamil Manji declares no conflict of interest. Tandy Hastings-Ison declares no conflict of interest. Abhay Khot declares no conflict of interest. Kerr Graham declares no conflict of interest.

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