Adverse effects following botulinum toxin A injections in children with cerebral palsy

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The study aimed to analyze the adverse events associated with botulinum toxin A (BoNT-A) injections in children with cerebral palsy (CP). The literature search was completed using the Medline, PubMed, Google Scholar, Scopus, and Cochrane Library databases from the earliest date possible up to December 2021. Search terms included 'botulinum toxin', 'cerebral palsy', 'spasticity', 'adverse effects', 'side effects', 'undesirable effects', 'complications', 'lower limb', 'upper limb', and 'children' including combinations of index and free-text terms. Fifty-five studies were included in the study. Data on 6333 pediatric patients and more than 14 080 BoNT-A injections were collected. Respiratory symptoms and respiratory tract infections were the most frequently registered adverse events (AEs). Other common AEs included procedural/focal AEs, flu-like symptoms, and asthenia. Sentinel events including four cases of death were reported. AEs were more frequent and severe in high-dose patients; however, the capacity of BoNT-A to spread systemically remains unclear. Since severe adverse events are not common, further research is needed to collect more definitive clinical and homogeneous data to support the findings of the present research and clarify the safety profile of BoNT-A, especially regarding the incidence of respiratory issues and complications in GMFCS IV or V patients. *J Pediatr Orthop B* 32: 435–451

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Introduction

Cerebral palsy (CP) is a heterogeneous, neurodevelopmental clinical syndrome characterized by altered muscle tone, movement, and motor skills [1].

The global prevalence of CP is estimated to be between 1.5 and 3 per 1000 live births, and it has a varied, multifactorial cause [1–3]. Although the brain insult is nonprogressive in itself, the clinical effects of the neurological involvement are dynamic and change as the brain matures. Thus, CP can be described as a 'static encephalopathy, with progressive musculoskeletal pathology' [3,4].

In addition to posture and movement disorder, motor disability may be also accompanied by significant comorbidities, directly or indirectly related to brain dysfunction. Some children have intellectual disability, behavioral and neurodevelopmental disorders, epilepsy, visual, hearing and speech impairment, gastrointestinal disorders (constipation, dysphagia, gastroesophageal reflux, and vomiting), growth disorders, respiratory disorders (recurrent aspirations and infections), urinary disorders (enuresis and incontinence), pain problems, and sleep disorders. In particular, children with more severe motor impairment are more likely to have comorbidities [2]. Among the primary problems, spasticity is considered the main cause of the development of secondary problems such as static muscle contractures and bony deformities [5]. Therefore, an effective management strategy should be focused on the reduction or normalization of muscular tone to prevent the development of secondary problems [3,4].

Over the years, spasticity has been addressed through a variety of treatments including rehabilitation protocols, oral medication, botulin toxin A (BoNT-A) and/or phenol injections, intrathecal baclofen, and selective dorsal rhizotomy [6].

In the following decades, many researchers have reported the efficacy of chemodenervation for the treatment of spasticity in CP patients, and the use of BoNT-A has become standard practice [4,5,7–9].

The Food and Drug Administration (FDA) defines an adverse event as any undesirable experience associated with the use of a medical product in an individual, including both local and systemic events [10,11].

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There is currently no single article that provides the full scope of adverse effects (AEs) associated with BoNT-A injections in the treatment of pediatric CP patients, and that comprehensively considers the type of AEs and their location.

AEs after BoNT-A treatment are usually transient, mild, and self-limiting since only a small amount of toxin should reach the systemic circulation due to the rapid and high-affinity binding of BoNT-A to the neuromuscular junction [6,12–14]. Nevertheless, severe and life-threatening systemic effects including deaths have been reported and need to be further investigated [6]. The aim of this narrative review is to report and analyze the adverse events associated with BoNT-A injections in children with CP.

Methods

Design and search strategy

The search was conducted and reported using the protocol described in the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.

Two authors (F.A. and F.C.) conducted separate electronic searches using the following medical databases from the earliest date possible up to December 2021: Medline, PubMed, Google Scholar, Scopus, and Cochrane Library. The review includes retrospective, prospective, and longitudinal cohort studies; narrative and systemic reviews; and editorials and correspondences were screened.

All references obtained from the search were imported into Endnote X7 (Thomson Reuters, Philadelphia, Pennsylvania, USA). Relevant studies were screened for eligibility, and the research was not limited by level of evidence as defined by the Oxford Centre for Evidence Based Medicine. The same two authors screened the titles and abstracts. After this initial screening, the full texts of all articles considered relevant were retrieved and assessed for eligibility. Furthermore, references of all selected articles were reviewed to find potential articles that might have been missed. Any remaining noneligible articles were excluded based on the criteria below, and duplicate articles were removed. In the situation of duplicate studies from the same author(s) and/or institution(s) reporting on the same or overlapping subjects, only the most recent study with the longest follow-up was included; however, older studies were included if certain data were not reported in the newer studies. Disagreements were resolved by consensus among the authors.

Search terms and delimiting

Search terms included 'botulinum toxin', 'cerebral palsy', 'spasticity', 'adverse effects', 'side effects', 'undesirable effects', 'complications', 'lower limb', 'upper limb', and 'children', including combinations of index and free-text terms, as recommended in the Cochrane Handbook for Systematic Reviews of Interventions. The search was restricted to the English language and human participants.

Selection criteria employed

Inclusion criteria consist of studies that focused on: (a) outcomes of BoNT-A in patients with CP, (b) short-medium and long-term effects of BoNT-A, (c) tolerability of BoNT-A, (d) safety of BoNT-A, (e) AEs of BoNT-A, and (f) interventions for children with CP. The review was not limited by specific CP type and pharmaceutical products used. Studies were excluded if patients were treated for drooling or if they only included adult patients.

The following data were extracted from the included papers using evidence summary templates: author(s), title, year of publication, journal, sample size in the hospital setting, characteristics of the study population [age, CP type, anatomical site(s) of injection, dosing, numbers, and type of treatments], pharmaceutical product used, definition of AEs, and results (associations between treatment and side effects, and characteristics of AEs).

Results

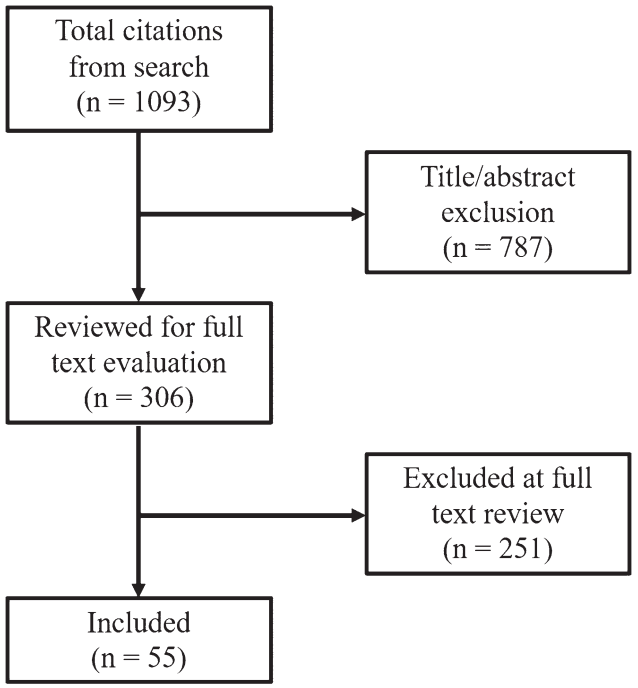
Figure 1 demonstrates the total search and study selection process and includes the number of articles excluded at each stage (Fig. 1). After applying the inclusion criteria in the first stage of the review process, 787 of 1093 studies (72%) did not meet the inclusion criteria based solely on the study title and abstract. After comprehensive full-,text examination of the 306 remaining studies, 251 were further excluded. The reasons for exclusion were basic science studies, animal studies, diagnostic studies, economic studies, prognostic studies, editorials, therapeutic studies, in which the AEs were not reported, older population, treated conditions different from CP (i.e., sialorrhea or drooling, dry eye syndrome, and blepharospasm), and missing details regarding treatment goals and injection technique (diagnosis, target muscles, and dosage).

Finally, 55 studies were included in the study [15–80]. Among these, 10 were focused on upper limb (Table 1), 34 on lower limb (Table 2), and 11 included CP patients who received BoNT-A treatment both for upper and lower limbs (Table 3). Data from the selected studies included 6333 pediatric patients and at least 14 080 BoNT-A injections. Table 4 outlines data regarding the dosages (Table 4).

The primary toxin types used included onabotulinum toxin A (ONA, Botox, Allergan, Irvine, California, USA) and abobotulinum toxin A (Dysport, Ipsen, Paris, France). Only one study used incobotulinum toxin A (Xeomin, Merz Pharmaceuticals GmbH, Frankfurt, Germany).

When mentioned, muscle targeting was performed using anatomic landmarks and palpation, electrical stimulation, and ultrasound guidance.

Fig. 1



Flow chart of the total search and study selection.

AEs can be differentiated into focal (local and distant), systemic, and procedural AEs. Tables 4 and 5 summarize all the AEs collected from our analysis.

Procedural AEs include all procedural issues such as bruising, pain, skin dysesthesia, injection site rash or papule, and local hematoma at the site of injection that most likely are caused by the needle itself, unrelated to the toxin effect. Procedural AEs were recorded in 330 cases, accounting for 13.3% of the total AEs among the included studies (Fig. 2).

Focal AEs include temporary and self-limiting localized muscle weakness or soreness, weakness of hand grasp, dropped fingers, muscle cramps, gait abnormalities and difficulty in walking causing accidental falls with possibly related injuries, transient unwillingness to walk, calf pain, calf atrophy, calf tenderness, and swelling of the injected muscle. Focal AEs were the most commonly reported undesirable effects among children treated for upper limb CP. Sporadic cases of AEs of BoNT-A injections such as muscle changes and atrophy following BoNT-A injections are reported [79,80].

Procedural effects, such as ecchymosis, pain, skin dysesthesia, and rash at the injection site, were the second most reported AEs (13%), followed by focal effects (muscle weakness or soreness, weakness in hand grip, finger drop, and muscle cramps) reported in 11.2% of cases.

Several systemic effects involving different systems with variable severity have been reported (Table 5). Respiratory symptoms and infections including upper respiratory tract infections, lower respiratory tract issue (LRTI), common colds, nasal congestion, cough, rhinitis, pharyngitis, tonsillitis, sore throat, croup, bronchitis, chest infection, and pneumonia were the most frequently reported side effects accounting for 23% of all AEs being registered in patients receiving both upper and lower limb injections, or lower limb only. Asthenia (also described as 'generalized fatigue', 'whole-body tiredness', or 'whole-body weakness') accounted for 9.8% of all AEs. Similarly, flu-like symptoms (in most cases unspecified, and in a few studies described as fever, malaise, or generalized fatigue) accounted for 8.6% of all AEs. Other common AEs were nausea and vomiting, constipation, diarrhea, fever, seizure, fecal or urinary incontinence, irritability, dysphagia, or swallowing troubles, and sialorrhea.

Discussion

Over the past 3 decades, BoNT-A injections have become a widely used medical practice in children with CP due to their effect on decreasing spasticity and improving function and range of motion [3,4,12]. However, there is currently no single article that provides the full scope of AEs associated with BoNT-A injections in the treatment of pediatric CP patients, and that comprehensively considers the type of AEs (procedural, focal, and systemic) and their location (upper or lower limb).

AEs after BoNT-A treatment are usually transient, mild, and self-limiting. However, even if rarely, the toxin may act systemically leading to potential life-threatening side effects, comparable with botulism-like symptoms. Due to the increasing number of botulinum indications, in 2007, some European pharmaceutical companies were asked to document the possibility of severe systemic side effects in a '"red hand letter"' [13]. Similarly, in 2008, a petition requested the FDA to provide a warning letter and regulatory actions to emphasize the risk of the potential severe effects of BoNT-A, including cases of hospitalization and death [14].

Previous recommendations, based on a consensus statement, clarified the procedure in terms of patient selection, dosing guidelines, and injection techniques for both upper and lower extremities in children with CP [3]. According to the authors, the dynamic tone of upper limbs should be the target of treatment, whereas one or two muscle groups should be selected in the lower limbs. Additionally, the use of up to 12 units/kg up to a maximum dose of 300 units was recommended, in a concentration of 100 units in 1 or 2 ml of normal saline. Moreover, to avoid the development of neutralizing antibodies and the consequent risk of secondary unresponsiveness, the injections should not be performed more frequently than every 3 months.

Table 1 **Studies showing adverse effects of botulinum toxin A injection for upper limbs spasticity in cerebral palsy**

Author and Title	Journal	Number of patients	Number of injections	CP type	Toxin	Target identification	AEs (cases and %)	AEs (details)
Chin and Graham. Botulinum toxin A in the management of upper limb spasticity in cerebral palsy	Hand Clin 2003	103	Not mentioned	Hemiplegia Tetraplegia	BoNT-A	Electrical stimulation	30 (29%)	Weakness of grasp (12; 11%); bruising (10; 9%); pain (4; 3%); dropped index finger (3; 2%); incontinence (1; 1%)
Sätilä *et al*. Upper limb function after botulinum toxin A treatment in cerebral palsy: two years follow-up of six cases	Pediatric Rehabilitation 2006	6	10	Hemiplegia Diplegia Tetraplegia	BoNT-A	EMG guidance	4 (40%)	Flu-like symptoms (1; 10%); slight reduction in finger forces (2; 20%); obstipation; pain in elbow joint (1; 10%)
Wallen *et al*. Functional outcomes of intramuscular botulinum toxin type A and occupational therapy in the upper limbs of children with cerebral palsy: a randomized controlled trial	Arch Phys Med Rehabil 2007	40	121	Hemiplegia Triplegia Quadriplegia	BoNT-A	Not mentioned	9 (22%)	Nausea and vomiting (2; 22%); flu symptoms (1; 11%); sick and coughing (1; 11%); fever overnight (1; 11%); sore wrist (1; 11%); upper respiratory tract infection (1; 11%); sore hand (1; 11%)
Russo *et al*. Upper-Limb botulinum toxin A injection and occupational therapy in children with hemiplegic cerebral palsy identified from a population register: a single-blind, randomized, controlled trial	Pediatrics 2007	21	Not mentioned	Hemiplegia	BoNT-A	Electrical stimulation	23 (47%)	Seizure (1; 10%); excessive weakness in the injected limb (5; 50%); headache (2; 20%); flu-like symptoms (1; 10%); fainting episode (1; 10%)
Rösblad *et al*. Effects of botulinum toxin type A and a programme of functional activity to improve manual ability in children and adolescents with cerebral palsy	Scand J Plast Reconstr Surg Hand Surg 2007	25	34	Hemiplegia Diplegia Dyskinetic CP	BoNT-A (Botox)	EMG guidance	3 (12%)	Reduction in grip strength (3; 100%)
Kawamura *et al*. A randomized controlled trial comparing botulinum toxin A dosage in the upper extremity of children with spasticity	Developmental Medicine & Child Neurology 2007	40	Not mentioned	Hemiplegia Triplegia	BoNT-A (Botox)	Anatomical landmarks	8 (20%)	Weak grasp (5; 62%); general fatigue (3; 37%)
Olesch *et al*. Repeat botulinum toxin A injections in the upper limb of children with hemiplegia: a randomized controlled trial	Developmental Medicine & Child Neurology 2009	11	59	Hemiplegia	BoNT-A (Botox)	Electrical stimulation	3 (27%)	Generalized maculopapular rash (1; 33%); weakness of the index finger (1; 33%); prolonged weakness in the finger flexors (1; 33%)
Hoare *et al*. Intensive therapy following upper limb botulinum toxin A injection in young children with unilateral cerebral palsy: a randomized trial	Developmental Medicine & Child Neurology 2012	35	Not mentioned	Hemiplegia	BoNT-A (Botox)	Electrical stimulation	9 (25%)	Excessive grip weakness (6; 17%); local soreness (1; 2%); vomiting (1; 2%)
Koman *et al*. Upper extremity spasticity in children with cerebral palsy: a randomized, double-blind, placebo-controlled study of the short-term outcomes of treatment with botulinum-A toxin	J Hand Surg 2013	36	Not mentioned	Hemiplegia Diplegia Tetraplegia	BoNT-A (Botox)	Anatomical landmarks or ultrasound guidance	69 (80%)	Soreness of injected muscles (13; 44%); muscle cramps (1; 3%); excessive weakness (2; 6%); whole-body weakness (1; 3%)
Karaca *et al*. Outcomes of botulinum toxin type A injection followed by rehabilitation in cases of cerebral palsy with upper extremity involvement	Journal of Child Neurology 2015	25	29	Hemiplegia Diplegia Triplegia	BoNT-A (Botox)	Electrical stimulation or EMG guidance	3 (12%)	Local weakness (3; 100%)

AEs, adverse effects; BoNT-A, botulinum toxin A; CP, cerebral palsy.

Table 2 Studies showing adverse effects of botulinum toxin A injection for lower limbs spasticity in cerebral palsy

Author and Title	Journal	Number of patients	Number of injections	CP type	Toxin	Target identification	AEs (cases and %)	AEs (details)
Koman *et al.* Management of cerebral palsy with botulinum-A toxin: preliminary investigation.	JPO 1993	24	87	Hemiplegia Diplegia Tetraplegia	BoNT-A	Anatomic landmarks	15 (64%)	Local soreness (10; 45%); generalized fatigue (3; 13%); local weakness (2; 6%)
Koman *et al.* Management of cerebral palsy with botulinum toxin A: report of a preliminary randomized, double-blind trial.	JPO 1994	6	Not mentioned	Hemiplegia Diplegia	BoNT-A	Anatomic landmarks	3 (50%)	Local soreness (3; 100%)
Cosgrove *et al.* Botulinum toxin in the management of the lower limb in cerebral palsy	Developmental Medicine & Child Neurology 1994	26	Not mentioned	Hemiplegia Diplegia Tetraplegia	BoNT-A	Anatomic landmarks	1 (3%)	Knee recurvatum (1; 100%)
Eames *et al.* The effect of botulinum toxin A on gastrocnemius length: magnitude and duration of response	Developmental Medicine & Child Neurology 1999	39	Not mentioned	Hemiplegia Diplegia	BoNT-A	Not mentioned	2 (5%)	Local pain (1; 50%); falls (1; 50%)
Wissel *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	33	219	Hemiplegia Diplegia	BoNT-A (Botox)	Not mentioned	10 (24%)	Transient unwillingness to walk (5; 50%); soreness at the injection site (2; 20%); mild transient weakness of an injected muscle (2; 20%); local hematoma (1; 10%)
Boyd *et al.* Biomechanical transformation of the gastroc–soleus muscle with botulinum toxin A in children with cerebral palsy	Developmental Medicine & Child Neurology 2000	25	Not mentioned	Hemiplegia Diplegia	BoNT-A	Not mentioned	1 (4%)	Generalized weakness and incontinence (1; 100%)
Ubhi *et al.* Randomized double-blind placebo-controlled trial of the effect of botulinum toxin on walking in cerebral palsy.	Arch Dis Child 2000	40	Not mentioned	Hemiplegia Diplegia	BoNT-A (Dysport)	Anatomic landmarks	6 (15%)	Wheeziness (1; 16%); seizure (1; 16%); falls (2; 33%); calf pain (2; 33%)
Desloovere *et al.* A randomized study of combined botulinum toxin type A and casting in the ambulant child with cerebral palsy using objective outcome measures	European Journal of Neurology 2001	34	171	Hemiplegia Diplegia	BoNT-A (Botox)	Not mentioned	14 (41%)	Generalized weakness (12; 85%); temporary incontinence (3; 21%); constipation (1; 7%)
Koman *et al.* Botulinum toxin type A neuromuscular blockade in the treatment of equinus foot deformity in cerebral palsy: a multicenter, open-label clinical trial	Pediatrics 2001	215	1062	Hemiplegia Diplegia	BoNT-A (Botox)	Anatomic landmarks	183 (85%)	Ear infections (68; 32%); common colds (58; 27%); flu symptoms (134; 6%); upper respiratory infections (33; 15%); fever (26; 12%); cough (21; 10%); chicken pox (19; 9%); falling (20; 9%); leg pain (5; 2%); leg weakness (5; 2%); generalized weakness (4; 2%); leg cramps (3; 1%); calf atrophy (22; 11%); death (1; 0.3%)
Baker *et al.* Botulinum toxin treatment of spasticity in diplegic cerebral palsy: a randomized, double-blind, placebo-controlled, dose-ranging study	Developmental Medicine & Child Neurology 2002	94	282	Dynamic equinus spasticity in diplegia	BoNT-A (Dysport)	Anatomic landmarks	48 (51%)	Pharyngitis (9; 18%); fever (8; 16%); pain (8; 16%); falls (7; 14%); URTI (6; 12%); infection (6; 12%); bronchitis (5; 10%); viral infection (5; 10%); asthenia (4; 8%); asthma (4; 8%); cough increased (4; 8%); convulsion (4; 8%); vomiting (4; 8%); cold (3; 6%); diarrhea (3; 6%); gastroenteritis (2; 4%); somnolence (2; 4%)
Polak *et al.* Double-blind comparison study of two doses of botulinum toxin A injected into calf muscles in children with hemiplegic cerebral palsy	Developmental Medicine & Child Neurology 2002	48	48	Hemiplegia	BoNT-A (Dysport)	Anatomic landmarks	18 (38%)	Accidental fall (1; 5%); generalized weakness (1; 5%); pain at injection site (12; 66%); headache, off food, nausea, dizziness, difficulty sleeping, sore throat (6; 18%)

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Table 2
(***Continued***)

Author and Title	Journal	Number of patients	Number of injections	CP type	Toxin	Target identification	AEs (cases and %)	AEs (details)
Fattal-Valevski *et al*. Parameters for predicting favorable responses to botulinum toxin in children with cerebral palsy	J Child Neurol 2002	26	67	Hemiplegia Diplegia	BoNT-A (Botox)	Anatomic landmarks	4 (15%)	Pain (2; 50%); general weakness (2; 50%); incontinence (1; 25%); weak irritability (1; 25%)
Reddihough *et al*. Functional outcome of botulinum toxin A injections to the lower limbs in cerebral palsy	Developmental Medicine & Child Neurology 2002	44	Not mentioned	Hemiplegia Diplegia	BoNT-A	Anatomic landmarks	21 (47%)	Pain (11; 52%); incontinence (4; 19%); muscle weakness (4; 19%); less specific complaints; ('out of sorts' and 'a little sick and sore') (2; 9%)
Sätilä *et al*. Botulinum toxin treatment of spastic equinus in cerebral palsy	Am J Phys Med Rehabil 2005	19	25	Equinus spasticity	BoNT-A	Anatomic landmarks	19 (76%)	Tenderness in calf (8; 32%) tiredness (3; 12%); irritability (5; 20%); clumsiness (3; 12%)
Papavasiliou *et al*. Evaluation of a multimodal management of prematurity-related spasticity	Pediatric Neurology 2006	57	173	Hemiplegia Diplegia Tetraplegia	BoNT-A (Botox)	Anatomic landmarks	6 (10%)	Enuresis (1; 16%); generalized muscular weakness (2; 33%); trunk weakness (3; 50%)
Sätilä *et al*. Treatment of spastic equinus gait with botulinum toxin a: does dose matter? analysis of a clinical cohort.	Neuropediatrics 2006	21	80	Equinus gait	BoNT-A	With or without EMG guidance	41 (51%)	Bruising or soreness (18; 22%); clumsiness (6; 7%); irritability (6; 7%); tiredness (4; 5%); constipation or diarrhea (2; 2%); flu-like symptoms (4; 5%); pain in the sole of the foot (1; 1%)
Molenaers *et al*. The effects of quantitative gait assessment and botulinum toxin A on musculoskeletal surgery in children with cerebral palsy	JBJS 2006	132	91	Hemiplegia Diplegia	BoNT-A	Not mentioned	4 (<5%)	Incontinence and constipation (4; 100%)
Willis *et al*. High dose botulinum toxin A for the treatment of lower extremity hypertonicity in children with cerebral palsy	Dev Med Child Neurol 2007	261	929	Hemiplegia Diplegia Tetraplegia	BoNT-A	Not mentioned	39 (4%)	Muscle weakness or fatigability (26; 66%); flu-like symptoms (5; 12%); increased dryness of pulmonary secretions (2; 5%); seizure (1; 2%); respiratory tract infection (1; 2%); diarrhea/irritability (4; 10%); injection site events – bruising, tenderness, swelling (8; 20)
Graham *et al*. Does botulinum toxin A combined with bracing prevent hip displacement in children with cerebral palsy and '"hips at risk"?'	JBJS 2008	47	204	Diplegia Tetraplegia	BoNT-A (Botox)	Anatomic landmarks	12 (6%)	Death (2; 4%); respiratory infection (4; 8%); bronchospasm (2; 4%); urinary incontinence (3; 6%); flu-like illness (1; 2%)
Moore *et al*. Two-year placebo-controlled trial of botulinum toxin A for leg spasticity in cerebral palsy	Neurology 2008	30	Not mentioned	Hemiplegia Diplegia Tetraplegia	BoNT-A (Dysport)	Anatomic landmarks	29 (97%)	Chest infection/cough (20; 34%); flu-like illness (41; 62%); nasal congestion (2; 6%); ear infection (9; 17%); croup (1; 3%); tonsillitis (5; 6%); summed respiratory tract/ear disturbance (78; 82%); incontinence (10; 20%); urinary tract infection (5; 10%); kidney infection (1; 3%); seizure (1; 3%); febrile convulsion (1; 3%); shunt disturbance (1; 3%); bad behavior (5; 10%); diarrhea and/or vomiting (25; 48%); constipation (2; 6%); mobility worse (19; 41%); falls (2; 6%); possibly related injury (4; 12%); apparently unrelated injury (3; 10%); lethargy/off food/temperature (11; 27%); identified systemic illness - viral/bacterial (10; 31%); local pain (5; 17%); local swelling (1; 3%); other (16; 31%)
Sätilä *et al*. Botulinum toxin type A injections into the calf muscles for treatment of spastic equinus in cerebral palsy	Am J Phys Med Rehabil 2008	17	25	Equinus spasticity	BoNT-A	Anatomic landmarks	8 (35%)	Calf tenderness (3; 50%) clumsiness (2; 33%); spasms in the injected calf (1; 16%)

(***Continued***)

Table 2
(***Continued***)

Author and Title	Journal	Number of patients	Number of injections	CP type	Toxin	Target identification	AEs (cases and %)	AEs (details)
Crowner and Racette. Prospective study examining remote effects of botulinum toxin A in children with cerebral palsy	Pediatr Neurol 2008	34	Not mentioned	Hemiplegia Diplegia	BoNT-A	Not mentioned	2 (5%)	Extremity weakness (2; 100%)
Fattal-Valevski *et al*. Long-term effect of repeated injections of botulinum toxin in children with cerebral palsy: a prospective study	J Child Orthop 2008	26	59	Hemiplegia Diplegia	BoNT-A (Botox)	Anatomic landmarks	6 (23%)	Local pain (2; 7%); generalized weakness (2; 7%); irritability (1; 3%); transient incontinence (1;3%)
Py *et al*. Evaluation of the effectiveness of botulinum toxin injections in the lower limb muscles of children with cerebral palsy. Preliminary prospective study of the advantages of ultrasound guidance	Annals of Physical and Rehabilitation Medicine 2009	54	130	Diplegia	BoNT-A (Botox)	Anatomic landmarks or ultrasounds guidance	1 (1.8%)	Asthenia (1; 100%)
Kanovsky *et al*. Long-term efficacy and tolerability of 4-monthly versus yearly botulinum toxin type A treatment for lower-limb spasticity in children with cerebral palsy	Developmental Medicine & Child Neurology 2009	214	Not mentioned	Diplegia	BoNT-A (Dysport)	Anatomic landmarks	177 (83%)	Pharyngitis (81; 37%); rhinitis (66; 30%); bronchitis (65; 30%); viral infection 22 (50; 23%); pain (41; 19%); infection (25; 16%); weakness (30; 14%); cough increased (26; 12%); surgical intervention (25; 11%); fever (22; 10%); convulsions (20; 0.9%)
Lee *et al*. Effects of different dilutions of botulinum toxin type A treatment for children with cerebral palsy with spastic ankle plantarflexor: a randomized controlled trial	J Rehabil Med 2009	38	not mentioned	Ankle plantarflexor spasticity in hemiplegia and diplegia	BoNT-A (Botox)	Anatomic landmarks	6 (10%)	Postinjection calf pain (6; 100%)
Xu *et al*. A randomized controlled trial to compare two botulinum toxin injection techniques on the functional improvement of the leg of children with cerebral palsy	Clinical Rehabilitation 2009	45	315	Hemiplegia Diplegia	BoNT-A	Anatomic landmarks or electrical stimulation	34 (75%)	Pain (23; 51%); falls (11; 24%)
Naidu *et al*. Systemic adverse events following botulinum toxin A therapy in children with cerebral palsy	Developmental Medicine & Child Neurology 2009	1147	1980	Monoplegia Hemiplegia Diplegia Tetraplegia	BoNT-A (Botox)	Anatomic landmarks, electrical stimulation or ultrasounds guidance	71 (6%)	Incontinence (19; 26%); URTI (9; 12%)
Tedroff *et al*. Botulinumtoxin A treatment in toddlers with cerebral palsy	Acta Paediatrica 2010	6	40	Spastic CP	BoNT-A (Botox)	Anatomic landmarks	3 (33%)	Weakness/skin dysesthesia/pain at the injection site (3; 100%)
Chaléat-Valayer *et al*. A French observational study of botulinum toxin use in the management of children with cerebral palsy: BOTULOSCOPE.	European Journal of Paediatric Neurology 2010	282	509	Hemiplegia Diplegia Tetraplegia	BoNT-A	Electrical stimulation	360 (55%)	Immediate pain (124; 25%); lack of energy (72; 41%); pain (67; 38%); enuresis (18; 10%); fall (14; 8%); flu-like syndrome (9; 5%); swallowing troubles (3; 2%); other (vomiting, headache, hematoma, cramp) (53; 30%)
Carraro *et al*. Safety profile of incobotulinum toxin A [Xeomin] in gastrocnemious muscles injections in children with cerebral palsy: Randomized double-blind clinical trial	European Journal of Paediatric Neurology 2016	35	238	Hemiplegia Diplegia Tetraplegia	BoNT-A (Xeomin); BoNT-A (Botox)	Not mentioned	35 (49%)	Fever (2; 5%); low-grade fever (1; 2%); indisposition (3; 8%); fatigue (22; 65%); general muscle weakness (1; 2%); general muscle pain (10; 34%); diarrhea (2; 5%); stomach pain (1; 2%); sleepiness (8; 28%); gait abnormalities (7; 20%); allergic reactions (1; 2%); ear pain (1; 2%)

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Table 2
(***Continued***)

Author and Title	Journal	Number of patients	Number of injections	CP type	Toxin	Target identification	AEs (cases and %)	AEs (details)
Delgado *et al.* Abobotulinumtoxin A for equinus foot deformity in cerebral palsy: a randomized controlled trial	Pediatrics 2016	160	Not mentioned	Hemiplegia Diplegia Tetraplegia	BoNT-A (Dysport)	Electrical stimulation or ultrasound guidance	11 (7%)	Muscular weakness (2; 1%); injection site pain (2; 1%); dysphagia (1; 1%); piloerection (1; 1%); arthralgia (1; 1%); pyrexia (1; 1%); asthenia (1; 1%); gait disturbance (1; 1%); fecal incontinence (1; 1%); injection site erythema (1; 1%); injection site reaction (1; 1%); injection site rash (1; 1%)
Delgado *et al.* Safety and efficacy of repeat open-label abobotulinumtoxin A treatment in pediatric cerebral palsy	Journal of Child Neurology 2017	216	652	Dynamic equinus foot deformity	BoNT-A (Dysport)	Electrical stimulation or ultrasound guidance	150 (73%)	Injection site pain (11; 6%); injection site papule (4; 3%); influenza-like illness (2; 1%); pyrexia (1; 0.5%); fecal incontinence (2; 1%); diarrhea (1; 0.5%); pain in extremity (1; 1%); urinary incontinence (1; 1%); fall (1; 1%); laceration (1; 1%); phlebitis (1; 0.4%)
Juneja *et al.* Effect of multilevel lower-limb botulinum injections & intensive physical therapy on children with cerebral palsy	Indian J Med Res 2017	29	69	Hemiplegia Diplegia Triplegia Tetraplegia	BoNT-A (Botox)	EMG guidance	5 (17%)	URTI (3; 60%); local weakness (2; 40%)

AEs, adverse effects; BoNT-A, botulinum toxin A; CP, cerebral palsy; LRTI, lower respiratory tract issue; URTI, upper respiratory tract infection.

Kinnet *et al.* [69] reviewed 22 articles published between 1993 and 2003 reporting that the maximum total dose injected was 400 units with a maximum dose of 29 units/kg, and concentrations varying from 50 to 500 units/ml, with the most common being 100 units/ml.

A search of Adverse Event Reporting System Database revealed nine cases of deaths in children and adolescents younger than 16 years of age that underwent BoNT-A procedures. All of the pediatric patients who died had underlying neuromuscular problems and the registered cause of death included the following: cardiorespiratory arrest (n = 4), seizure (n = 2), fatal arrhythmia (n = 1), pneumonia (n = 1), and stroke (n = 1) [70]. Dose ranges for serious systemic adverse reactions were reported for ONA (Botox) from 6.25 to 32 units/kg, and administration of at least one very high dose (32 units/kg) was reported among the children who died. It is worth noting that this dose is far beyond the amount that has been recommended in the pediatric literature [11,70].

Bakheit *et al.* [59] evaluated the effect of total dose on incidence of AEs caused by BoNT-A used in the management of 758 children with chronic muscle spasticity. Of all 1594 treatments, 7% resulted in AEs, and the incidence was related to the total dose administrated rather than the dose calculated based on the patient's body weight. The highest incidence of AEs was observed in patients who received more than 1000 IU of BoNT-A per treatment session. Another interesting finding was that the highest doses of BoNT-A did not only result in higher incidence of AEs, but they were also associated with reduced therapeutic responses and, in some cases, functional decline. Eames *et al.* [27] pointed out BoNT-A does cause a detectable lengthening of muscle in ambulant children, which varies and is related directly to the dynamic present immediately before an injection; repeated injections display similar correlations, the dynamic component being the important factor rather than the number of the injection. Another explanation may be that children who received large doses of BoNT-A had a higher levels of disability, more severe contractures, and less potential for functional improvement [59].

In contrast, the study conducted by Sätilä *et al.* [39] found that the amount, type, and severity of side-effects did not differ between the two dose treatment groups (cut-off 6 units/kg body weight), suggesting that BoNT-A is a safe modality for treating local spasticity. Polak *et al.* [34] and Baker *et al.* [33] reported similar findings. However, they did not report any significant differences in terms of incidence of AEs between patients treated by 8 units/kg body weight versus 24 units/kg body weight although the side effects tended to be milder in low-dose patients.

As highlighted by Heinen *et al.* [13] in the last European Consensus in 2009, with the development of the multilevel treatment strategy, it has become apparent that an adequate focal treatment effect can only be achieved

Table 3 **Studies showing adverse effects of botulinum toxin injection for combined upper and lower limbs spasticity in cerebral palsy**

Title and Author	Journal	Number of patients	Number of injections	CP type	Toxin	Target identification	AEs (cases and %)	AEs (details)
Denišlič and Meh. Botulinum toxin in the treatment of cerebral palsy	Neuropediatrics 1995	13	N/A	Dyskinetic CP	BoNT-A	Anatomic landmarks	6 (47%)	Transient weakening of hand grip (4; 31%); malaise (1; 8%); headache (1; 8%)
Bakheit *et al*. Safety profile and efficacy of botulinum toxin A (Dysport[a]) in children with muscle spasticity	Developmental Medicine & Child Neurology 2001	758	1594	Hemiplegia Diplegia Tetraplegia	BoNT-A (Dysport)	Not mentioned	>45 (7%)	Focal muscle weakness (16; 1%); urinary incontinence (16; 1%); muscle weakness (6; 0.4%); falls (7; 0.7%); other (pain at the site of the injection, fatigue, somnolence, influenza-like symptoms, fever, and purpuric skin rash) (<1%)
Kolaski *et al*. Safety profile of multilevel chemical denervation procedures using phenol or botulinum toxin or both in a pediatric population	Am J Phys Med Rehabil 2008	79	194	Hemiplegia Diplegia Tetraplegia	BoNT-A (Botox)	Anatomic landmarks and electrical stimulation	5 (2%)	Tenderness/soreness (2; 2%); bruising (1; 1%); focal weakness (1; 1%); difficult walking (1; 1%)
O'Flaherty *et al*. Adverse events and health status following botulinum toxin type A injections in children with cerebral palsy	Developmental Medicine & Child Neurology 2011	334	596	Hemiplegia Diplegia Tetraplegia	BoNT-A (Botox)	Ultrasound guidance	139 (23%)	Procedural events (local pain, bruising, nausea, vomiting) (28; 4%); localized weakness (23; 3%); sphincter problems (12; 2%); flu-like illness (9; 1%); generalized weakness (1; 0.2%); worsening dysphagia (6; 1%); LRTI (7; 1%); URTI (26; 4%); seizure/s (11; 1%); other (16; 2%)
Papavasiliou *et al*. Safety of botulinum toxin A in children and adolescents with cerebral palsy in a pragmatic setting	Toxins 2013	454	1382	Spastic CP	BoNT-A (Botox) (Dysport)	Anatomic landmarks and electrical stimulation or ultrasound guidance	52 (3%)	Generalized weakness (6; 0.4%); trunk weakness (5; 0.36); limb weakness (12; 0.86); hypertonia (2; 0.1%); dystonia (1; 0.07%); difficult swallowing (3; 0.22%); speech disturbances (2; 0.14%); seizures (1; 0.07%); constipation (10; 0.07%); vomiting (1; 0.07%); anorexia (1; 0.07%); pain (3; 0.22%); strabismus (1; 0.07%); excessive sweating (1; 0.07%); pallor (3; 0.22%); sleep disturbances (1; 0.07%); lethargy (5; 0.36%); sialorrhea (1; 0.07%); flu-like syndrome (1; 0.07%)
Copeland *et al*. Botulinum toxin A for nonambulatory children with cerebral palsy: a double-blind randomized controlled trial	J Pediatr 2014	23	Not mentioned	Nonambulatory CP children	BoNT-A	Ultrasound guidance and/or electrical stimulation	25 (78%)	Drooling (2; 8%); weak vocalization (1; 4%); seizure (4; 16%); LRTI (1; 4%); hypotonia (1; 4%); bruising (1; 4%); URTI (3; 12%); pneumonia (2; 4%); ear infection (1; 4%)
Mesterman *et al*. Botulinum toxin type A in children and adolescents with severe cerebral palsy: a retrospective chart review	Journal of Child Neurology 2014	60	242	Spastic CP Dyskinetic CP	BoNT-A	Not mentioned	12 (13%)	Swelling/bruising/localized muscle weakness (12; 100%)
Ploypetch *et al*. Retrospective review of unintended effects after single-event multilevel chemoneurolysis with botulinum toxin A and phenol in children with cerebral palsy	Physical Medicine and Rehabilitation Journal 2015	40	40	Hemiplegia Diplegia Tetraplegia	BoNT-A (Botox)	Electrical stimulation	11 (27%)	Increased drooling (2; 5%) Nausea/vomiting/irritability/fatigue (3; 7%) Weakness/increased falling (8; 20%)
Edwards *et al*. Safety of botulinum toxin type A for children with nonambulatory cerebral palsy	Pediatrics 2015	41	Not mentioned	Nonambulatory CP children	BoNT-A (Botox)	Not mentioned	43 (73%)	Serious (floppy, no vocalization, increased drooling, irritability and poor sleep, LRTI, seizure) (5; 12%) Moderate (URTI, floppy, increased drooling, increased seizures, weakness, gagging, vomiting, constipation, cough, fever, rhinorrhea) (33; 77%) Mild (bruising, rash, URTI, rhinorrhea) (20; 48%)

(***Continued***)

Table 3
(***Continued***)

Title and Author	Journal	Number of patients	Number of injections	CP type	Toxin	Target identification	AEs (cases and %)	AEs (details)
Blaszczyk *et al*. Questionnaire about the adverse events and side effects following botulinum toxin A treatment in patients with cerebral palsy	Toxins 2015	74	105	Unilateral and bilateral spastic CP, dyskinetic CP, mixed type CP	BoNT-A (Botox) (Dysport)	Electrical stimulation	95 (61%)	Generalized muscle weakness (18; 18%); fatigue (3; 3%); flu-like symptoms (5; 5%); swallowing difficulties (5; 5%); speech disorders (3; 3%); dry mouth (4; 4%); drooling (2; 2%); respiratory troubles (2; 2%); pneumonia (1; 1%); diarrhea (1; 1%); nosebleeds (2; 2%); hot flashes (1; 1%); urinary incontinence (3; 3%)
Paget *et al*. Systemic adverse events after botulinum neurotoxin A injection in children with cerebral palsy	Developmental Medicine & Child Neurology 2018	591	2219	Not mentioned	BoNT-A (Botox)	Not mentioned	77 (3.6%)	Generalized weakness (16; 0.7%); dysphagia (33; 1.5%); LRTI (33; 1.5%); death (1; 0.04%)

AEs, adverse effects; BoNT-A, botulinum toxin A; CP, cerebral palsy; LRTI, lower respiratory tract issue; URTI, upper respiratory tract infection.

when the injected dose/muscle remains the same. Therefore, the total dose/session increases with the number of treated muscles, but this needs to be distinguished from '"overdosing"' a single muscle.

Dose dependency of AEs in multilevel treatments has been debated [13,71–73]. As several muscles are injected within the same session, multilevel treatments may require a higher total dosage when compared with single-level treatments. The total dosage is defined by the sum of the standardized dosages per muscle group. The dose injected in one muscle depends on the muscle volume, the amount of spasticity, and the degree of muscle involvement in the motor impairment [73].

Sätilä *et al*. [44] compared, in a randomized trial, two groups of children who receive a standard dose of botulinum toxin A injection into one site or two sites on both heads of the gastrocnemius, respectively. Although not significantly, their results showed higher incidence of AEs in the multiple injection site group [44]. All AEs (mainly tenderness of the injected calf and clumsiness) were considered mild by the caregivers.

Despite the dose escalation in multilevel treatments, there have been few reports of serious AEs [30,42,51,74,75].

Most adverse and undesirable events have been mild, self-limiting, and usually transient [42,51,75]. Moreover, controversies exist regarding the safest method to localize the optimal injection sites, and different methods, such as palpation and anatomic landmarks, ultrasound guidance, or electrical stimulation, are all used, either individually or in combination [32,47,76].

Focal AEs such as pain at the site of injection and muscle weakness have been more often reported after upper limb BoNT-A injections. Despite most of the authors adjusted the dosage to the smaller diameter of the muscles (Table 4), it is still not clear if soreness, weakness, and reduced strength of hand grasp may be more related to the local spread of the toxin, the technique used to localize the injection site, or the diameter of the needle [10,14,59],

Naidu *et al*. [51] analyzed the incidence of side effects in a pediatric population of 1147 children who totally received 1980 injections. They found higher BoNT-A doses to be related to increased risk of systemic and respiratory complications, independently of Gross Motor Function Classification System (GMFCS) level. In particular, higher doses were strongly associated with increased risk of urinary or fecal incontinence and unplanned hospital admission for respiratory complications (urinary tract and respiratory infection requiring antibiotic prescription). Moreover, a weaker association was found between higher doses and increased odds of emergency department consultation.

Table 4 Injected doses of botulinum toxin

Study	Dose U/kg	Dose U/muscle	Number of injections per muscle	AEs
Upper limb				
Chin and Graham [15]	1–3 U/Kg depending on site	5–20 U/muscle for thumb-in-palm	1–4	29%
Sätilä *et al.* [16]	4.3 U/kg of BW (range 1.5–9.5)	1–2.5 U/kg of BW/muscle	1–4	40%
Wallen *et al.* [17]	N/A	0. 5–2 U/kg of BW/muscle	1	22%
Russo *et al.* [18]	Mean 8.0 U/kg of BW (range, 5–11.6)	N/A	1	47%
Rösblad *et al.* [19]	N/A	0.5–1 U/kg of BW/muscle	1–4	12%
Kawamura *et al.* [20]	N/A	0.75–1.5 U/kg of BW/muscle (low dose) 1.5–3 U/kg of BW/muscle (high dose)	1	20%
Olesch *et al.* [21]	Mean 5 U/kg (range, 3–6)	0.3–0.6 U/kg of BW for AP and OP 0.5U/kg for AP, FPL and FDS 1U/kg for FDP, FCR, FCU, PT 2U/kg for the biceps brachii	1	27%
Hoare *et al.* [22]	Maximum dose 15U/kg	N/A	1	25%
Koman *et al.* [23]	1.4–12.5 U/kg of BW	N/A	1–3	80%
Karaca *et al.* [24]	Botox mean 2.8 U/kg (0.8–7.2) Dysport mean 4.7 U/kg (3.33–6.66)	N/A	1	12%
Lower limb				
Koman *et al.* [7]	1–5 U/kg of BW	N/A	1–4	64%
Koman *et al.* [25]	1–2 U/kg of BW for each leg	N/A	2	50%
Cosgrove *et al.* [26]	5–28 U/kg of BW	50–320 units to each muscle group	1	3%
Eames *et al.* [27]	Botox 8–10 U/kg Dysport 20–25 U/kg	N/A	1	5%
Wissel *et al.* [28]	Mean 6 U/kg of BW (low dose) Mean 11.6 U/kg of BW (high dose)	20–40 U per muscle belly (low dose) 40–80 U per muscle belly (high dose)	1	24%
Boyd *et al.* [29]	Total 5–14 U/kg of BW Mean total 11 U/kg of BW (diplegia) Mean total 7 U/kg of BW (diplegia	4–9 U per muscle	1–2	4%
Ubhi *et al.* [30]	25 U/kg of BW (diplegia) 15 U/kg of BW (hemiplegia)	Mean 99 U per medial or lateral gastrocnemius Mean 64 U per soleus	1	15%
Desloovere *et al.* [31]	Mean total 24.4 U/kg BW (diplegia) Mean total 16.4 U/kg BW (hemiplegia)	N/A	1	41%
Koman *et al.* [32]	Total dose 4 U/kg BW	2 ml of BoNT-A per muscle site	N/A	85%
Baker *et al.* [33]	10, 20, or 30 U/kg BW	N/A	3	51%
Polak *et al.* [34]	8 U/kg BW (low dose) 24 U/kg BW (high dose)	N/A	1	38%
Fattal-Valevski *et al.* [35]	Maximum total dose 12 U/kg BW	≥6 U/kg BW per muscle	1	15%
Reddihough *et al.* [36]	8–20 units/kg BW Mean total dose 13.5 units/kg BW	6 units/kg muscle	2	47%
Sätilä *et al.* [37]	Total dose 12 units/kg (diplegia) 6 units/kg (hemiplegia)	3 units/kg per site 6 units/kg per gastrocnemius	1	76%
Papavasiliou *et al.* [38]	12–20 U/kg/session	3–6 U/kg in large muscles 1–2 U/kg in small muscles	2.5	10%
Sätilä *et al.* [39]	Total mean 11.6 U/kg BW (low dose) Total mean 16 U/kg BW (high dose)	Mean 5.2 U/kg BW per GS (low dose) Mean 8.2 U/kg BW per GS (high dose)	1–5	51%
Molenaers *et al.* [40]	14–31 U/kg BW (diplegia) 6–23.5 U/kg BW (hemiplegia)	Maximum 50 U per muscle group	N/A	< 5%
Willis *et al.* [41]	Total 0–25 U/kg BW	Hamstrings mean 8.1 muscle/kg Adductors mean 7.7 muscle/kg Gastrocnemius mean 4.5 muscle/kg Soleus mean 4.8 muscle/kg	N/A	4%
Graham *et al.* [42]	Mean dose 13.9 U/kg per child	N/A	6	6%
Moore *et al.* [43]	15–30 U/kg	N/A	Up to 8	97%

(***Continued***)

Table 4
(***Continued***)

Study	Dose U/kg	Dose U/muscle	Number of injections per muscle	AEs
Sätilä *et al.* [44]	N/A	4 U/kg per gastrocnemius head	N/A	35%
Crowner and Racette [45]	Mean 12.6 U/kg BW	N/A	1	5%
Fattal-Valevski *et al.* [46]	Maximum 12 U/kg BW	Up to 6 U/kg BW per muscle	1–5	23%
Py *et al.* [47]	5–6 U/kg	N/A	N/A	1.8%
Kaňovsky *et al.* [48]	30 LD_{50} units/kg total BW	N/A	3 or 7	83%
Lee *et al.* [49]	N/A	3 U/kg BW per gastrocnemius	N/A	10%
Xu *et al.* [50]	3–10 U/kg BW	Maximum 10 U per site	6–8	75%
Naidu *et al.* [51]	Median dose 13.4 U/kg	N/A	N/A	6%
Tedroff *et al.* [52]	6 U/kg BW	N/A	2	33%
Chaléat-Valayer *et al.* [53]	Botox 7–13 U/kg Dysport 17.9–30 U/kg	N/A	1–3	55%
Carraro *et al.* [54]	N/A	5 U/kg per gastrocnemius	1	49%
Delgado *et al.* [55]	10–15 U/kg/leg Maximum dose 1000 U or 30 U/kg	N/A	≥1	7%
Delgado *et al.* [56]	5–20 U/kg/leg Maximum dose 1000 U or 30 U/kg	N/A	1–4	73%
Juneja *et al.* [57]	Maximum dose 25U/kg/session	2–5 U/kg/muscle	1–6	17%
Upper and lower limb				
Denišlič and Meh [58]	Mean total dose was 357 U	BTA dose per muscle 500 U	2–5	47%
Bakheit *et al.* [59]	Mean dose 22. 9 IU/kg BW	N/A	N/A	7%
Kolaski *et al.* [60]	BoNT-A mean dose 17.5 U/kg BoNT-B mean dose 382.8 U/kg	N/A	N/A	2%
O'Flaherty *et al.* [61]	GMFCS I 6 IU/kg GMFCS II 8 IU/kg GMFCS III 13 IU/kg GMFCS IV–V 12 IU/kg	N/A	1–3	23%
Papavasiliou *et al.* [62]	Onabotulinumtoxin A: mean14.2–15 IU/kg/session Abobotulinumtoxin A: mean 27.5–35. 7 IU/kg/session	N/A	N/A	3%
Copeland *et al.* [63]	Maximum dose 12 U/kg BW Mean total dose 10.5 U/kg Mean LL 10.3 U/kg Mean UL 8.2 U/kg	0.5–4 U/kg/muscle group	1	78%
Mesterman *et al.* [64]	3–21 U/kg BW	N/A	1–7	13%
Ploypetch *et al.* [65]	Total 11.64 U/kg BW	N/A	1	27%
Edwards *et al.* [66]	Maximum dose 12 U/kg BW	0.5–4 U per muscle	2	73%
Blaszczyk *et al.* [67]	Botox 1.6–21 U/kg BW Dysport 2.6–22.2 U/kg BW	N/A	1	61%
Paget *et al.* [68]	Mean dose 9.6 units/kg	N/A	N/A	3.6%

AEs, adverse effects; AP, adductor pollicis; BoNT-A, botulinum toxin A; BW, body weight; FCR, flexor carpi radialis; FCU, flexor carpi ulnaris; FDP, flexor digitorum profundus; FDS, flexor digitorum superficialis; FPL, flexor pollicis longus; GS, gastrosleus; LL, lower limb; LRTI, lower respiratory tract issue; OP, opponens pollicis; PT, pronator teres; UL, upper limb.

Table 5 Summary of adverse effects mentioned in the included studies

Effect	Upper limb	Lower limb	Upper and lower limb	AE (%)
Procedural effects (bruising, pain, skin dysesthesia, injection site rash)	15	280	35	13
Focal effects (muscle weakness or soreness, weakness of hand grasp, dropped fingers, muscle cramps)	59	157	62	11.2
Flu-like symptoms	3	196	15	8.6
Respiratory affections (URTI, LRTI, cold, cough, rhinitis, pharyngitis, tonsillitis, sore throat, croup, bronchitis, chest infection, pneumonia)	2	513	75	23
Ear infection/ear pain		78	1	3.19
Wheeziness		1		0.03
Bowel affections (constipation, diarrhea, stomach pain)	1	35	11	1.9
Urinary infections		6		0.24
Urinary incontinence	1	47	25	2.95
Fecal incontinence		3	6	0.3
Fatigue/asthenia/general weakness	4	170	70	9.8
Accidental falls		59	7	2.6
Worse mobility/gait abnormalities		27	1	6.9
Unwillingness to walk		5		0.20
Somnolence/lethargy		2	5	0.28
Nausea, vomiting, gagging	3	16	1	0.80
Headache	2		1	0.12
Fever	1	61		2.5
Skin rash	1			0.04
Asthma, bronchospasm		6		0.24
Anorexia		11	1	0.48
Dizziness		6		0.24
Sleep disorders/sleepiness		8	1	0.36
Irritability		25	3	5.91
Seizure	1	28	16	1.81
Enuresis		19		0.76
Shunt disturbance		1		0.04
Dysphagia		4	47	2.06
Allergic reactions		1		0.04
Excessive sweating			1	0.04
Piloerection		1		0.04
Arthralgia		1		0.04
Phlebitis		1		0.04
Hypertonia			2	0.08
Dystonia			1	0.04
Hypotonia			1	0.04
Speech disturbances, weak vocalization			6	0.24
Pallor			3	0.12
Dry mouth			4	0.16
Sialorrhea/drooling			7	0.28
Nosebleeds			2	0.08
Strabismus			1	0.04
Hot flashes			1	0.04
Clumsiness		11		0.44
Fainting	1			0.04
Calf atrophy		76		3.07
Knee recurvatum		22		0.88
Chicken pox/viral or bacterial systemic infections		1		0.04
Other		69	16	3.43
Death		3	1	0.16
Total	94	1950	429	100

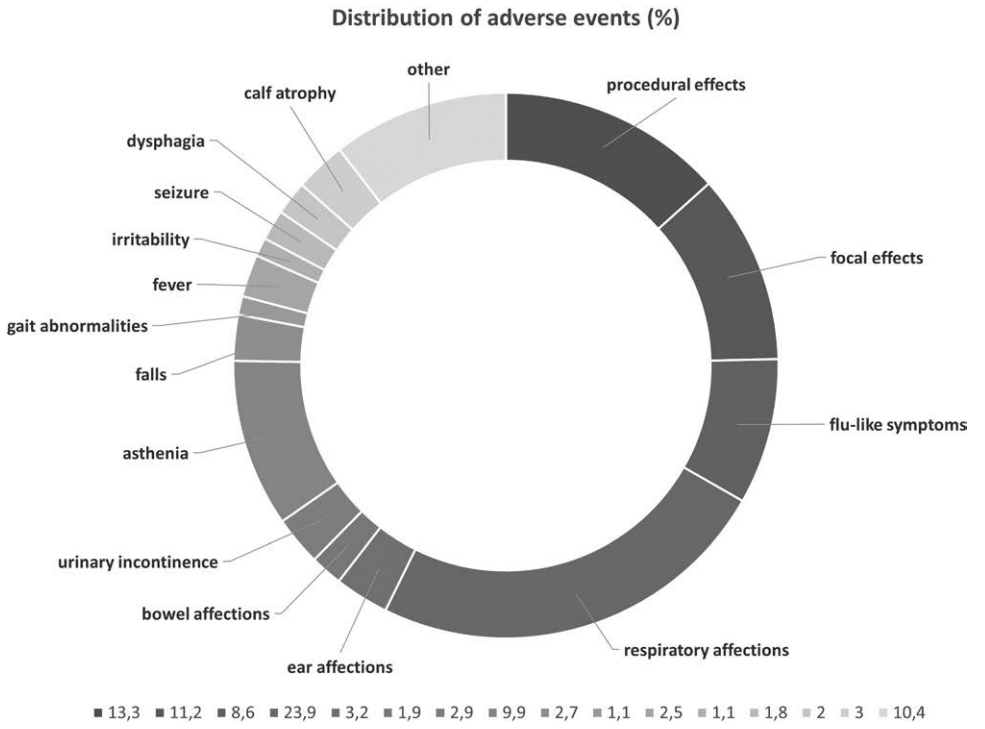
AE, adverse effect; LRTI, lower respiratory tract issue; URTI, upper respiratory tract infection.

Most likely, in a previously continent child, urinary and fecal incontinence is caused by the cholinergic-mediated sphincteric relaxation consequent to the systemic spread of BoNT-A [51]. In fact, in our analysis, this complication was reported in 72 children, most of them treated for lower limb CP. Despite some authors warn about the potential local effect in children receiving injections in lower limb proximal muscles [61,77–79], the possibility of toxin spread and chemical denervation of distant muscles must also be considered [10,14,59]. De Coulon *et al.* [79] found that BoNT-A-injected gastrocnemius and soleus muscles had increased signal intensity on the MRI performed more than 2 years after the first injection, when compared with the contralateral, not placebo injected (NaCl) leg; no studies have investigated the changes induced in muscle structures in ambulatory children with CP managed by BoNT-A injections.

Some of the AEs such as vomiting and nausea seem to be more strongly related to the drugs administered during sedation or general anesthesia as nitrous oxide, for instance [17].

Similarly, few studies reported AEs that are unlikely related to the procedure. Koman *et al.* [32] observed 19 serious AEs, but none were related to BoNT-A according to the authors. The unrelated AEs included ear infections

Fig. 2



Percentages of distribution of AEs in the included studies. AE, adverse effect.

(32%), common colds (27%), flu symptoms (16%), upper respiratory infections (15%), fever (12%), cough (10%), and chicken pox (9%). However, several other studies reported similar complications [43,54,63,66].

Koman *et al*. [32] also reported one case of death in their multicenter, open-label clinical trial involving CP children with equinus foot deformity. The death was attributable to herpes simplex encephalopathy and, therefore, was unrelated to the treatment procedure.

In two other studies included in our review, fatal complications were reported. During the trial of Graham *et al*. [42], the two children in the intervention group died at 3.1 weeks and 26.4 weeks after injection of BoNT-A. In both cases, autopsy findings suggested that the deaths resulted from asphyxiation related to epilepsy. Similarly, Paget *et al*. [68] reported the death of a patient who received BoNT-A injection 28 days before as part of palliative treatment for severe intractable dystonia and in which death was already an expected event.

O'Flaherty *et al*. [61] assessed changes in health status before and after, as well as AEs after BoNT-A injections, reporting complications in 23.2% of children. Although all AEs were temporary, attention was paid to 'sentinel' events such as worsening dysphagia, generalized weakness, death, and LRTI, including in this group either lower respiratory tract issues of infection, aspiration, and asthma. Since all LRTIs occurred in children classified as GMFCS level IV or V, the authors were vigilant about the increased susceptibility of these categories of patients. In fact, patients GMFCS level IV or V is known to have increased respiratory problems and dysphagia, and all children who experienced an LRTI or worsening of dysphagia after BoNT-A had preexisting dysphagia.

Surprisingly, very few studies analyzed the incidence of AEs in relation to GMFCS level (Table 6). Despite GMFCS level has been suggested to be associated with increased rates of adverse events and unplanned hospital admissions after BoNT-A injections [51,62], none of the studies reporting results on spasticity treatment of lower or upper limb only describes any specific relationship between AEs and GMFCS. As a result, the wide heterogeneity of the data did not allow the identification of a cause-and-effect relationship between the type and incidence of AEs and the severity of CP according to the GMFCS scale. Paget *et al*. [68] found no statistically significant association between GMFCS level and systemic adverse events, suggesting that the severity of CP should be measured in terms of comorbidities such as dysphagia and aspiration pneumonia rather than GMFCS level when considering the increased risk of systemic adverse events of BoNT-A [68]. Similarly, Coté *et al*. [80] reported that AEs occurred predominantly in female patients when BoNT-A was used therapeutically rather

Table 6 Studies reporting incidence of adverse effects according to GMFCS level

Study	AEs	AEs according to GMFCS
O'Flaherty *et al.* [61]	139 (23%)	GMFCS I 18.1% GMFCS II 26.1% GMFCS III 12.9% GMFCS IV 19.6% GMFCS V 23.1%
Papavasiliou *et al.* [62]	52 (3%)	Deep sedation, swallow breathing and decreased O_2 saturation in 5 GMFCS V (AEs conscious sedation-related) Disturbance in swallowing in 1 GMFCS II, 1 GMFCS IV and 1 GMFCS V
Blaszczyk *et al.* [67]	95 (61%)	Generalized muscle weakness and/or fatigue: GMFCS I–III 32% GMFCS IV–V 68% Change in treatment due to AEs: 1 GMFCS I 2 GMFCS II 3 GMFCS V
Paget *et al.* [68]	77 (3.6%)	Among the 19 patients hospitalized: 12 LRTI (1 GMFCS I; 2 GMFCS IV; 9 GMFCS V) 2 dysphagia (GMFCS III; GMFCS V) 2 dysphagia + LRTI (GMFCS V) 1 prolonged decreased LOC (GMFCS IV) 1 generalized weakness + LRTI (GMFCS V) 1 death (GMFCS V)

AEs, adverse effects; LOC, level of consciousness; LRTI, lower respiratory tract issue.

than cosmetically and emphasized the role of underlying conditions predisposing to AEs more than the drug itself.

During our review process, we encountered some limitations: (a) retrospective, prospective and longitudinal cohort studies, as well as reviews, were included; (b) the number of patients and follow-up length were considerably heterogeneous; (c) procedure details, patient characteristics, and AEs peculiarities were not always specified, causing inaccuracies in the analysis of the data; and moreover, (d) in some studies, the incidence of AEs was based on the number of treated patients, whereas in others, the total number of AEs was related to the total number of treatments, leading to considerably lower AE rates.

Conclusion

Therefore, as severe AEs are not common, further research (very large randomized controlled trials) is needed in order to collect more clinical and homogeneous data to support the findings of the present research and to clarify the BoNT-A safety profile, especially regarding the incidence of respiratory issues and complications in GMFCS IV or V patients. In addition, since BoNT-A injections are very common [8,9], there is a great need for standardized procedures.

Nevertheless, a conscious and reflective approach based on the accurate assessment of treatment goals, indications for using Botulinum toxin A, potential benefits, and risks remains fundamental for optimal management of children with CP.

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Conflicts of interest

There are no conflicts of interest.

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