Botulinum Toxins Type A (Bont-A) in the Management of Lower Limb Spasticity in Children: A Systematic Literature Review and Bayesian Network Meta-analysis

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Abstract

Background: Botulinum neurotoxins type A (BoNT-As) are used in pediatric lower limb spasticity, which affects more than 2.5 million children worldwide. Botulinum neurotoxins type-A improve active function and delay musculoskeletal complications. The objective of this analysis was to evaluate the efficacy and safety of abobotulinumtoxinA versus other botulinum neurotoxins type A in pediatric spasticity, in the absence of head-to-head evidence. **Methods:** A systematic literature review was conducted to identify relevant randomized controlled trials. The evidence base was synthesized with Bayesian network meta-analyses. Outcomes analyzed included Modified Ashworth Scale, Tardieu Scale (TS) spasticity grade, and Goal Attainment Scale (standard mean difference only) at 12 weeks postinjection, and adverse events occurring during study periods. **Results:** Thirty-eight studies were identified, 10 of which met inclusion criteria for quantitative synthesis. On Modified Ashworth Scale, abobotulinumtoxinA 15 U/kg/leg was significantly more efficacious than onabotulinumtoxinA 4 U/kg/leg (−0.99 [−1.34, −0.64]) and onabotulinumtoxinA 4 U/kg/leg+casting (−0.81 [−1.16, −0.46]) and numerically better than onabotulinumtoxinA 8 U/kg (−0.40 [−0.67, −0.14]). AbobotulinumtoxinA 10 U/kg/leg was significantly more efficacious than onabotulinumtoxinA 4 U/kg/leg (± casting). On Goal Attainment Scale, abobotulinumtoxinA 15 U/kg/leg and 10 U/kg/leg were significantly more efficacious than onabotulinumtoxinA 12 U/kg/leg. On Tardieu Scale spasticity grade, abobotulinumtoxinA was comparable to other treatments. AbobotulinumtoxinA demonstrated adverse event rates comparable to all doses of onabotulinumtoxinA. **Conclusions:** In pediatric lower limb spasticity, abobotulinumtoxinA offered significant or numerical efficacy advantages on tone (Modified Ashworth Scale) and functional outcomes (Goal Attainment Scale), and comparable efficacy on Tardieu Scale spasticity grade. AbobotulinumtoxinA was comparable to onabotulinumtoxinA on tolerability. Results should be interpreted in the context of heterogeneity and sparsity of the evidence base.

Keywords
botulinum toxin type A, spasticity, systematic review, network meta-analysis

Spasticity is defined as hypertonia in which the resistance to externally imposed movement increases with increasing speed of stretch.[1] Cerebral palsy is the most common condition associated with spasticity in children and adolescents and affects more than 2 children per 1000 live births.[2] Cerebral palsy is the leading cause of childhood disability affecting function and development, and up to 80% of children with cerebral palsy present with spasticity.[3]

Treatment options for spasticity in cerebral palsy include casting, passive stretching, facilitation of posture and movement, spasticity-reducing oral medication (baclofen, diazepam, clonazepam, dantrolene and tizanidine), surgery, and botulinum neurotoxin type A (BoNT-A). The American Academy

of Neurology recommended botulinum neurotoxin type A for localized/segmental lower limb spasticity in children with cerebral palsy.[4] Botulinum neurotoxin type A is used to reduce

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spasticity and muscle tone, facilitate mobility and dexterity, minimize contractures and deformities, facilitate brace use, reduce muscle pain and spasms, and improve patient ease of care, hygiene/self-care, and overall function.[4]

Globally, there are currently 3 commercially available injectable forms of botulinum neurotoxin type A, supplied as lyophilized powder: abobotulinumtoxinA (Dysport), onabotulinumtoxinA (Botox), and incobotulinumtoxinA (Xeomin).[5,6] AbobotulinumtoxinA was first registered for the treatment of blepharospasm and hemifacial spasm in the United Kingdom in 1990 and is now licensed in many countries for various indications, including pediatric lower limb spasticity due to cerebral palsy in Europe[7] and the United States.[8] OnabotulinumtoxinA has also been approved for many indications including pediatric dynamic equinus foot deformity due to spasticity in Europe.[9] IncobotulinumtoxinA has been approved in Europe and United States for various indications in adults but not yet for pediatric lower limb spasticity.[10,11]

Both abobotulinumtoxinA and onabotulinumtoxinA have demonstrated an established efficacy and safety profile in pediatric lower limb spasticity. In a recent large (n = 241) pediatric lower limb spasticity phase III study[12] in children with hemiparetic, diplegic, or tetraplegic cerebral palsy, abobotulinumtoxinA showed a significantly higher response rate versus placebo on the muscle tone improvement measured with the Modified Ashworth Scale, and a significant overall improvement versus placebo measured with the Physician Global Assessment. For onabotulinumtoxinA, a recent large clinical trial (N = 384) was presented at the American Academy of Neurology conference in April 2018.[13] It demonstrated a significant change from baseline on Modified Ashworth Scale-ankle score at weeks 4 and 6 compared to baseline for both doses (though nonsignificant at weeks 10 and 12). Earlier studies showed a better efficacy of botulinum neurotoxin type A compared to a standard of care: for abobotulinumtoxinA as measured by video gait analysis[14] and knee-knee distance[15] and for onabotulinumtoxinA as measured by dynamic gait pattern composite score,[16] Tardieu Scale and surface electromyography,[17] or Canadian occupational performance measure.[18] Various outcomes and scales were used to measure efficacy in these pediatric lower limb spasticity studies. While studies versus placebo/standard of care remain to be an important starting point, evidence-based health care decision making often requires comparison to alternative active interventions. In the absence of head-to-head studies involving a direct comparison of relevant interventions, network meta-analysis and indirect treatment comparisons provide useful evidence.[19]

The objective of this network meta-analysis was to evaluate the relative efficacy and tolerability of botulinum neurotoxin type A treatments for spasticity in children with cerebral palsy by means of Bayesian network meta-analyses of randomized controlled trials identified through a systematic literature review.

Methods

Systematic Literature Review

A systematic literature review was performed using a predefined search strategy (Figure 1 and Appendix A) to identify randomized controlled trials reporting efficacy and safety outcomes of treatment in children with spasticity. Medline, Medline In-Process, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), and Database of Abstracts of Reviews of Effects (DARE) were searched in March 2016 without restriction on publication year; CENTRAL and CDSR as well as 2 conference websites (the International Conference of Cerebral Palsy [ICPC] and other Childhood-onset Disabilities [EACD] and the International Neurotoxin Association [INA-TOXINS]) were searched from January 2014 to June 2016. The trial registry clinical trials.gov was also searched.

All retrieved records were screened using prespecified criteria (Appendix B). The population of interest included children (≤18 years) with spastic symptoms. Interventions of interest were any pharmacologic treatments including botulinum neurotoxin type A.

A further targeted literature review was conducted in August 2018 to assess whether additional studies meeting the prespecified selection criteria had been published since the original search in June 2016.

For each citation identified, abstracts were screened for eligibility by 2 independent researchers, and for those fulfilling the selection criteria, full texts were retrieved and assessed. Any disagreements were resolved by a third party. Full-text articles and abstracts that met the inclusion criteria were included for data extraction, and every study was critically appraised using the NICE critical appraisal tool for assessing risk of bias.[20] Details on study design, baseline patient characteristics, and outcomes results were extracted in a predefined Excel spreadsheet.

The feasibility of the network meta-analysis was assessed following the recommendations by Cope et al.[21]

Network Meta-analysis

The relative efficacy and tolerability of treatments was evaluated using Bayesian network meta-analysis.[22] A linear model with normal likelihood distribution was used for continuous outcomes and a binomial likelihood with a logit link for dichotomous outcomes. For continuous outcomes, mean differences in change from baseline between pairwise treatments and the corresponding 95% credible intervals were obtained. For studies reporting change from baseline without an associated sampling variance, standard errors were imputed based on available data. For binary outcomes, odds ratios with 95% credible intervals were estimated.

Noninformative prior distributions were assumed for all outcomes. For credible intervals that did not include 0 (for continuous outcomes) or 1 (for binary outcomes), results were considered statistically significant.[23] Prior normal distributions of the relative treatment effects were assumed normal, with zero as a mean and a variance of 10 000, whereas a uniform distribution [0, 5] was used for the between-study standard deviation in the random effects models.

Fixed and random effects models were evaluated for each outcome, with the latter allowing a certain degree of variation in patient populations, when the variation does not concern treatment effect modifiers.[19,24,25] The model selection was based on the deviance information criterion[26] and convergence. Posterior densities were estimated using Markov-chain Monte Carlo simulations based on 80 000 iterations on 2 chains, with a burn-in of 20 000 iterations. All models
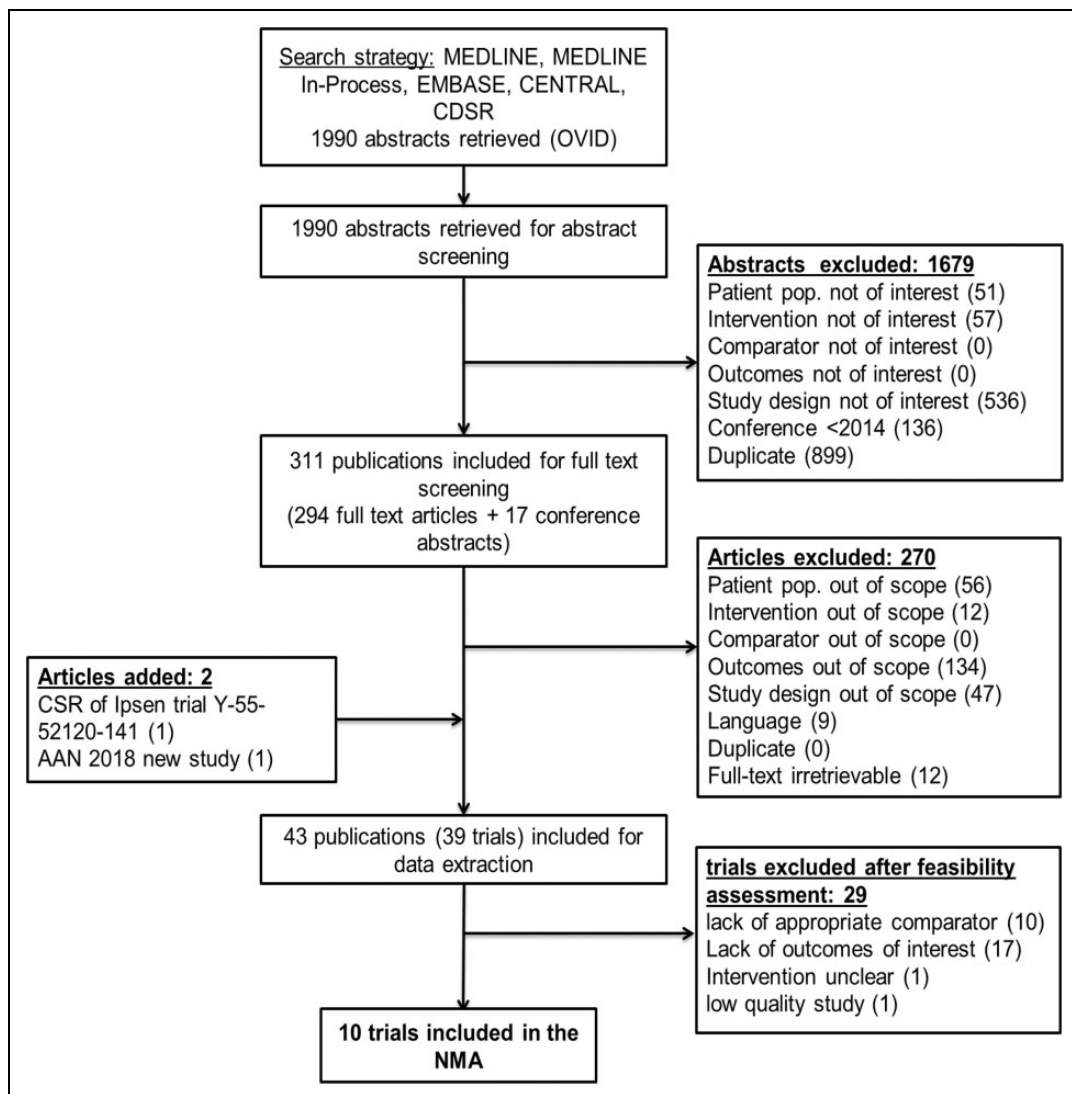
Figure 1. Study selection flow chart.

were implemented using the OpenBUGS version 3.2.2 software package and R version 3.3.2, and were based on the models defined by Dias et al.[26] For each outcome, posterior distributions of relative treatment effects between interventions were obtained, as well as a probability for one treatment being better than another.[26] Ranking probabilities based on surface under the cumulative ranking curve were calculated per treatment.[27] The surface under the cumulative ranking curve values range from 0 to 100%, with 100% meaning that the therapy is expected to be the best treatment.

To study potential risk of bias due to variation in treatment effect modifiers, several scenario analyses were defined a priori after feasibility assessment, addressing (1) variability in doses studied and (2) variability in adverse events' outcomes definitions. The scenarios are explained in detail in the next section.

Results

Evidence Base and Network Meta-Analysis Feasibility

Of the 1990 abstracts identified by the database search, 1679 were excluded as not meeting selection criteria and hence

irrelevant to our meta-analysis. The remaining 311 publications (294 full-text articles and 17 conference abstracts) were retained for a more detailed evaluation against the inclusion criteria (Appendix B). The PRISMA flowchart is presented in Figure 1 and the overall network is presented in Figure 2. Ten of the 38 individual randomized controlled trials (described in 42 publications) included for data extraction met all inclusion criteria and were included in the network meta-analysis. In addition, the study[13] found by hand search in the American Academy of Neurology 2018 conference abstracts (stated as completed in clinicaltrials.gov [NCT01603628]) was added to the network meta-analysis.

The interventions investigated in these selected studies included abobotulinumtoxinA and onabotulinumtoxinA at different dosages (abobotulinumtoxinA 10, 15, and 30 U/kg/leg, onabotulinumtoxinA at 0.5 to 4, 2.8 to 7.3, 3, 4, and 12 U/kg/leg or 4 U/kg/leg+casting). The targeted literature review performed in August 2018 did not identify any further studies that met the predefined inclusion criteria.
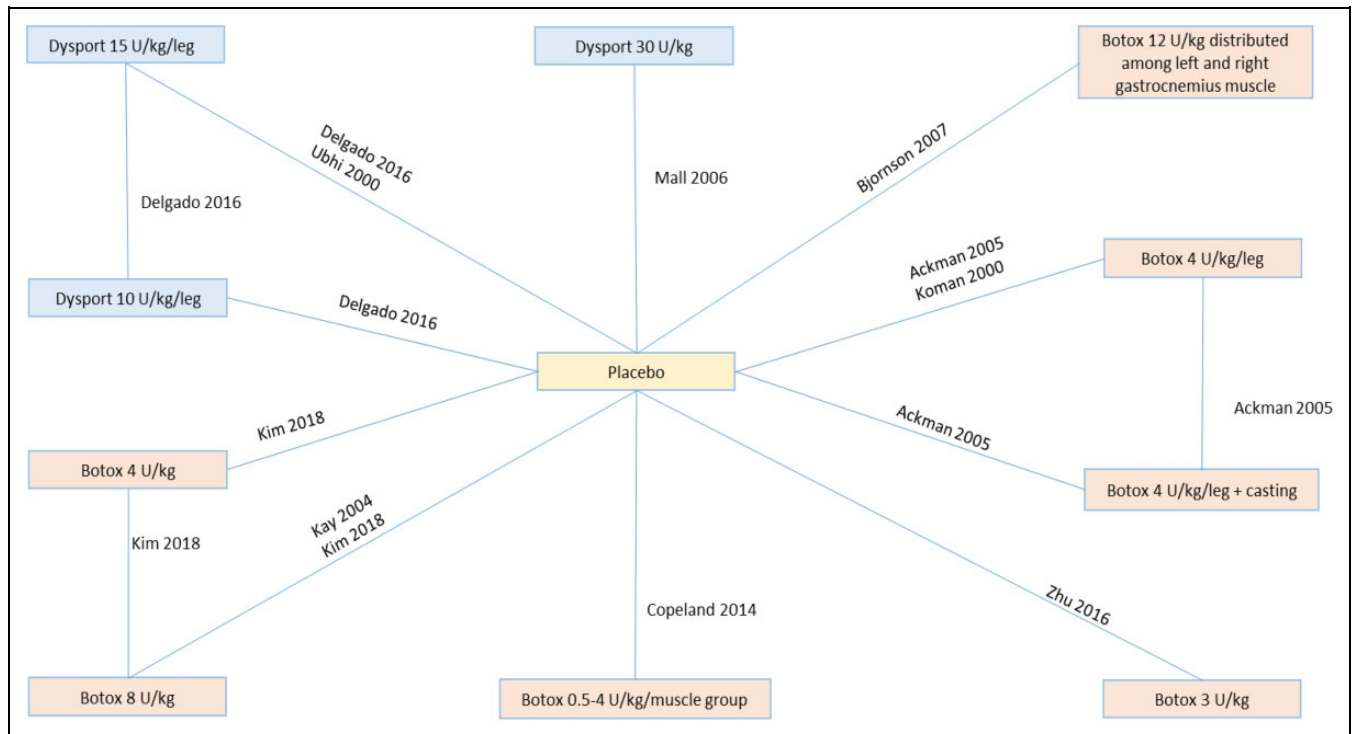
Figure 2. Network of studies, all outcomes considered.

At the feasibility assessment step, 29 studies were excluded. Eleven studies had an intervention of interest but could not be linked to the rest of the network because of a lack of a common comparator with the other studies and were therefore excluded. Seventeen studies were excluded because of no outcome of interest. Eleven studies were then assessed for network meta-analysis feasibility, and 1 study[28] was deemed of too low quality and excluded.

The feasible efficacy endpoints of interest (those that were common for at least 2 studies on both interventions of interest) for the network meta-analysis were Modified Ashworth Scale, Tardieu Scale spasticity grade, and Goal Attainment Scale. Other potentially relevant endpoints such as physician's global assessment and observational gait scale did not meet the feasibility assessment, as it was not possible to form a network including both abobotulinumtoxinA and onabotulinumtoxinA treatment arms with the available evidence. In the base case, tolerability was assessed based on any adverse events reported in the final study pool.

For the Modified Ashworth Scale, the percentages of responders ($\geq$1-point change) for abobotulinumtoxinA and onabotulinumtoxinA were derived from the change from baseline point estimate as well as the 95% credible intervals. Change from baseline in Modified Ashworth Scale score was assumed to follow a normal distribution with a mean of 1 unit and a standard deviation equal to the average of the reported standard deviations.

Twelve weeks was chosen as the time point of interest, considering that it was the most common time point reported

across the studies, allowing to build a more powerful network of comparisons.

The major characteristics of the 11 included studies (10 studies retained from the systematic literature review and the recent study retrieved from the American Academy of Neurology 2018 abstract book) are presented in Appendix C (Table 1). The study locations were diverse, including: 1 international study[12], 2 US,[29,30] 2 Australian,[18,28] 2 European,[14,15] 1 Chinese,[17] and 3 unspecified.[13,16,31] The 11 studies were published between 2000 and 2018, with a study duration of between 12 and 26 weeks (9 studies), with the exception of 2 studies[29,30] that had a duration of 52 weeks. The number of patients ranged from 11 to 130 patients per treatment arm, with 8 studies having fewer than 40 patients per treatment arm, and only 2[12,16] having more than 40 patients per treatment arm.

Patient characteristics are presented in Appendix C (Table 2). Mean age ranged from 1.7 to 7.4 years and the percentage of male patients ranged from 38% to 80%. Modified Ashworth Scale score at baseline ranged from 2.4[29] to 3.5.[13] In 4 studies,[14,16,17,31] all patients were botulinum neurotoxin type A naïve, whereas in another study[12] only half of the patients were botulinum neurotoxin type A naïve, and in the other 6 studies[13,15,18,28-30] no information on prior botulinum neurotoxin type A usage was reported. All patients in 3 studies[13,17,31] and some patients in 2 studies[12,30] (between 42% and 72%) received concomitant physiotherapy; the information was not reported in the other 6 studies.[14-16,18,28,32] Concomitant orthosis/casting was given to all patients in 2 of the 3 treatment arms in 1 study,[29] in all arms in another study[30] and some patients in

Table 1. Base Case Analysis: Pairwise Treatment Comparisons (Mean Change From Baseline, 95% Crl and Probability Being Better Treatment) for Modified Ashworth Scale at 12 Weeks.

		Placebo		Ona 4 U/kg/leg		Ona 4 U/kg/leg + casting		Ona 4 U/kg		Ona 8 U/kg		Abo 10 U/kg/leg	
Ona 4 U/kg/leg	Mean CFB	0.49											
	95% Crl	0.24	0.74										
	P_{better}	0%											
Ona 4 U/kg/leg+ casting	Mean CFB	0.31		−0.18									
	95% Crl	0.06	0.55	−0.39	0.04								
	P_{better}	1%		95%									
Ona 4 U/kg	Mean CFB	−0.10		−0.59		−0.41							
	95% Crl	−0.19	−0.01	−0.86	−0.32	−0.67	−0.15						
	P_{better}	98%		>99%		>99%							
Ona 8 U/kg	Mean CFB	−0.10		−0.59		−0.41		0.00					
	95% Crl	−0.19	−0.01	−0.85	−0.32	−0.67	−0.15	−0.10	0.10				
	P_{better}	98%		>99%		>99%		48%					
Abo 10 U/kg/leg	Mean CFB	−0.30		−0.79		−0.61		−0.20		−0.20			
	95% Crl	−0.60	0.001	−1.18	−0.40	−1.00	−0.22	−0.52	0.11	−0.52	0.11		
	P_{better}	97%		>99%		>99%		89%		90%			
Abo 15 U/kg/leg	Mean CFB	−0.50		−0.99		−0.81		−0.40		−0.40		−0.20	
	95% Crl	−0.75	−0.25	−1.34	−0.64	−1.16	−0.46	−0.67	−0.13	−0.67	−0.14	−0.47	0.08
	P_{better}	>99%		>99%		>99%		>99%		>99%		92%	

Abbreviations: CFB, change from baseline; Crl, credible interval.
Cells highlighted in gray indicate that intervention is significantly better than the comparator; cells highlighted in dark gray indicate that intervention is significantly inferior than the comparator, and cells without shading show comparable results between intervention and comparator.

Table 2. Base Case Analysis: Pairwise Treatment Comparisons (Mean, 95% Crl and Probability Being Better Treatment) for GAS at 12 Weeks.

		Placebo		Ona 12 U/kg		Abo 10 U/kg/leg	
Ona 12 U/kg	Mean CFB	0.00					
	95% Crl	−1.19	1.19				
	P_{better}	50.0%					
Abo 10 U/kg/leg	Mean CFB	6.73		6.73			
	95% Crl	2.70	10.74	2.50	10.91		
	P_{better}	100.0%		100.0%			
Abo 15 U/kg/leg	Mean CFB	4.71		4.72		−2.01	
	95% Crl	0.77	8.70	0.61	8.88	−5.92	1.95
	P_{better}	99.0%		99.0%		16.0%	

Abbreviations: CFB, change from baseline; Crl, credible interval; GAS, Goal Attainment Scale.
Cells highlighted in gray indicate that intervention is statistically significantly better than the comparator, and cells without shading indicate comparable results between intervention and comparator.

2 studies[12,18] (between 49% and 72%). Prior and concomitant treatments were unclear in most of the studies. Love et al[28] did not report any patient characteristics.

The results of the critical appraisal of identified studies are shown in Appendix C (Table 3). All studies were double-blind, except Zhu et al.[17] Only half of the studies reported the randomization process. The allocation concealment was adequate in 4 and unclear in 7 trials. Although the information was not clearly reported across the studies, 10 of the 11 studies were deemed of good quality. The study by Love et al[28] was an exception, because of a particular lack of clarity on the critical questions for the quality assessment of the study design. This was a small study, including 12 patients per arm. This study reported only Modified Ashworth Scale scores at 12 weeks, and it was reported as a mean difference between treatments; thus, there was no possibility to check if the value of the control arm was in line with the other control arm values. Furthermore, the patients in Love et al[28] were less involved, with only patients with a Gross Motor Function Classification System level 1 included, in contrast to other studies that included Gross Motor Function Classification System levels from 1 to 3 or 4. For all these reasons, the Love et al study was excluded from the analyses. The remaining 10 studies were included in the network meta-analysis.

A network was developed to connect the 10 eligible randomized controlled trials (Figure 2). The different dosages of abobotulinumtoxinA and onabotulinumtoxinA were considered as different treatments in the network meta-analysis. Most treatments were linked in the overall network by only 1 randomized controlled trial. There was no head-to-head study comparing the key alternative treatment options (ie, abobotulinumtoxinA and onabotulinumtoxinA). Placebo in this network meta-analysis was defined as placebo and/or physiotherapy and/or orthosis and/or oral drug.

As the next step, the networks per outcome were constructed, as presented in Appendix D. The number of studies included in outcome-specific networks was relatively small; 2 studies[12,31] reported Tardieu Scale spasticity grade at 12 weeks; 3 studies[12,15,31] reported Goal Attainment Scale scores at 12 weeks, and 6 studies[12,13,28-31] reported Modified Ashworth Scale scores at 12 weeks. Five studies[12,13,16,18,29] reported adverse events. Delgado et al[12] was the only study assessing all outcomes of interest.[33]

Table 3. Base Case Analysis: Pairwise Treatment Comparisons (Mean, 95% CrI and Probability Being Better Treatment) for Tardieu Scale Spasticity Grade at 12 Weeks.

		Placebo	Ona 3 U/kg	Abo 10 U/kg/leg
Ona 3 U/kg	Mean CFB	−0.70		
	95% CrI	−1.10 −0.31		
	P_{better}	100%		
Abo 10 U/kg/leg	Mean CFB	−0.40	0.30	
	95% CrI	−0.62 −0.18	−0.15 0.76	
	P_{better}	100%	10%	
Abo 15 U/kg/leg	Mean CFB	−0.40	0.30	0.00
	95% CrI	−0.62 −0.18	−0.15 0.76	−0.22 0.22
	P_{better}	100%	10%	50%

Abbreviations: CFB, change from baseline; CrI, credible interval.
Cells highlighted in gray indicate that intervention is statistically significant better than the comparator, and cells without shading indicate comparable results between intervention and comparator.

There were differences across studies in measuring specific outcomes. For instance, Delgado et al[12] reported Goal Attainment Scale scores at 12 weeks, whereas Bjornson et al[31] reported Goal Attainment Scale score change from baseline at 12 weeks. However, both studies were included in the base case in accordance with the *Cochrane Handbook*,[34] stating that studies with change from baseline outcomes could be combined in a meta-analysis with studies with final measurement outcomes when using the (unstandardized) mean difference method. In Mall et al,[15] the Goal Attainment Scale score was not reported because the overall Goal Attainment Scale T scores and the Goal Attainment Scale–defined goals were unrealistic or invalid as stated in the CSR of this study.[35] In Kim et al,[13] the Goal Attainment Scale score was reported as active and passive functional goal attainment rather than an overall score. Furthermore, Bjornson et al[31] reported results on the original Ashworth Scale rather than the Modified Ashworth Scale, as confirmed by personal correspondence with the authors. In addition, adverse events were self-reported by the patients in 1 study[16] whereas they were systematically collected by a health care provider for the 3 other studies.[12,18,29] The definition was treatment-emergent adverse events in Delgado et al[12] extracted from the CSR[33] and treatment related in the publication, definitely or probably related to injection in Copeland et al,[18] and probably, possibly, or remotely treatment related in Koman et al,[16] whereas no definition for adverse events was given in Ackman et al.[29] There was a high variation in the percentage of patients experiencing at least 1 adverse event, with percentages varying from 0% to 83% in the placebo arms.

Two scenarios described below were implemented to test the robustness of the results, in the light of the reported variabilities across studies:

In scenario analysis 1, all doses were pooled together by intervention (ie, placebo, onabotulinumtoxinA or abobotulinumtoxinA). This scenario aimed at minimizing an uncertainty around the estimates of treatment effect and assessing a compiled relative treatment effect of onabotulinumtoxinA and abobotulinumtoxinA. Scenario 1 was performed for outcome-specific networks including more than one dose of each botulinum neurotoxin type A, that is, for Modified Ashworth Scale score and adverse events.

Scenario analysis 2 concerned only adverse event outcomes. In the base case, tolerability assessment was based on any adverse events reported across the final study pool (including treatment-emergent adverse events reported in Delgado et al,[12] retrieved from the CSR). Scenario analysis 2 was restricted to treatment-related adverse events, reported in the underlying studies.

Network Meta-analysis Results

Because of the low number of studies included, and the fact that most trials were small, the "default" practice of using vague priors for the between-trial standard deviation was likely to result in posteriors with unrealistically high levels of heterogeneity. The solution advised by NICE[36] in this case is to use informative priors, based on expert opinion or on meta-epidemiologic data. This could not be applied as no references of informative priors in spasticity were found.

It was therefore decided to focus on the fixed effects models. In addition, an inconsistency check was not deemed necessary as the closed loops correspond only to 3 arm studies; hence, it is direct evidence alone.

All outcome-specific networks are presented in Appendix D, and all individual study data are presented in Appendix E.

In the base case, abobotulinumtoxinA 15 U/kg/leg was found to be significantly better than placebo for Modified Ashworth Scale, Goal Attainment Scale, and Tardieu Scale spasticity grade outcomes at week 12 (−0.50 [−0.75, −0.25], 4.71 [0.77, 8.70], and −0.40 [−0.62, −0.18], respectively) and abobotulinumtoxinA 10 U/kg/leg was found significantly better than placebo for Goal Attainment Scale and Tardieu Scale spasticity grade (6.73 [2.70, 10.74] and −0.40 [−0.62, −0.18], respectively) All related pairwise comparison results are presented in Tables 1, 2, and 3, respectively. OnabotulinumtoxinA 4 and 8 U/kg were found comparable to placebo, whereas onabotulinumtoxinA 4 U/kg/leg and onabotulinumtoxinA 4 U/kg/leg+casting were found to be inferior (statistically significant) than placebo for Modified Ashworth Scale (0.49 [0.24, 0.74] and 0.31 [0.06, 0.55], respectively; Table 1 and Figure 3). OnabotulinumtoxinA 12 U/kg was found comparable to placebo for Goal Attainment Scale (0.00 [−1.19, 1.19]; Table 2 and Figure 4). OnabotulinumtoxinA 3 U/kg was found to be better than placebo for Tardieu Scale spasticity grade (−0.70 [−1.10, −0.31]; Table 3 and Figure 5). For adverse events, abobotulinumtoxinA 15 U/kg/leg and abobotulinumtoxinA 10 U/kg/leg were found to be comparable to placebo (1.59 [0.85, 2.98] and 1.81 [0.99, 3.36], respectively), whereas

onabotulinumtoxinA 4 U/kg/leg was significantly inferior to placebo on occurrence of any adverse events (4.00 [1.32, 15.02]; Figure 6 and Appendix F).

Standard pairwise meta-analyses were performed to assess the pooled effect of active intervention versus placebo when this was feasible (when more than 1 study connected 2 interventions in networks per outcomes): onabotulinumtoxinA 8 U/kg for change from baseline Modified Ashworth Scale scores (Figure 7), abobotulinumtoxinA 15 U/kg/leg (Figure 8), and onabotulinumtoxinA 4 U/kg/leg (Figure 9) for adverse events. The pooled mean difference in Modified Ashworth Scale score was –0.1 [–0.19, –0.01] for onabotulinumtoxinA 8 U/kg versus placebo ($I^2 = 0\%$). The pooled odds ratio of adverse events was 1.7 [0.93, 3.23] ($I^2=30\%$) for abobotulinumtoxinA 15 U/kg/leg versus placebo and 3.7 [1.12, 12.17] ($I^2 = 0\%$) for onabotulinumtoxinA 4 U/kg/leg versus placebo. These results were consistent with the network meta-analysis results.

For Modified Ashworth Scale score at week 12, abobotulinumtoxinA 15 U/kg/leg was found to be significantly better compared to onabotulinumtoxinA 4 U/kg/leg (–0.99 [–1.34, –0.64]), onabotulinumtoxinA 4 U/kg/leg+casting (–0.81 [–1.16, –0.46]), onabotulinumtoxinA 4 U/kg (–0.40 [–0.67, –0.13]), and onabotulinumtoxinA 8 U/kg (–0.40 [–0.67, –0.14]). The mean difference of change from baseline Modified Ashworth Scale scores was in favor of abobotulinumtoxinA 15 U/kg/leg, with a mean difference almost equal to 1 unit. AbobotulinumtoxinA 10 U/kg/leg was found to be significantly better compared to onabotulinumtoxinA 4 U/kg/leg (–0.79 [–1.18, –0.40]), onabotulinumtoxinA 4 U/kg/leg+casting (–0.61 [–1.00, –0.22]) and numerically (although not statistically significant) better than onabotulinumtoxinA 8 U/kg (–0.20 [–0.52, 0.11], $P_{better}=89\%$; Table 1).
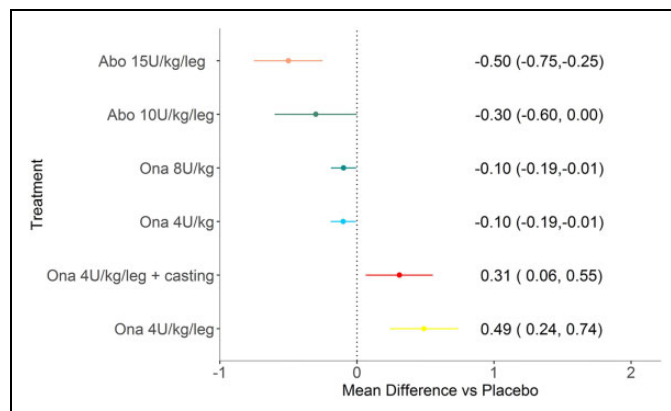

Figure 3. Forest plot: network meta-analysis for Modified Ashworth Scale score change from baseline in active treatments versus placebo at 12 weeks.
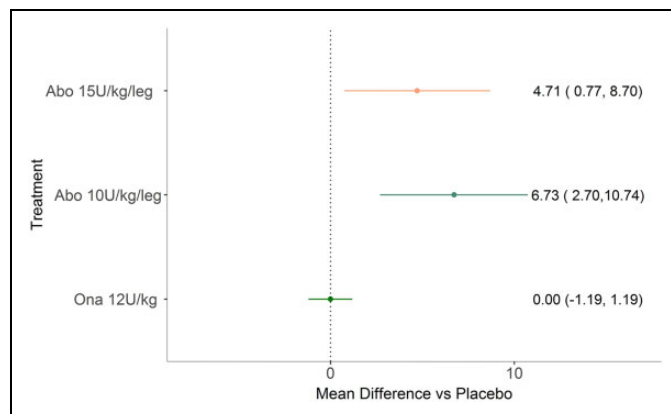

Figure 4. Forest plot: network meta-analysis for GAS score change from baseline in active treatments versus placebo at 12 weeks.
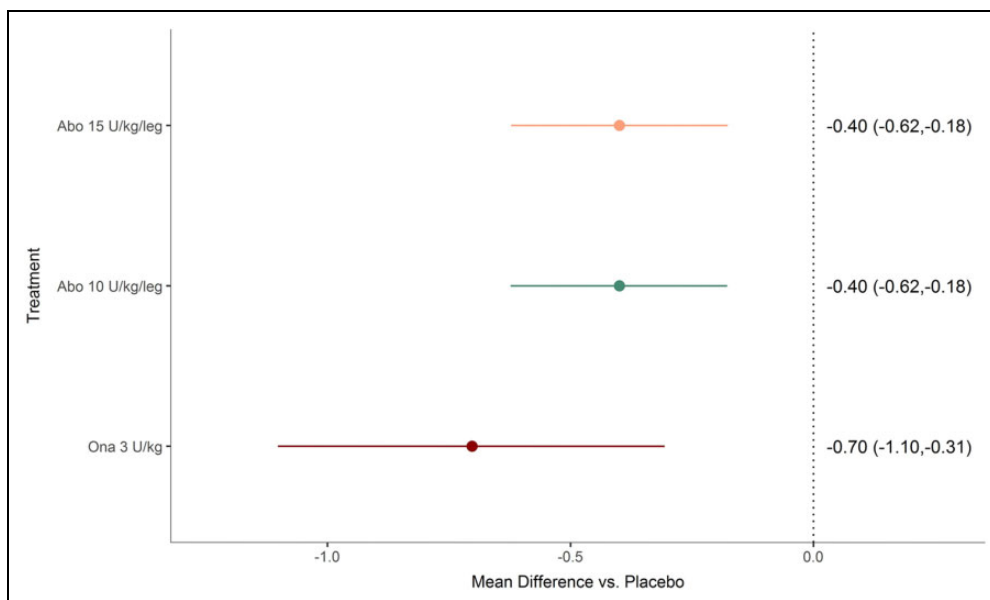

Figure 5. Forest plot: network meta-analysis for Tardieu Scale spasticity grade change from baseline in active treatments versus placebo at 12 weeks.
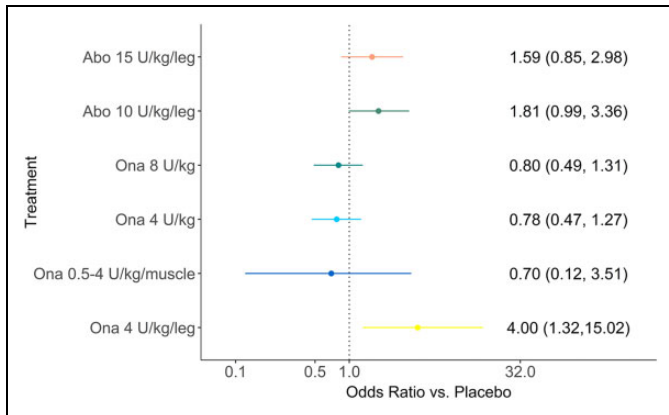
Figure 6. Forest plot: network meta-analysis for adverse events occurrence in active treatments versus placebo at 12 weeks.

Percentages of Modified Ashworth Scale responders and their 95% credible intervals were derived using a normal distribution, with a mean of 1 unit and a standard deviation of 1.04 (average of reported standard deviations in Delgado et al[12] and Kay et al[30]) and median Modified Ashworth Scale score change from baseline with their 95% credible intervals (median change from baseline or median absolute effects are in Appendix G). Percentages of responders were 53.8% (38.1%, 68.9%) for abobotulinumtoxinA 15 U/kg/leg, 46.1% (30%, 63.1%) for abobotulinumtoxinA 10 U/kg/leg, 38.5% (26.6%, 51.3%) for onabotulinumtoxinA 8 U/kg, 38.5% (26.7%, 51.5%) for onabotulinumtoxinA 4 U/kg, 35% (24%, 47.2%) for placebo, 24.7% (14%, 38.6%) for onabotulinumtoxinA 4 U/kg/leg+casting and 19.6% (10.4%, 32.2%) for onabotulinumtoxinA 4 U/kg/leg. AbobotulinumtoxinA 15 U/kg/leg was found to
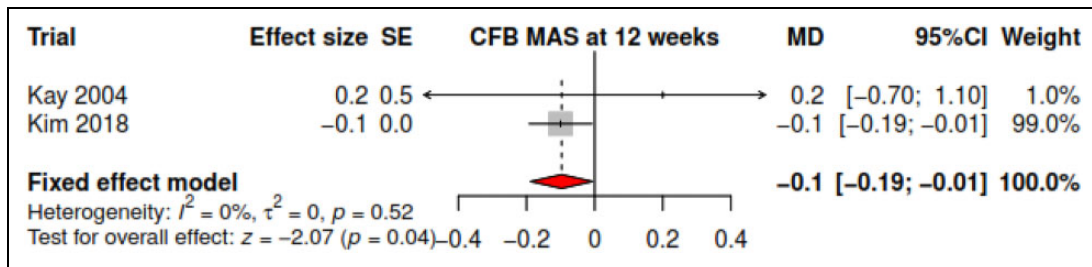

Figure 7. Forest plot: meta-analysis of onabotulinumtoxinA 8 U/kg versus placebo for Modified Ashworth Scale score change from baseline at 12 weeks.
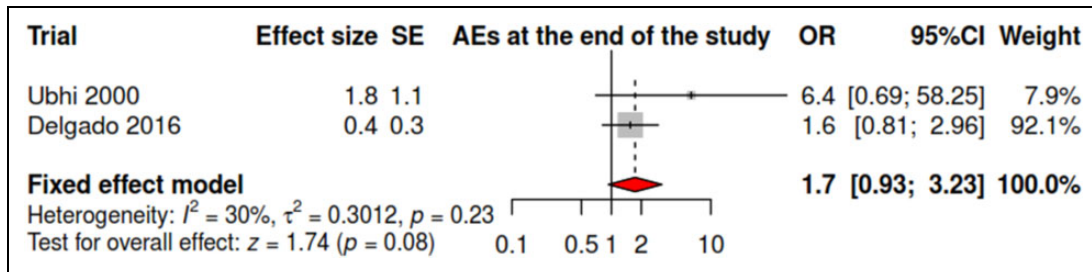

Figure 8. Forest plot: meta-analysis of abobotulinumtoxinA 15 U/kg/leg versus placebo for adverse events.
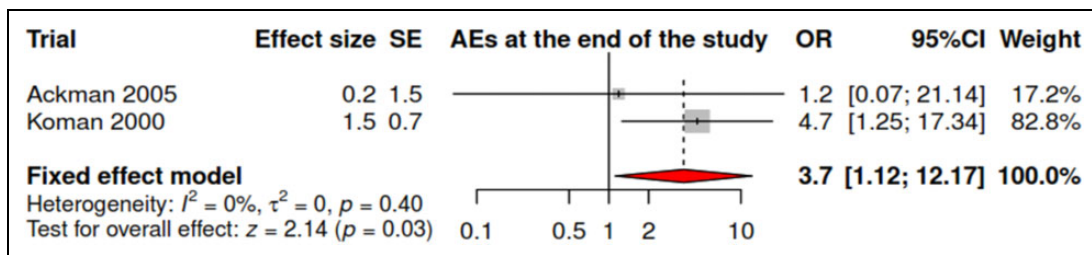

Figure 9. Forest plot: meta-analysis of onabotulinumtoxinA 4 U/kg/leg versus placebo for adverse events.

have the highest surface under the cumulative ranking curve value of 98.6%, followed by abobotulinumtoxinA 10 U/kg/leg (80.7%).

Scenario analysis 1, where all dosages were pooled, showed a favorable trend for abobotulinumtoxinA over onabotulinumtoxinA. All pairwise comparison results for the scenarios are presented in Appendix F.

For Goal Attainment Scale score at week 12, abobotulinumtoxinA 15 U/kg/leg and abobotulinumtoxinA 10 U/kg/leg were significantly better compared with onabotulinumtoxinA 12 U/kg (Table 2). AbobotulinumtoxinA 10 U/kg/leg showed the highest surface under the cumulative ranking curve (94.7%) value, followed by abobotulinumtoxinA 15 U/kg/leg (71.2%).

For Tardieu Scale spasticity grade at week 12, abobotulinumtoxinA 15 U/kg/leg and abobotulinumtoxinA 10 U/kg/leg were not significantly different from onabotulinumtoxinA 3 U/kg. OnabotulinumtoxinA 3 U/kg showed the highest surface under the cumulative ranking curve value, followed by abobotulinumtoxinA 10 U/kg/leg and abobotulinumtoxinA 15 U/kg/leg. Scenario analysis 1 showed consistent results (Table 3).

For adverse events, abobotulinumtoxinA 15 U/kg/leg and 10 U/kg/leg demonstrated fewer adverse events than onabotulinumtoxinA 4 U/kg/leg. OnabotulinumtoxinA 4 U/kg showed the highest surface under the cumulative ranking curve value followed by onabotulinumtoxinA 0.5 to 4 U/kg/muscle, and onabotulinumtoxinA 4 U/kg/leg showed the lowest surface under the cumulative ranking curve value on adverse events (worst safety profile). In scenario 1 (pooled doses), abobotulinumtoxinA was found to have comparable results to onabotulinumtoxinA in terms of adverse events. Scenario 2 showed consistent results to the base case. All pairwise comparison results for the base case and scenario are presented in Appendix F.

Discussion

The aim of this network meta-analysis was to evaluate the relative efficacy and safety of botulinum neurotoxin type A treatments in children with spasticity, based on the currently available randomized controlled trial evidence. The network meta-analysis was based on 10 randomized controlled trials for the base case analyses and 2 scenario analyses. The analyses were performed on Modified Ashworth Scale, Goal Attainment Scale, and Tardieu Scale spasticity grade outcomes and adverse events at 12 weeks. In the base case, and in consistency with scenario analyses, abobotulinumtoxinA 15 U/kg/leg and 10 U/kg/leg were significantly more efficacious than placebo for all efficacy outcomes (Modified Ashworth Scale score, Goal Attainment Scale score, and Tardieu Scale spasticity grade), which is in line with the findings from the pivotal study of abobotulinumtoxinA by Delgado et al.[12] Compared to onabotulinumtoxinA 4 U/kg/leg, in the base case analysis, abobotulinumtoxinA 15 U/kg/leg was found to be significantly more efficacious on Modified Ashworth Scale change from baseline at 12 weeks, with a mean difference almost equal to the 1-unit threshold used to define response in Delgado et al.[12]

AbobotulinumtoxinA 15 U/kg/leg was also more efficacious compared to onabotulinumtoxinA 4 U/kg, onabotulinumtoxinA 4 U/kg/leg+casting, and onabotulinumtoxinA 8 U/kg/leg. The same pattern of observed results was obtained for the comparison of abobotulinumtoxinA 10 U/kg/leg versus onabotulinumtoxinA 4 U/kg and 4 U/kg/leg+casting. For Goal Attainment Scale score at week 12, both doses of abobotulinumtoxinA were statistically significantly better than onabotulinumtoxinA 12 U/kg/leg. On Tardieu Scale spasticity grade, both doses of abobotulinumtoxinA were comparable to onabotulinumtoxinA 3 U/kg. AbobotulinumtoxinA 15 U/kg/leg showed the highest surface under the cumulative ranking curve values on the Modified Ashworth Scale and Goal Attainment Scale. On tolerability, both doses of abobotulinumtoxinA were found comparable to onabotulinumtoxinA 4 U/kg/leg and 0.5 to 4 U/kg/muscle. On tolerability, abobotulinumtoxinA demonstrated adverse event rates comparable to all doses of onabotulinumtoxinA.

This analysis was the first to compare indirectly and rank botulinum neurotoxin type A treatments in this disease area. It was based on a rigorously planned and performed systematic literature review identifying evidence from inception of databases to March 2016. This network meta-analysis provided estimates of relative efficacy and safety for abobotulinumtoxinA and onabotulinumtoxinA in the context of a lack of head-to-head randomized controlled trial evidence for children with spasticity. Two scenario analyses demonstrated the robustness of the findings.

However, there were several limitations to these analyses. The evidence base was limited, with only 10 randomized controlled trials included, where 7 of them had less than 30 patients per arm, whilst the number of treatment arms considered was relatively high (11 treatment options: abobotulinumtoxinA 30U/kg, abobotulinumtoxinA 15 U/kg/leg, abobotulinumtoxinA 10 U/kg/leg, onabotulinumtoxinA 12 U/kg, onabotulinumtoxinA 8 U/kg, onabotulinumtoxinA 4 U/kg/leg, onabotulinumtoxinA 4 U/kg/leg + casting, onabotulinumtoxinA 4 U/kg, onabotulinumtoxinA 3 U/kg, onabotulinumtoxinA 0.5 to 4 U/kg/muscle group and placebo). This led to a weak overall network in which most treatments were linked via placebo with 1 randomized controlled trial. The outcome networks were even smaller, as not all studies reported data on all outcomes. The limited number of studies restricted a number of possible scenarios and did not allow neither for incorporation of covariate analysis to adjust for potential treatment effect modifiers nor for risk of bias assessment since the power of the tests was too low to distinguish a chance from real asymmetry.[34] Furthermore, key clinical characteristics of patients (eg, baseline spasticity severity), and prior and concomitant treatments were unclear in most of the included studies. The efficacy and tolerability outcome measures or scales were also unclear and/or inconsistent in some of the included studies. There was a lack of data to explore common and clinically relevant efficacy outcomes such as the physician global assessment.

Finally, onabotulinumtoxinA, while found to be significantly or at least numerically inferior to abobotulinumtoxinA

on key outcomes in these analyses, is an approved treatment option in pediatric lower limb spasticity, widely recognized as a common treatment choice in this indication. At the same time, endpoints selected as primary in onabotulinumtoxinA studies[16,18,29-31] (except the Tardieu Scale spasticity grade in Zhu et al,[17] see introduction) differed from the outcome measures in the network meta-analyses, widely recognized in this disease area (such as Modified Ashworth Scale and Goal Attainment Scale) and considered feasible for inclusion for reasons detailed above. More information is needed to understand why improvement on endpoints assessed in the above onabotulinumtoxinA studies did not systematically translate in a respective improvement on the Modified Ashworth Scale, Goal Attainment Scale, and Tardieu Scale spasticity grade where measured. In the most recent large study, onabotulinumtoxinA lost a statistical significance of difference to placebo on Modified Ashworth Scale after week 8, and the Clinical Global Impression score was not significant at weeks 8 and 12, whereas an improvement on the Modified Tardieu Scale was not significantly different from placebo at weeks 4, 8, and 12.[13]

Finally, the systematic literature review was conducted in March 2016. To our knowledge, the only relevant study published since then was Kim et al,[13] and the present network meta-analysis has been updated with the results of this study and recently presented at the American Academy of Neurology 2018 conference.

Conclusions

Our analyses suggested that abobotulinumtoxinA could offer a favorable efficacy on muscle tone, measured by Modified Ashworth Scale, and functional outcomes, measured by Goal Attainment Scale, compared to onabotulinumtoxinA, while remaining comparable on spasticity assessed with Tardieu Scale spasticity grade in the management of children with lower limb spasticity. AbobotulinumtoxinA and onabotulinumtoxinA had a comparable safety profile. The results must be interpreted in the context of heterogeneity and scarcity of the evidence base.

Author Contributions

All authors were involved in defining the scope of the project. PG, CK and CM conducted the systematic literature review and performed the network meta-analysis. PG, CK and CM wrote the manuscript and ND was involved in critical revision and final approval of the manuscript.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: PG, CK, and CM have disclosed that they are employees of ICON plc and served as paid consultants to IPSEN. ND is an employee of IPSEN.

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Supplemental Material

Supplemental material for this article is available online.

Ethical Approval

All the studies included in the meta-analysis were approved by local ethics committees (Ubhi 2000, Koman 2000 [grant number: M01RR07122], Ackman 2005, Mall 2006 [Freiburg, Germany, vote July 1998], Copeland 2014 [grant number: EC00175] and Zhu 2016 [grant number: 2015 Medical Review No. (02)]) or Institutional Review Boards/IRBs (Kay 2004, Bjornson 2007, Delgado 2016, Kim 2018 [IRB regulations: US 21 CFR Part 56.103]) for each study site and written informed consents were given by all study participants.

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