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Systematic Literature Review of AbobotulinumtoxinA in Clinical Trials for Lower Limb Spasticity

Khashayar Dashtipour, MD, PhD, Jack J. Chen, PharmD, Heather W. Walker, MD, and Michael Y. Lee, MD, MHA

Abstract: To elucidate clinical trial efficacy, safety, and dosing practices of AbobotulinumtoxinA (ABO) treatment in adult patients with lower limb spasticity.

A systematic literature review was performed to identify randomized controlled trials of ABO in the treatment of adult lower limb spasticity.

Of the 295 records identified, 6 primary publications evaluated ABO for the management of lower limb spasticity of various etiologies and were evaluated. Total ABO doses ranged between 500 and 2000 U for lower limb spasticity, depending on the muscles injected. All studies in lower limb spasticity showed statistically significant reduction in muscle tone based on Modified Ashworth Scale of ABO versus placebo. Significant effects on active movement and pain were demonstrated albeit less consistently. ABO was generally well tolerated across the individual studies; most adverse events reported were considered unrelated to treatment. Treatment-related adverse events included but not limited to fatigue, local pain at injection site, hypertonia, dry mouth, weakness of the noninjected muscle, abnormal gait, and urinary tract infection.

These data from 6 randomized clinical studies provide the beginnings of an evidence base for the use of ABO to reduce lower limb spasticity. Ongoing studies in this area will add to this evidence base.

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Abbreviations: ABO = AbobotulinumtoxinA, ALLS = adult lower limb spasticity, AULS = adult upper limb spasticity, BoNT = botulinum neurotoxin, MAS = Modified Ashworth Scale.

INTRODUCTION

Adult lower limb spasticity (ALLS) is 1 of the disabling complications of multiple-neurological disorders such as stroke, multiple sclerosis, spinal cord injury, and even some central neurodegenerative disorders. People with ALLS can present with a variety of abnormal postures; the most common lower limb postures being spastic drop foot with hyper plantar flexion, equinovarus, knee flexion or hyperextension, and toe flexion.¹ The increased tone due to spasticity can cause significant discomfort, and patients describe it as a leg spasm, cramp or dull pain. In many cases, ALLS can be more disabling than adult upper limb spasticity (AULS) because even mild spasticity can significantly affect patients' stride, gait, and balance. If left unmanaged, patients with ALLS are often predisposed to secondary complications of reduced mobility such as tendon shortening, joint deformity, and eventually immobilization.² These secondary complications can themselves cause more systemic complications including deep vein thrombosis³ and pressure ulcers.⁴

The integral role of botulinum neurotoxin (BoNT) in the management of focal spasticity is recognized by guidelines from around the world.⁵⁻⁷ At present, there is no FDA approved botulinum toxin for the treatment of lower limb spasticity in the United States. On the other hand, there is an accumulating body of evidence to support efficacy and safety of BoNT in managing ALLS. Although most literature reviews examine the effectiveness of all BoNT products as a class, the differences in dosing units and recommended schemes provide a clear rationale for reviewing the efficacy, safety, and dosing information for each product separately. We have previously reported on a systematic review evaluating the effectiveness of AbobotulinumtoxinA (ABO) in the management of AULS⁸; this report focuses on the results of a parallel systematic review of clinical studies of ABO in ALLS.

METHODS

The systematic literature review presented here is 1 part of a larger systematic review of all potential indications for ABO, the results of which will be presented separately per each relevant indication. The literature search strategy and methods for this systematic review were specified in advance and documented in a protocol.⁸ Components of the protocol include the literature search strategy, screening criteria, data extraction methods, and risk of bias appraisal used to assess studies selected for inclusion.

Screening Criteria

Specific study characteristics of interest were defined in the protocol. They include: study type—randomized controlled trials and other comparative clinical studies; patient population—adult patients with LLS; treatment—ABO; and outcomes—primary and secondary efficacy, safety, and dosing.

Literature Search Strategy and Data Sources

The literature search strategy was developed using a combination of Medical Subject Heading (MeSH) terms and keywords. Keywords of relevance to the review of ALLS were: AbobotulinumtoxinA (alternative spellings included: Abobotulinumtoxin A and Abobotulinum toxin A), Dysport, spasticity, and clinical trial. Language (English only) and date limits (January 1991 to January 2013) were also applied.⁸ Subsequently, the search was updated to include ALLS papers published between January 2013 and April 2015. The search was performed in 3 foundational and comprehensive electronic medical literature databases (PubMed, Cochrane Library, and Embase). Bibliographic reference lists of systematic reviews identified during screening were searched to identify any relevant studies that were not identified through the electronic database searches.

Study Selection

At level 1 screening, all publications reporting preclinical, Phase 1, prognostic/biomarker, genetic retrospective, registry, case report, and/or noncomparative studies were excluded, as were letters, consensus reports, editorials, and nonsystematic reviews. Although, systematic reviews and meta-analyses were not included in their own right, they were used for identification of additional primary studies. At level 2 screening, all publications that reported only biochemical or immunologic endpoints were excluded. Also at this stage, nonrandomized, controlled Phase 2 or 3 clinical trials, comparative long-term follow-up studies (eg, open-label follow-up of randomized, controlled clinical trials) and comparative prospective Phase 4 postmarketing trials were excluded, provided that adequate information from randomized phase 2 and phase 3 trials had been identified. The systematic literature review process of study selection was depicted in a PRISMA flow diagram.

Data Extraction

Study methodology, patient, and treatment-level data were extracted from the full-text publications under predefined headings (eg, efficacy, safety, dosing). Each included study underwent quality assessment for risk of bias based on Cochrane metrics. The quality assessment for RCTs systematically addresses 6 types of bias: selection, performance, detection, attrition, reporting, and other sources of bias not covered by other domains. If non-RCTs or other study types were deemed relevant for data extraction, quality assessment was performed using Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) appraisal criteria for non-RCTs.⁹

Role of the Funding Source

The study was partially funded by Ipsen for data collection and editorial support. KD developed the protocol and data collection was coordinated by RTI Health Solutions and designates. Aside from procuring the data collection and editorial support, Ipsen did not contribute to the study conduct or reporting of results. All authors had full access to all data,

contributed to manuscript revisions, and had final approval for submission. KD wrote the initial draft and had final responsibility for the decision to submit the paper for publication. JJC wrote the revision draft.

RESULTS

Publications Identified

A total of 295 records were identified from the medical literature databases. Of these, 6 primary publications that evaluated ABO for the management of ALLS in adult patients were included in the final data report (Table 1).^{10–15} Figure 1 shows the PRISMA diagram for the full systematic review of all randomized controlled trials of ABO. With the exception of the study by Burbaud et al,¹⁰ that was judged high risk, most of studies included in this report fulfilled criteria for low-risk selective reporting bias (Supplementary Table). Studies used a wide range of outcome measures including measures of spasticity (usually assessed with the Modified Ashworth Scale; MAS), range of movement (passive and active), walking parameters, pain, global clinical impression, activities of daily living, and goal attainment.

Efficacy in ALLS

Statistically significant reductions in muscle tone versus baseline were reached for the majority of evaluations using MAS. When assessed, ABO treatment was consistently associated with significant effects on pain. Effects on walking parameters were less consistent but generally favored ABO injections. Table 2 provides an overview of efficacy and safety outcomes from each of the studies.

Burbaud et al¹⁰ evaluated the efficacy and safety of ABO in 23 hemiparetic patients with spasticity of the ankle plantar flexors and foot invertors due to stroke or traumatic hemiparesis in a randomized double blind, placebo controlled crossover study.¹⁰ Patients received 1 injection of ABO and 1 of placebo in random order at day 0 and day 90. Injections were performed with electromyographic (EMG) guidance. Treatment efficacy was subjectively assessed by patients (on a scale of 0–3) and objectively assessed using clinical rating scales (assessing active dorsiflexion in the supine, sitting and standing position, and gait). The MAS and the Fugl–Meyer scale for the inferior limb were also applied. Treatment was with 1000 U ABO (diluted with 5 mL saline) and distributed among the various muscles according to their involvement in spasticity judged by the injector physician. The range of ABO dosages for individual muscles were as follows: triceps surae (500–1000 U), soleus

TABLE 1. Etiology of Lower Limb Spasticity

Hyman et al ¹⁴	Multiple sclerosis (definite or probable) (100%)
Hesse et al ¹¹	Stroke (100%)
Burbaud et al ¹⁰	Stroke (83%, 19/23) Ischemic (61%) Hemorrhage (22%) Traumatic (17%)
Johnson et al ¹²	Stroke (100%)
Pitcock et al ¹³	Stroke (100%)
Gusev et al ¹⁵	Multiple sclerosis (definite or probable) (100%)

TABLE 2. Evidence Table of Completed Trials for Lower Limb Spasticity

Study Identifier Design, Objective	Patient Population, Sample Size Intervention	Efficacy Outcomes	Safety Outcomes																														
<p>Burbaud et al., 1996</p> <p>Design: Randomized, double-blind placebo-controlled trial (cross-over)</p> <p>Objective: To confirm the apparent effectiveness of ABO in hemiparetic patients with ankle plantar flexor and foot inverter spasticity</p>	<p>Patient population: Poststroke and traumatic hemiparesis foot spasticity</p> <p>Sample size: N = 23</p> <p>Intervention:</p> <ul style="list-style-type: none"> Arm 1: ABO (1,000 U) first Arm 2: PBO first <p>Note: Each arm received ABO and PBO; however, the order of injection was random</p>	<p>Primary outcome: Improvement (patient perception)</p> <ul style="list-style-type: none"> 87% of ABO-treated patients reported improvement; the subjective score increased by 2 points in 65% of those who reported improvement ABO-treated patients reported significantly greater improvement compared with PBO-treated patients ($P = 0.004$) <p>Influence of first injection</p> <p><i>PBO injection day 0, ABO injection day 90</i></p> <ul style="list-style-type: none"> Slight, but NS evolution in gait velocity and Ashworth ankle scores with PBO between day 0 to 90 sessions (P value NR) Except for gait velocity, all clinical scores significantly improved between day 90 and day 120 ($P = 0.01$) <p><i>ABO injection day 0, PBO injection day 90</i></p> <ul style="list-style-type: none"> Significant improvement in video ($P = 0.0103$) and Fugl-Meyer score ($P = 0.0067$) found between day 0 and day 90 (but not day 120) Between day 0 and day 30, significant improvement was found in ankle scores (Ashworth extensors, Ashworth inverters, and active dorsiflexion) ($P < 0.0001$) Significance sustained through day 90 and day 120 for both extensor ($P = 0.0067$, $P = 0.0058$), and inverter ($P = 0.0087$, $P = 0.0114$) Ashworth scores Improvement in dorsiflexion scores was not sustained from day 0 to day 90 or day 120 (NS, $P = 0.2964$; $P = 0.2616$) <p>Evolution of clinical ratings: pooled data 1 month post-ABO injection (n = 23)</p> <table border="1"> <thead> <tr> <th>Clinical scales</th> <th>Before ABO (n = 23) mean (SD)</th> <th>After ABO (n = 23) mean (SD)</th> </tr> </thead> <tbody> <tr> <td>Video score (0-4)</td> <td>3.1 (0.6)</td> <td>2.0 (0.6)***</td> </tr> <tr> <td>Gait velocity (cm/s)</td> <td>25.1 (17.1)</td> <td>29.4 (16.4)</td> </tr> <tr> <td>Fugl-Meyer score</td> <td>23.5 (4.9)</td> <td>25.0 (4.7)*</td> </tr> <tr> <td>Ashworth ankle extensors</td> <td>3.7 (0.7)</td> <td>2.4 (0.9)***</td> </tr> <tr> <td>Ashworth ankle invertors</td> <td>2.8 (0.9)</td> <td>1.8 (0.9)***</td> </tr> <tr> <td>Active ankle dorsiflexion (global score 0-6)</td> <td>2.2 (1.5)</td> <td>3.3 (1.4)***</td> </tr> </tbody> </table> <p>*$P < 0.05$; ***$P < 0.001$.</p> <p>Significant improvement for all clinical rating scales, except gait velocity, was observed after ABO injection.</p> <p>Influence of severity and duration of spasticity on ABO efficacy</p> <table border="1"> <thead> <tr> <th>Clinical improvement</th> <th>Ashworth ankle extensors</th> <th>Subjective score mean</th> </tr> </thead> <tbody> <tr> <td>Ankle Ashworth score < 7 (n = 11)</td> <td>1.3 (0.6)</td> <td>1.5 (0.8)</td> </tr> <tr> <td>Ankle Ashworth</td> <td>1.4 (0.9)</td> <td>1.4 (0.8)</td> </tr> </tbody> </table>	Clinical scales	Before ABO (n = 23) mean (SD)	After ABO (n = 23) mean (SD)	Video score (0-4)	3.1 (0.6)	2.0 (0.6)***	Gait velocity (cm/s)	25.1 (17.1)	29.4 (16.4)	Fugl-Meyer score	23.5 (4.9)	25.0 (4.7)*	Ashworth ankle extensors	3.7 (0.7)	2.4 (0.9)***	Ashworth ankle invertors	2.8 (0.9)	1.8 (0.9)***	Active ankle dorsiflexion (global score 0-6)	2.2 (1.5)	3.3 (1.4)***	Clinical improvement	Ashworth ankle extensors	Subjective score mean	Ankle Ashworth score < 7 (n = 11)	1.3 (0.6)	1.5 (0.8)	Ankle Ashworth	1.4 (0.9)	1.4 (0.8)	<p>Safety outcomes: No general or local side effects were reported by patients except for local pain at injection site (n = 3)</p>
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<p>Hesse et al., 1995</p> <p>Design: Randomized, active controlled, clinical trial</p> <p>Objective: To determine whether additional electrical stimulation enhances the effectiveness of ABO in the treatment of unilateral lower-limb spasticity following stroke</p>	<p>Patient population: Poststroke lower-limb spasticity</p> <p>Sample size: N = 10</p> <p>Intervention:</p> <ul style="list-style-type: none"> Arm 1: EMG-guided ABO injection (2,000 U) Arm 2: EMG-guided ABO (2,000 U for first patient only; 1,500 U for remaining patients) + neuromuscular stimulation <p>Note: Due to AEs in Arm 2, patient 1, the dose for subsequent patients in Arm 2 was reduced</p>	<p>Primary outcomes:</p> <p>Muscle tone (MAS)</p> <p>Arm 1: ABO (2,000 U) only</p> <ul style="list-style-type: none"> 25% (1 of 4) patients in the ABO alone reported a slight improvement in MAS—reduction of 1 point (<i>P</i> values NR) Minor qualitative improvement in cyclogram No change was observed in other subjective or functional parameters (<i>P</i> values NR) <p>Arm 2: ABO (1,500 U) + neuromuscular stimulation</p> <ul style="list-style-type: none"> Reduction of 1 point in MAS was observed in 40% (2 of 5) of patients (<i>P</i> values NR) Reduction of 2 points in MAS was observed in 60% (3 of 5) (<i>P</i> values NR) Cyclogram showed qualitative improvement in all patients who received neuromuscular stimulation The toxin caused plantar weakness in all patients Arm 2 <p>Pre- and post-gait variables</p> <table border="1"> <thead> <tr> <th>Gait variables</th> <th>Pre Mean (SD)</th> <th>Post Mean (SD)</th> </tr> </thead> <tbody> <tr> <td>Velocity (m/s)</td> <td></td> <td></td> </tr> <tr> <td>ABO alone</td> <td>0.28 (0.11)</td> <td>.30 (0.10)</td> </tr> <tr> <td>ABO + neuromuscular stimulation</td> <td>0.39 (0.37)</td> <td>0.49 (0.40)*</td> </tr> <tr> <td>Stride (m)</td> <td></td> <td></td> </tr> <tr> <td>ABO alone</td> <td>0.56 (0.11)</td> <td>0.58 (0.14)</td> </tr> <tr> <td>ABO + neuromuscular stimulation</td> <td>0.64 (0.33)</td> <td>0.77 (0.37)*</td> </tr> <tr> <td>Cadence (steps/min)</td> <td></td> <td></td> </tr> <tr> <td>ABO alone</td> <td>60 (13.8)</td> <td>62.1 (10.8)</td> </tr> <tr> <td>ABO + neuromuscular stimulation</td> <td>58.5 (31.2)</td> <td>67.6 (29.0)</td> </tr> <tr> <td>Stance symmetry (%)</td> <td></td> <td></td> </tr> <tr> <td>ABO alone</td> <td>72.6 (7.2)</td> <td>68.0 (9.6)</td> </tr> <tr> <td>ABO + neuromuscular stimulation</td> <td>70.0 (14.5)</td> <td>84.8 (6.8)*</td> </tr> <tr> <td>Swing symmetry (%)</td> <td></td> <td></td> </tr> <tr> <td>ABO alone</td> <td>56.2 (16.4)</td> <td>52.0 (23.6)</td> </tr> <tr> <td>ABO + neuromuscular stimulation</td> <td>56.0 (24.6)</td> <td>65.2 (26.6)*</td> </tr> <tr> <td>Double support (% cycle duration)</td> <td></td> <td></td> </tr> <tr> <td>ABO alone</td> <td>53.7 (13.8)</td> <td>53.4 (16.9)</td> </tr> <tr> <td>ABO + neuromuscular stimulation</td> <td>54.9 (22.1)</td> <td>44.9 (9.3)</td> </tr> </tbody> </table>	Gait variables	Pre Mean (SD)	Post Mean (SD)	Velocity (m/s)			ABO alone	0.28 (0.11)	.30 (0.10)	ABO + neuromuscular stimulation	0.39 (0.37)	0.49 (0.40)*	Stride (m)			ABO alone	0.56 (0.11)	0.58 (0.14)	ABO + neuromuscular stimulation	0.64 (0.33)	0.77 (0.37)*	Cadence (steps/min)			ABO alone	60 (13.8)	62.1 (10.8)	ABO + neuromuscular stimulation	58.5 (31.2)	67.6 (29.0)	Stance symmetry (%)			ABO alone	72.6 (7.2)	68.0 (9.6)	ABO + neuromuscular stimulation	70.0 (14.5)	84.8 (6.8)*	Swing symmetry (%)			ABO alone	56.2 (16.4)	52.0 (23.6)	ABO + neuromuscular stimulation	56.0 (24.6)	65.2 (26.6)*	Double support (% cycle duration)			ABO alone	53.7 (13.8)	53.4 (16.9)	ABO + neuromuscular stimulation	54.9 (22.1)	44.9 (9.3)	<p>AEs believed to be drug-related:</p> <p>First patient treated in Arm 2 (ABO 2,000 U + neuromuscular stimulation)</p> <ul style="list-style-type: none"> Bladder pareses requiring catheterization for 14 days <p>AEs not confirmed to be drug-related:</p> <ul style="list-style-type: none"> Symptomatic grand mal seizures monthly 1 severe seizure 3 weeks after injection
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TABLE 2. (Continued)

Study Identifier Design, Objective	Patient Population, Sample Size Intervention	Efficacy Outcomes	Safety Outcomes
<p>Johnson et al., 2004</p> <p>Design: Non-blinded randomized controlled trial</p> <p>Objective: To investigate the effect of combined ABO and functional electric stimulation (FES) treatment on spastic drop foot in stroke</p>	<p>Patient population: Poststroke spastic drop foot</p> <p>Sample size: N = 21</p> <p>Intervention:</p> <ul style="list-style-type: none"> ▪ Arm 1: PT + ABO (1,200 U) + FES ▪ Arm 2: PT alone 	<p>Primary outcomes:</p> <p>Walking speed</p> <ul style="list-style-type: none"> ▪ Over the 12 weeks, walking speed increased for both control ($P = 0.20$) and treatment groups (PT + ABO + FES: $P = 0.042$; PT + ABO [nonstimulated]: $P = 0.004$) ▪ The overall increase in mean walking speed at 12 weeks relative to controls was 0.09 m/s in the PT + ABO + FES group and 0.04 m/s in the PT + ABO (nonstimulated) group <p>Secondary outcomes:</p> <ul style="list-style-type: none"> ▪ A statistically significant downward trend in median PCI observed for treatment groups (PT + ABO + FES: $P = 0.020$; and PT + ABO [nonstimulated]: $P = 0.020$), but not for the control group (NS, $P = 0.292$) ▪ A downward, but not significant, trend observed in the median MAS of the ankle plantar flexors in the treatment group (NS, $P = 0.282$); no trend evident in the control group (NS, $P = 0.742$) ▪ From baseline to week 8, MAS was statistically significant in the treatment group ($P = 0.022$) ▪ A downward but not significant trend observed in the median MAS of the quadriceps femoris in the treatment group (NS, $P = 0.051$); no trend evident in the control group (NS, $P > 0.20$) ▪ No statistically significant change in median MAS of the hamstrings in either treatment group (NS, treatment, $P = 0.326$; control, $P = 0.553$) ▪ No change in median MAS of the dorsiflexors for either group, where there was a median score of 0, representing an absence of spasticity on clinical examination ▪ A statistically significant upward trend in median RMA (mobile disability) total and gross scores was seen in the treatment group ($P = 0.024$, $P < 0.001$, respectively), but not in the control group (NS, $P = 0.200$, $P > 0.200$, respectively) ▪ Leg and trunk sections of the RMA showed no significant difference between control or treatment groups (all $P > 0.20$) ▪ No statistically significant trends in any dimension of the SF-36 in either control or treatment groups (NS, P value NR) 	<p>Few AEs reported, and those that were reported are not well described: PT-only group (control)</p> <ul style="list-style-type: none"> ▪ Stroke (n = 1) ▪ Minor health problems: lower back strain and seizure (n = 2) <p>Treatment (undefined treatment group)</p> <ul style="list-style-type: none"> ▪ Headaches possibly due to stimulation (n = 1) ▪ Intercurrent illness (n = 3) ▪ Fall, hearing loss, and cardiac problems (n = 1) <p>No other AEs were reported or considered related to study treatment</p>

TABLE 2. (Continued)

Study Identifier Design, Objective	Patient Population, Sample Size Intervention	Efficacy Outcomes	Safety Outcomes																													
Pittock et al., 2003 Design: Prospective, randomized, double-blind, placebo-controlled, dose-ranging study Objective: To assess the effects of three doses of ABO on calf spasticity causing spastic equinovarus deformity, and to evaluate its impact on walking	Patient population: Poststroke lower-limb spasticity Sample size: N = 234 Intervention: <ul style="list-style-type: none"> ▪ Arm 1: PBO ▪ Arm 2: ABO (500 U) ▪ Arm 3: ABO (1,000 U) ▪ Arm 4: ABO (1,500 U) 	Primary outcome: <table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <thead> <tr> <th rowspan="2">Time points</th> <th colspan="4">Distance covered during a 2-minute walking test (m)</th> </tr> <tr> <th>PBO (n = 54) Mean</th> <th>ABO 500 U (n = 55) Mean</th> <th>ABO 1,000 U (n = 55) Mean</th> <th>ABO 1,500 U (n = 57) Mean</th> </tr> </thead> <tbody> <tr> <td>Baseline</td> <td>41.4</td> <td>41.4</td> <td>42.9</td> <td>40.5</td> </tr> <tr> <td>4 weeks</td> <td>46.5</td> <td>44.3</td> <td>46.6</td> <td>46.0</td> </tr> <tr> <td>8 weeks</td> <td>48.5</td> <td>49.0</td> <td>47.8</td> <td>48.2</td> </tr> <tr> <td>12 weeks</td> <td>50.5</td> <td>49.5</td> <td>50.6</td> <td>48.9</td> </tr> </tbody> </table> <ul style="list-style-type: none"> ▪ Distance increased significantly ($P \leq 0.05$) in each of the treatment groups, including PBO. No statistically significant difference was observed between groups ($P > 0.05$). ▪ If distance at baseline was less than 30 m, only a small improvement was seen in Arms 1, 2, and 3 (~ 4 m), but a greater mean increase (~ 6 m) was seen in Arm 4 (P value NR) ▪ If distance at baseline was between 30 and 60 m, a more marked improvement was seen in all arms (~ 12 m) (P value NR) ▪ If distance at baseline was > 90 m, only a small or no change was observed in Arm 1 (~ 3 m), Arm 3 (~ 5 m), and Arm 4 (-0.4 m), but a greater change was seen in Arm 2 (10 m) (P value NR). Secondary outcomes: Stepping rate and step length discrepancy <ul style="list-style-type: none"> ▪ Increased significantly in each treatment group ($P < 0.05$), but no statistically significant differences between groups (P value NR). ▪ Statistically significant correlation between the baseline discrepancy in step length (cm) and the change observed after treatment within each treatment group, including PBO, at each time point (4, 8, and 12 weeks: Arm 1, $P = 0.001$, $P = 0.0014$, $P = 0.0002$; Arm 2, $P = 0.060$, $P < 0.0001$, $P = 0.0002$; Arm 3, $P < 0.0001$, $P < 0.0001$, $P < 0.0001$; Arm 4, $P = 0.0086$, $P = 0.0036$, $P = 0.0006$) ▪ The greatest reduction in the step length discrepancy was seen in Arm 3 at 8 weeks after treatment ($P < 0.0001$) Rivermead Motor Assessment (RMA) <ul style="list-style-type: none"> ▪ No statistically significant differences between groups (P value NR). Use of walking aids <ul style="list-style-type: none"> ▪ Greatest changes in the need of walking aids observed at 4 weeks after treatment in all groups ▪ Statistically significant difference in number of patients reporting reduced dependence on aids in Arm 3 ($P = 0.0100$) and Arm 4 ($P = 0.0000$) compared with Arm 1 Calf spasticity (MAS scores differences at each assessment vs. baseline) <ul style="list-style-type: none"> ▪ In all groups, spasticity decreased throughout the 12-week study period ▪ Greatest improvements in spasticity vs. PBO in Arm 4, at all time points (4 weeks: $P = 0.012$; 8 weeks: $P = 0.017$; 12 weeks: $P = 0.019$) 	Time points	Distance covered during a 2-minute walking test (m)				PBO (n = 54) Mean	ABO 500 U (n = 55) Mean	ABO 1,000 U (n = 55) Mean	ABO 1,500 U (n = 57) Mean	Baseline	41.4	41.4	42.9	40.5	4 weeks	46.5	44.3	46.6	46.0	8 weeks	48.5	49.0	47.8	48.2	12 weeks	50.5	49.5	50.6	48.9	Safety outcomes: AEs per group (PBO, 500 U, 1,000 U, 1,500 U): <ul style="list-style-type: none"> ▪ 29%, 29%, 25%, 33% Severe AEs per group: <ul style="list-style-type: none"> ▪ PBO: 5 (1 pain, 1 edema, 1 paraesthesia, 1 hypertonia, and 1 pancreatitis) ▪ 500 U: 2 (1 pharyngitis, 1 Dysphagia) ▪ 1,000 U: 3 (1 headache, 1 somnolence, 1 dizziness) ▪ 1,500 U: 5 (2 pain, 1 asthenia, 1 somnolence, 1 abnormal gait) Mild to Moderate AEs per group (PBO, 500 U, 1,000 U, 1,500 U):not consistently related to treatment. Those occurring at a frequency of 5% or greater (3 patients per group) <ul style="list-style-type: none"> ▪ Pain (7.3%, 8.5%, 8.3%, 10%) ▪ Asthenia (0, 0, 0, 8.3%) ▪ Convulsion (0, 5.1%, 0, 0) ▪ Myasthenia (0, 0, 5%, 0)
	Time points	Distance covered during a 2-minute walking test (m)																														
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TABLE 2. (Continued)

Study Identifier Design, Objective	Patient Population, Sample Size Intervention	Efficacy Outcomes	Safety Outcomes
<p>Gusev et al., 2008</p> <p>Design: Randomized, double-blind, placebo-controlled trial</p> <p>Objective: To assess the efficacy of ABO in the treatment of adults with adductor muscle spasticity due to definite or probable multiple sclerosis</p>	<p>Patient population: Hip adductor spasticity in MS</p> <p>Sample size: N = 106</p> <p>Intervention:</p> <ul style="list-style-type: none"> ▪ Arm 1: PBO ▪ Arm 2: ABO (1,000 U or 1,500 U) <p>Note: ABO dose modified according to degree of spasticity, asymmetry of spasticity, variations of body and muscle mass, and previous experience with BoNT</p>	<p>Primary outcome: Improvement in patient-selected functional outcome measure at week 4</p> <ul style="list-style-type: none"> ▪ The outcome most patients (ABO and PBO groups) selected and wanted to most improve was "dressing of lower body" ▪ Second and third patient choices were "maintenance of perineal hygiene" and "transfer to toilet" ▪ The majority of patients in both treatment groups reported "great deal of difficulty" performing their chosen outcome measure (ABO 40% vs. PBO 39%, reports NS, <i>P</i> value NR) <p>Secondary outcomes: Key functional outcome measure (patient selected) at weeks 4, 8 and 12: Responder (showing an improvement in at least one point from baseline)</p> <ul style="list-style-type: none"> ▪ At week 4, 29% of patients in both treatment groups reported an improvement of ≥ 1 grade in their key functional outcome measure (NS, <i>P</i> = 0.745); significance was not reached by week 8 or 12 (NS, <i>P</i> = 0.469 and <i>P</i> = 0.497) ▪ Treatment response for "maintenance of perineal hygiene" trended toward but did not reach significance (ABO 40% vs. PBO 24%, NS, <i>P</i> = 0.096) <p>Changes in MAS in both legs</p> <ul style="list-style-type: none"> ▪ Some improvement in MAS response rates was seen at all time points (weeks 4, 8, and 12) for ABO-treated patients compared with PBO (NS, <i>P</i> value NR) ▪ At week 8, the proportion of patients who had an improvement of ≥ 1 point on the MAS for leg adductor muscle tone approached but did not reach significance (NS, <i>P</i> = 0.067) <p>Changes in distance between knees under passive and active abduction</p> <ul style="list-style-type: none"> ▪ Distance between knees increase under passive and active abduction for ABO-treated patients was greater than compared with PBO, but did not reach significance (NS, <i>P</i> value NR) <p>Retreatment</p> <ul style="list-style-type: none"> ▪ Retreatment was indicated or requested by more ABO treated patients compared with PBO (53% vs. 49%, <i>P</i> value NR) 	<p>Safety outcomes: AEs observed in 53% of ABO treated patients compared with 27% of PBO treated patients; <i>P</i> value NR</p> <p>Most AEs mild to moderate intensity and resolved in a few days</p> <p>Most frequent AEs:</p> <ul style="list-style-type: none"> ▪ Asthenia (ABO:22% vs. PBO: 6%; <i>P</i> value NR) ▪ Pain, hypertonia and dry mouth reported more often in the ABO group compared with PBO (data and <i>P</i> value NR) <p>Serious AEs possibly due to ABO:</p> <p>One ABO treated patient had mild asthenia, moderate dysphasia, and moderate dysarthria</p>

TABLE 2. (Continued)

Study Identifier Design, Objective	Patient Population, Sample Size Intervention	Efficacy Outcomes	Safety Outcomes																																			
Hyman et al., 2000 Design: Randomized, double-blind, placebo-controlled dose-ranging study Objective: To define a safe and effective dose of ABO for treating hip adductor spasticity	Patient population: Hip adductor spasticity in MS Sample size: N = 74 Intervention: <ul style="list-style-type: none"> ▪ Arm 1: ABO 500 U ▪ Arm 2: ABO 1,000 U ▪ Arm 3: ABO 1,500 U ▪ Arm 4: PBO 	Primary outcomes: <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th>Measure</th> <th>PBO</th> <th>ABO 500</th> <th>ABO 1,000</th> <th>ABO 1,500</th> </tr> </thead> <tbody> <tr> <td colspan="5">Distance between knees (cm)</td> </tr> <tr> <td>Week 0 median (SD)</td> <td>28.2 (12.8)</td> <td>29.8 (12.1)</td> <td>24.9 (11.9)</td> <td>28.5 (10.3)</td> </tr> <tr> <td>Week 4 median (SD)</td> <td>32.1 (12.3)</td> <td>36.7 (12.8)</td> <td>31.9 (9.2)</td> <td>39.2* (10.4)</td> </tr> <tr> <td colspan="5">Passive hip abduction (degrees)</td> </tr> <tr> <td>Week 0 median (SD)</td> <td>42.6 (27.5)</td> <td>39.4 (20.6)</td> <td>39.4 (21.3)</td> <td>48.2 (23.0)</td> </tr> <tr> <td>Week 4 median (SD)</td> <td>53.9 (19.7)</td> <td>56.5 (24.8)</td> <td>63.4 (24.3)</td> <td>61.3 (25.4)</td> </tr> </tbody> </table>	Measure	PBO	ABO 500	ABO 1,000	ABO 1,500	Distance between knees (cm)					Week 0 median (SD)	28.2 (12.8)	29.8 (12.1)	24.9 (11.9)	28.5 (10.3)	Week 4 median (SD)	32.1 (12.3)	36.7 (12.8)	31.9 (9.2)	39.2* (10.4)	Passive hip abduction (degrees)					Week 0 median (SD)	42.6 (27.5)	39.4 (20.6)	39.4 (21.3)	48.2 (23.0)	Week 4 median (SD)	53.9 (19.7)	56.5 (24.8)	63.4 (24.3)	61.3 (25.4)	AEs: <ul style="list-style-type: none"> ▪ 55% of ABO-treated patients ▪ 63% of PBO-treated patients Most frequent AEs in ABO-treated patients: <ul style="list-style-type: none"> ▪ Hypertonia (22%) ▪ Weakness of noninjected muscles (14%) ▪ Fatigue (7%) ▪ Urinary tract infection (5%) ▪ Headache (5%) ▪ Micturition frequency (5%) ▪ Back pain (5%) ▪ Diarrhea (5%) The PBO group reported similar AEs, with the exception of muscle weakening 2 times the number of AEs were reported by ABO 1,500 U group compared with the ABO 500 U and ABO 1,000 U groups SAEs: n = 6 reported for ABO and PBO Not believed to be related to ABO: <ul style="list-style-type: none"> ▪ n = 1 had diarrhea and urinary tract infection, 36 days after receiving ABO 1,500 U ▪ n = 1 had urinary tract infection, chest infection and hypothermia, 69 days after receiving ABO 1,000 U The remaining 4 SAEs were in the PBO group and resulted in hospitalizations due to: <ul style="list-style-type: none"> ▪ Bowel spasticity ▪ Gastroparesis ▪ Pulmonary embolism
		Measure	PBO	ABO 500	ABO 1,000	ABO 1,500																																
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		<p>*P = 0.02.</p> <p>Distance from the knees and passive hip abduction improved in all groups from week 0 to week 4; however, statistically significant improvement was seen only for distance between the knees in the ABO 500 group compared with PBO (P = 0.02)</p>																																				
		Secondary outcomes: <ul style="list-style-type: none"> ▪ Active hip abduction improved minimally across treatment groups from week 0 to week 4 (NS, P value NR) ▪ MAS improved similarly across treatment groups from week 0 to week 4 (NS, P value NR) ▪ Muscle tone improved similarly across treatment groups, but more so with the increase in ABO dose (NS, P value NR) ▪ Spasm frequency reduced similarly across all treatment groups, but more so in the ABO 1,000 group (NS, P value NR) ▪ Clinical global rating improved by 1 point across treatment groups, but between-group comparisons, differences were not observed (NS, P value NR) ▪ The proportion of pain-free (upper leg) patients across groups increased from week 0 to week 4 (NS, P value NR) ▪ Hygiene improvement was not changed from week 0 to week 4 for PBO and ABO 500 groups; however, improvement by 1 point was seen in ABO 1,000 and ABO 1,500 U groups (NS, P value NR) ▪ Investigator and patient opinions of response to treatment were overall similar, with positive opinion for two-thirds of the ABO 500 U group and half of patients in the ABO 1,000 U and ABO 1,500 groups (NS, P value NR) ▪ The highest percentage of PBO patients requested or had retreatment indicated before week 12 compared with the ABO-treated groups (NS, P value NR) ▪ Time to retreatment was significantly longer for all ABO groups (ABO 500 U, P = 0.042; ABO 1,000 U, P = 0.017; ABO 1,500 U, P = 0.015) compared with PBO 																																				
Optimal dosing:																																						

Act = active ankle dorsiflexion; ADL = activity of daily living; AE = adverse event; AR = associated reaction; ABO = AbotulinumtoxinA; FES = functional electrical stimulation; FM = Fugl-Meyer score; MAS = Modified Ashworth Scale; MS = multiple sclerosis; NR = not reported; PBO = placebo; PCI = physiological cost index; PT = physical therapy; ROM = range of motion; Vel = Gait velocity; Vid = Video score.

ABO = AbotulinumtoxinA, Act = active ankle dorsiflexion, ADL = activity of daily living, AE = adverse event, AR = associated reaction, FES = functional electrical stimulation, FM = Fugl-Meyer score, MAS = Modified Ashworth Scale, MS = multiple sclerosis, NR = not reported, PBO = placebo, PCI = physiological cost index, PT = physical therapy, ROM = range of motion, Vel = gait velocity, Vid = video score.

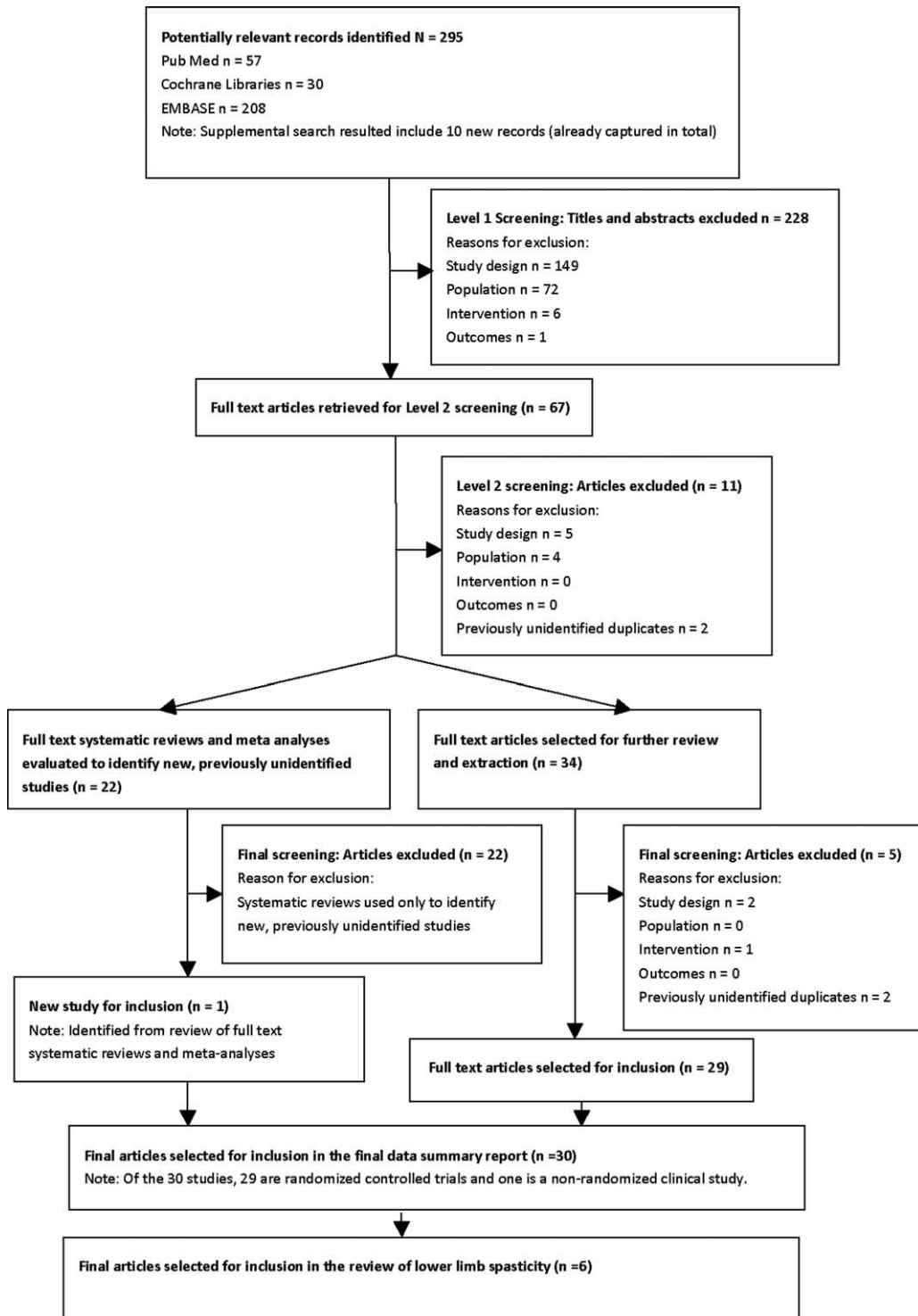


FIGURE 1. PRISMA flow diagram reporting the results of the systematic literature search.

(200–400 U), tibialis posterior (200–350 U), and flexor digitorum longus (150–300 U). Only 3 of the 23 patients reported no improvement after ABO injection. There was a clear difference ($P = 0.0014$) in patients' subjective scores between ABO and placebo. Significant changes were noted in MAS values for

ankle extensors ($P < 0.0001$) and invertors ($P = 0.0002$) and for active ankle dorsiflexion ($P = 0.0001$) and significant improvements were also noted in Fugl–Meyer scores ($P = 0.0028$). During active ankle dorsiflexion, 18/22 patients showed ≥ 1 point improvement in dorsiflexion score. Gait velocity was

slightly but not significantly improved after ABO injections. The authors concluded that the efficacy of ABO injection in the treatment of spastic foot suggests that ABO may be particularly useful during the first year after a stroke.¹⁰

In an open-label study, Hesse et al¹¹ examined the effect of ABO with or without electrical stimulation (ES) treatment postinjection on ALLS in 10 hemiparetic subjects with the history of stroke. Five subjects were randomized into each treatment group: 2000 U ABO followed by ES treatment (30 min, 6 times/d during the 3 days following the injection), 2000 units ABO without ES. Injections were performed into the following muscles using EMG guidance: soleus, tibialis posterior, and both heads of gastrocnemius muscles. Study results indicated that there were no significant differences in MAS across groups. However, the group receiving ABO + ES treatment demonstrated the greatest reduction in MAS ($P=0.011$). The result of other measures, including limb position at rest and ability to perform 3 identified ADLs, were variable.

The effect of combined use of ABO and functional electric stimulation (FES) in the treatment of spastic drop foot following stroke was also investigated by Johnson et al.¹² Twenty-one subjects participated in this nonblinded randomized controlled study and 18 of them completed the study. Every subject received ABO injection into the medial and lateral heads of the gastrocnemius and tibialis posterior. Injections were performed with EMG guidance. Walking speed increased in both injection and control groups over 12 weeks study with statistically significant difference in favor of the group with FES. Authors concluded that the combined treatment improved walking and function.

Pitcock et al evaluated the effect of ABO injections on calf muscle hypertonicity following stroke in a prospective, multicenter, double-blind, placebo-controlled, and dose-ranging study. Two-hundred and thirty-four stroke patients were randomized into the ABO group and were dosed with 500, 1000, or 1500 U.¹³ Within the calf, upper, and lower injection sites were determined by palpation of the femoral and calcaneal insertions of the gastrocnemius muscle; 1/4 and 1/3 of the total length from the femoral insertions, respectively, and EMG guidance was not used. The primary outcome measures, 2-min walking distance and stepping rate, increased significantly in each group with no significant difference between groups. There were also small, but statistically significant improvements in calf spasticity, limb pain, and reduction in the use of walking aids compared with placebo. Authors concluded that ABO injection resulted in a significant reduction in muscle tone, limb pain, and dependence on walking aids. The best benefit was achieved with 1500 U of ABO.

Hyman et al¹⁴ investigated the effectiveness and safety of ABO for treating hip adductor spasticity. In this double-blind study, 74 patients with multiple sclerosis and spasticity affecting the hip adductor muscles of both lower limbs were recruited and randomized to 4 groups of ABO 500, 1000, and 1500 U or placebo. The primary efficacy variables—passive hip abduction and distance between the knees—improved for all groups, and the distance between the knees for the 1500 U group was significantly greater than placebo ($P=0.02$). Spasm frequency was reduced in all groups, but muscle tone was reduced in the ABO groups only. Pain was reduced in all groups, but improvements in hygiene scores were evident only in the 1000 and 1500 U groups.¹⁴

Gusev et al¹⁵ also assessed the effectiveness of ABO in the treatment of adults with adductor muscle spasticity due to

definite or probable multiple sclerosis. In this double-blind study, 106 subjects were recruited, and randomized to receive injections with placebo, or ABO: 1000–1500 U in a 1:1 ratio. The subjects received injection into adductor muscles of each lower limb (500–750 U/leg). ABO was shown to provide effective pain relief in patients with severe adductor spasticity. Other predefined outcome measures, including functional performance (primary outcome), did not reach statistical significance. However, there was a significant improvement in favor of ABO for maintenance of perineal hygiene ($P=0.0096$) and there were trends to significance for MAS response rates and in the distance between knees under passive abduction.¹⁵

Table 3 shows the injection methodology and adjunct therapies that were used in each study.

Safety in ALLS

ABO was well tolerated across the individual studies.^{10–15} Most adverse events reported were considered unrelated to treatment. Adverse events considered associated with ABO treatment included: local pain at injection site, fatigue, asthenia, somnolence, hypertonia, dry mouth, bladder paresis, urinary tract infection, urinary frequency, diarrhea, weakness of non-injected muscles, headache, abnormal gait, and dysphagia. Most of the AEs were more common at higher doses of ABO.

Dosing Across Indications

Total ABO doses ranged between 500 and 2000 U for ALLS. The most commonly injected muscles were the triceps surae, soleus, tibialis posterior, flexor digitorum longus, adductor magnus, adductor longus, adductor brevis, and gastrocnemius. Dose ranges for different muscles are summarized overall in Table 4 and by each individual study in Table 5.

DISCUSSION

The main aim of this systematic review was to provide guidance for physicians who manage ALLS using ABO. Other reviews are available regarding assessment of BoNT for treatment of ALLS with no emphasis on the dosing per muscles for ABO. This is essential since the dosing units of each BoNT-A product are not interchangeable with another toxin. In this review, all studies showed the efficacy of ABO in spasticity but using different outcome measures such as MAS, pain, or gait velocity. All of the studies showed reductions in spasticity using MAS, but not all of them reached statistical significance versus placebo. This may be due to the relatively small sample sizes employed and other study design issues. For example, most patients in the study of ABO for hip adductor spasticity reported by Gusev et al¹⁵ received doses that were lower than the 1500 U dose that Hyman et al¹⁴ had previously reported to be effective.

All 6 studies included in this review used different range of dosing that was shown to be safe and effective for the variety of postures in ALLS. Five of the 6 studies utilized EMG guidance as technique to optimize injection site localization and it is unknown if the use of other localization techniques (eg, ultrasonography) would provide substantively different results. The dosing table provided here is based on the published studies and does not suggest that other doses should not be applied; physicians should always use clinical judgment on dosing schedules based upon on the severity of impairment. A recent international survey of routine therapeutic usage revealed that experienced European ABO injectors report injecting doses between 100 and 3000 U for ALLS (mean total dose ranged from 600 to 832 U), depending on the patient's needs.¹⁶

TABLE 3. Injection Methodology and Adjunctive Therapies

Author	Dysport Injection Methodology	Adjunct Therapy
Johnson et al ¹²	Injections were given under EMG guidance	Functional electric stimulation The Oddstock Dropped Foot Stimulator Mark III was used
Hesse et al ¹¹	EMG-guided injections	Dual channel stimulator for group B patients
Hyman et al ¹⁴	Muscles were located by palpation and were injected with EMG guidance	Oral antispastic and analgesic medications being taken by the patient at the time of entry was permitted at a constant dose throughout the study Standard of care physiotherapy was also permitted to continue unchanged throughout the study Other concomitant medications were permitted at the discretion of the investigator
Burbaud et al ¹⁰	EMG guidance	Physiotherapy allowed
Gusev et al ¹⁵	Muscles were located by palpation and were injected with EMG guidance	Intrathecal baclofen was not permitted for the duration of the study Any existing oral antispastic medication was continued at the same dose throughout the study and no new therapies were started Standard of care physiotherapy, speech therapy, and occupational therapy could be initiated at study entry, but wherever possible the regimen remained constant throughout the study period
Pittock et al ¹³	Upper calf and lower calf injection sites were determined by palpation of the femoral and calcaneal insertions of the gastrocnemius muscle; 1/4 and 1/3 of the total length from the femoral insertions, respectively. EMG guidance was not used	Use and nature of walking aids and orthoses were recorded Concomitant medication and adjunctive treatments (eg, physiotherapy) were allowed

Likewise, all 6 studies preselected only a certain number of muscles for injection. Due to complexity of ALLS, it is vital that the injector has a proper understanding of the patients' individual clinical needs. Clinical trials often prespecify muscles in an attempt to standardize findings, but it is likely that this restricted approach may have affected the outcome of the studies. When deciding on dosing strategies, the injector must consider multiple patient factors such as the muscles affected, patient functionality, size of the patient, residual deficit, and the etiology of the spasticity. For example, whereas some patients with poststroke spasticity may gradually improve their function with proper rehabilitation, patients with spasticity secondary to central neurodegenerative disorders will usually worsen. In patients with multiple sclerosis, the degree of deficit is subject

to remission and exacerbation. Each of these different disease states requires a different dosing approach. Overall, additional research is needed in order to better define the optimal ABO dose and dilution parameters for individual muscles, the number and location of injection sites, and the most suitable technique for injection localization (eg, surface anatomy, EMG guidance, ES, and ultrasonography).

The degree of functional impairment is 1 of the most important factors to consider for managing spasticity. Unfortunately, spasticity research is hampered by the lack of outcome measures that are able to properly assess functional impairment before and after toxin injection,¹⁷ and this methodological limitation was evident in these 6 studies as well. For many patients, the impact of ALLS on their walking ability and gait significantly impacts their safety, comfort, social integration, and quality of life.¹⁸ Speed of gait was included in all 4 of the poststroke studies included in this review; however, statistical differences between ABO and placebo were difficult to show despite the fact that tone was consistently decreased after ABO injection.^{10–13} As Burbaud and colleagues note, there are many factors that can affect speed of gait—for example, a poststroke patient who no longer requires a walking stick or ankle orthosis to help them walk may walk more slowly because they are cautious of their regained ability.¹⁰ Further, it is worth noting that significant effects on speed of gait seemed to rely on the presence of concomitant physiotherapy. Whereas all patients in the Hesse study (which found a positive effect on speed of gait) had concomitant physiotherapy,¹¹ only 38% of patients in the trial reported by Pittock et al received any physiotherapy (and, of these, most only received 1 session).¹³ It is important to note

TABLE 4. Dose Range of ABO for Each Individual Muscle

Muscles	Dose Range, U
Triceps surae	500–1000
Soleus	200–500
Tibialis posterior	200–500
Flexor digitorum longus	150–300
Gastrocnemius medial	200–500
Gastrocnemius lateral	200–500
Adductor magnus	250–375
Adductor brevis	125.0–187.5
Adductor longus	125.0–187.5

TABLE 5. Doses of ABO Used in Individual Muscles by Study

	Burbaud et al ¹⁰	Hesse et al ¹¹	Johnson et al ¹²	Pittock et al ¹³	Gusev et al ¹⁵	Hyman et al ¹⁴
Total, U	1000	1500 and 2000	800	500 and 1000 and 1500	Per leg: 500 and 750	500 and 1000 and 1500
Triceps surae, U	500–1000	–	–	–	–	–
Soleus, U	200–400	500	–	Dose NR	–	–
Tibialis posterior, U	200–350	500	400	–	–	–
Flexor digitorum longus, U	150–300	–	–	–	–	–
Gastrocnemius medial, U	–	250 and 500	200	Dose NR	–	–
Gastrocnemius lateral, U	–	250 and 500	200	Dose NR	–	–
Adductor magnus, U	–	–	–	–	Per leg: 250 and 375	250 and 500 and 750
Adductor brevis, U	–	–	–	–	Per leg: 125 and 187.5	125 and 250 and 375
Adductor longus, U	–	–	–	–	Per leg: 125 and 187.5	125 and 250 and 375

NR = not reported.

* Dose (low or high) dependent on body weight of patient, severity of spasticity, and previous BoNT exposure.

that many factors affect can impact functional outcomes. For example, as Burbaud and colleagues note, a lack of improvement in gait velocity could also reflect a detrimental effect of the toxin, which might produce too much weakness in plantar flexion.¹⁰ Gusev and colleagues note that if toxin spreads and weakens muscles adjacent to leg adductors, it is conceivable that the weakness could have negative influenced the ability to perform functional tasks with the legs.¹⁵ Such observations confirm the need for a highly individualized and multidisciplinary approach to manage ALLS, where functional outcomes and physical intervention are vital for achieving patient-specific treatment goals. Future research should also consider measurement of activity-based outcomes, such as total step count profiles, which have been found to be useful when assessing for meaningful changes in ambulatory performance in patients with spinal cord injury, spinocerebellar ataxias, and chronic stroke.^{19–21}

This systematic literature review is part of a larger review where the use of ABO in other indications such as AULS has also been evaluated.⁸ When comparing the present results with the strength of the literature for AULS, it is apparent that more high-quality studies are required to inform practice. This need for more research is not limited to the use of ABO in ALLS, but there is also a clear and urgent need to better understand the burden of the condition² and also the effectiveness of other treatments (including other BoNT formulations).²² Such work is ongoing and over 10 clinical trials of interventions for ALLS are listed on clinicaltrials.gov (including a double-blind study with ABO NCT01249404 and its open label extension study NCT01251367).

LIMITATIONS

This systematic review employed strict inclusion criteria as described in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.²³ Based on our criteria a large number of uncontrolled, exploratory studies were excluded and affected our sample size. While this obviously eliminated some clinically relevant information, this established methodology is considered necessary to avoid bias by using explicit, systematic methods. A key aim of this systematic review was to produce a comprehensive, evidenced-based data report that provides information on the injection schema used and associated outcomes for ABO in ALLS. However, the substantial heterogeneity among patients included in these 6 studies regarding their geographical location, etiology and severity of spasticity significantly limits our ability to draw firm conclusions. The heterogeneity of outcome measures made it difficult to directly compare studies, and so we preferred to review the effectiveness of ABO in each study separately. Another limitation is due to lack of long follow up after ABO injection.

CONCLUSIONS

This systematic review provided current evidence regarding safety and efficacy of ABO injection for ALLS. Based on the evidence reviewed, it can be concluded that ABO injections consistently reduce tone and can be effectively employed in the management of ALLS of various etiologies. However, the review also revealed lack of large trials of ABO to manage ALLS, and highlighted the need for future trials to employ relevant outcome measures that properly assess patients' functional ability.

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