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**Botulinum Toxin
A for Upper and
Lower Limb
Spasticity:
A Systematic
Review**

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Canadian Coordinating Office for Health Technology Assessment

**Botulinum Toxin A for Upper and
Lower Limb Spasticity:
A Systematic Review**

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February 2005

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CCOHTA takes sole responsibility for the final form and content of this report. The statements and conclusions in this report are those of CCOHTA and not of its Panel members or reviewers.

Authorship

All authors participated in the planning of the project.

Kirsten Garces developed the protocol, contributed to designing the literature search strategy; reviewed abstracts and selected articles for inclusion; assessed trial quality; abstracted and analyzed data; and prepared drafts and the final version of this report.

Anna McCormick assisted with protocol development; provided clinical expertise; and reviewed and assisted with writing drafts of this report.

Lynda McGahan assisted with developing the protocol and designing the literature search strategy; reviewed the abstracts and selected articles for inclusion; assessed trial quality; abstracted and analyzed data; wrote the results section regarding spasticity in various disorders; and assisted with revising and writing drafts of the report.

Becky Skidmore designed and executed the literature search strategies and updates; wrote the methods section and associated appendix on literature searching; wrote the glossary section; and verified and formatted bibliographic references.

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Conflicts of Interest

Anna McCormick received an unrestricted education grant from Allergan for a research project regarding the use of Botox in adults with cerebral palsy. She maintains rights to all data and publication. She received honoraria and travel assistance for presentations.

No other conflicts were declared.



Botulinum Toxin A for Upper and Lower Limb Spasticity: A Systematic Review

Technology Name

Botulinum toxin A (BTX-A)

Disease or Condition

Spasticity is a symptom that can cause disability in affected patients. It is characterized by increased muscle tone. Because it may interfere with voluntary movements, it can affect the activities of daily living. Spasticity is treated in an effort to decrease muscle tone, alleviate distressing symptoms, improve motor function or prevent contractures.

Technology Description

BTX-A inhibits the release of acetylcholine from the neuron, resulting in muscle relaxation. It is injected directly into affected muscles. The dose generally depends on which muscle is being injected. Repeat doses may be needed because the pharmacological effect of BTX-A usually lasts two to four months. The clinical effects may last longer when other treatments are also used. BTX-A differs from many other pharmacologic treatments in that individual muscles can be directly targeted, depending on the goals of treatment.

The Issue

BTX-A is approved in Canada to treat spasticity in patients with cerebral palsy and stroke. As the use of BTX-A increases and the population being treated with BTX-A expands, there is a need to review the evidence regarding its efficacy and safety.

Assessment Objective

The objective was to determine whether BTX-A is efficacious and safe when it is used by patients with upper and lower limb spasticity as compared to other interventions.

Methods

CCOHTA did a systematic review of the literature reporting on the efficacy and safety of BTX-A in any disorder. The outcomes examined were muscle tone, range of motion, function and disability, pain, quality of life and adverse events.

Of the 33 RCTs included in the review, 12 focused on patients with stroke, 15 on patients with cerebral palsy, two on patients with multiple sclerosis and four on patients with other disorders.

Conclusions

- BTX-A decreases muscle tone across most disease states.
- Increased range of motion, improved gait and improved function occur in many studies. Statistical significance is not always reached. The variability across studies may be a result of the variety of disorders studied and their unique expression; and differences in outcome measures and study design. Combining the results to improve clarity is sometimes impossible.
- The adverse events reported in most trials are low in number and often temporary. Improved methods of reporting, however, would allow for more robust conclusions about the comparative safety of BTX-A.
- Long-term patient-specific goal-focused outcomes are needed to further define clinically meaningful improvements in therapeutic outcomes.

This summary is based on a comprehensive health technology assessment available from CCOHTA's web site (www.ccohta.ca): Garces K, McCormick A, McGahan L, Skidmore B. *Botulinum toxin A for upper and lower limb spasticity: a systematic review.*

EXECUTIVE SUMMARY

The Issue

Botulinum toxin-A (BTX-A) is approved in Canada to treat spasticity in patients with cerebral palsy and stroke. As the use of BTX-A increases and the population being treated with BTX-A expands, there is a need to review the evidence regarding its efficacy and safety.

Objective

Our aim is to determine whether BTX-A is efficacious and safe when used to reduce focal spasticity in patients with upper and lower limb spasticity, compared to other pharmacologic and non-pharmacologic interventions.

Methods

Relevant trials were identified by systematically reviewing the literature. A trial was selected for review if it met the eligibility criteria established a priori by two independent reviewers. Two reviewers independently assessed trial quality using the Jadad scale and abstracted data on muscle tone, passive range of motion (PROM) and active range of motion (AROM), motion analysis, function and disability, pain, quality of life and adverse events.

Results

The systematic review included 33 randomized controlled trials (RCTs). Quality scores according to the Jadad scale varied (high=4 trials, moderate=16 trials, low=13 trials) and the techniques used to prevent bias by concealing the allocation sequence were often unclear. These measures may not have accurately reflected the quality of some trials. Despite the low scores of some trials (5 single blind trials, 5 trials reported in an abstract), they provided important clinical information.

Patients with stroke and upper limb spasticity: Nine trials compared BTX-A to placebo in patients with stroke and upper limb spasticity. Patients receiving BTX-A had decreased muscle tone and increased PROM, but statistically significant differences when compared to placebo were not demonstrated in all studies. One trial reported increases in AROM. There were no statistically significant differences in adverse events.

Patients with stroke and lower limb spasticity: Three trials involved patients with stroke and spasticity in the lower limbs. One trial compared BTX-A to phenol, the other to placebo and the last compared BTX-A, functional electrical stimulation (FES) and physiotherapy to physiotherapy alone. Muscle tone was decreased compared to phenol and placebo. PROM and AROM were greater in patients receiving BTX-A compared with placebo, but it was not reported whether the difference was statistically significant. Walking speed was significantly faster with BTX-A, FES and physiotherapy compared with physiotherapy alone, but was not significantly different compared with placebo. Patients and investigators thought that the overall condition improved with BTX-A treatment compared with placebo. Only one trial reported the overall incidence of adverse events and found it to be similar to placebo. The injections of phenol were reported to be more painful than those of BTX-A.

Patients with cerebral palsy and upper limb spasticity: Two trials involved patients with cerebral palsy and upper limb spasticity. One compared BTX-A to placebo and the other compared BTX-A and occupational therapy to occupational therapy alone. Muscle tone at the elbow and wrist was significantly decreased compared with placebo for at least two weeks. There were no statistically significant differences in muscle tone and PROM in patients receiving BTX-A and occupational therapy compared

with occupational therapy alone. AROM was significantly greater with BTX-A treatment compared with placebo at two weeks. One study showed statistically significant improvement in the quality of upper extremity skills test, a standardized, validated test of upper extremity function. Patients, parents and caregivers reported improved function with BTX-A treatment in both trials. Neither trial reported the overall incidence of adverse events.

Patients with cerebral palsy and lower limb spasticity: Thirteen trials investigated the use of BTX-A in patients with cerebral palsy and lower limb spasticity. Eight trials compared BTX-A to placebo, two to casting, two to physiotherapy and one to orthosis. There were no significant differences in tone between BTX-A treatment and casting in two trials. Another trial reported a significant decrease in hip adductor and calf tone compared to physiotherapy. Of the three trials comparing BTX-A to placebo, increases in PROM were reported, but statistical significance was inconsistent. Compared with casting and physiotherapy, there were no significant differences in PROM. Three trials measured significant differences compared with placebo in AROM. Gait, as measured using video gait analysis and a physician rating scale was significantly greater compared to placebo. There were no statistically significant differences in global motor function measure (GMFM) scores between patients receiving BTX-A and placebo, physiotherapy, orthosis or casting. Other scales rated by patients, parents or physicians (physician rating scale (PRS), questionnaires, Vulpe assessment battery, and subjective functional assessment) generally indicated an increased improvement in function compared to placebo. One trial, designed to look specifically at pain, reported a significant difference compared to placebo after adductor release surgery. When the incidence of adverse events from three trials was combined, patients receiving BTX-A experienced significantly more adverse events than those receiving placebo. Common adverse events were local pain and weakness.

Patients with multiple sclerosis and lower limb spasticity: Two trials compared BTX-A to placebo in patients with multiple sclerosis and lower limb spasticity. One of these trials reported a significant decrease in tone. Significant differences in PROM, AROM, assessments of function and/or disability and adverse events were not reported.

Patients with various diseases and spasticity: Four trials involved patients with various diseases. A wide range of results were reported and no overall conclusions could be made from these because of the diverse patient population and treatment protocols.

The physiologic outcomes that are included in this review may not translate into clinically meaningful improvements. Several trials have utilized functional and goal oriented outcomes and shown statistically significant improvements in these outcome measures with the use of BTX-A. Goal focused outcomes are valued outcomes that measure clinically meaningful improvements in these diverse populations. Many trials that are underway investigate goal-focused outcomes and represent a change in the way that improvements in spasticity are monitored and quantified.

Conclusion

BTX-A treatment resulted in decreased muscle tone across most trials and diseases. Increased range of motion, improved gait and improved function were shown in many studies, but statistical significance was not always reached. The variability in results across studies may be due to the wide variety of disorders studied; the unique expressions of disease state in each clinical condition; and the differences in study designs and outcomes measures used. Combining results to improve clarity was seldom possible. The adverse events reported in most studies are low in number and often temporary. Improved methods of reporting, however, would lead to more robust conclusions about the comparative safety of BTX-A. Long term patient-specific goal-focused outcomes are needed to further define the clinically meaningful improvements in therapeutic outcomes.

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ABBREVIATIONS

AROM	active range of motion
CVA	cerebral vascular accident
CP	cerebral palsy
EAS	expanded Ashworth scale
EMG	electromyogram
FES	functional electrical stimulation
GMFM	gross motor function measurements
MAS	modified Ashworth scale
MS	multiple sclerosis
OT	occupational therapy
PEDI	pediatric evaluation of disability inventory
PRS	physician rating scale
PT	physical (physiotherapy) therapy
PROM	passive range of motion
ROM	range of motion
SCI	spinal cord injury
TBI	traumatic brain injury
VGA	video gait analysis

GLOSSARY

Active range of motion (AROM): Movement of joint provided entirely by individual performing exercise

Adverse events: Adverse (injurious, undesirable) effects or complications of diagnostic, therapeutic, prophylactic, anesthetic or surgical procedures

Ashworth scale: A five-point rating scale for measuring muscle tone (whether mechanical or neural origin) with ratings from zero (“no increase in tone”) to four (“limb rigid in flexion or extension”)

Blepharospasm: Spasm of eyelid muscle

Cast or splint or orthosis:

Cast: A rigid dressing, moulded to the body to give firm support

Splint: Material or a device used to protect and immobilize body part

Orthosis: Apparatus used to support, align, prevent or correct deformities or to improve function of movable parts of body

Cervical dystonia (see also Torticollis): Involuntary muscle contractions in the neck region due to disordered tonicity of muscle

Diplegia: Paralysis affecting like parts (e.g., legs) on both sides of body

Dorsiflexion: Flexion in a dorsal direction, e.g., flexion of foot in an upward direction

Electromyogram (EMG): A recording of electrical activity of a muscle or group of muscles

Equinovalgus (talipes equinovaglus): A foot deformity in which heel is elevated and turned outward from midline of body

Equinovarus (talipes equinovarus): A foot deformity in which heel is turned inward from midline of leg and foot is plantar flexed

Eversion: A turning outward, as of the sole of the foot or the eyelid

Expanded Ashworth scale (EAS): An expanded version of original Ashworth Scale, used to measure muscle tone

Fixed joint contracture: A condition whereby a joint is permanently fixed in flexed position

FES: Functional electrical stimulation used to stimulate or improve muscle activity for performance of a functional task

Gait: Manner or style of walking

Goniometric measurements: Numeric representation of range of motion of joint

Gross motor function measurements (GMFM): Standardized observational instrument designed and validated to measure change in gross motor function over time in children with cerebral palsy

Hemiplegia: Paralysis of one side of body

Modified Ashworth scale (MAS): A modification of the Ashworth Scale, MAS includes one additional item for measuring muscle tone

Motion analysis: Analysis of body movement by component parts

Paraplegia: Paralysis of legs and lower part of body

Passive range of motion (PROM): Movement applied to joint solely by another person or persons or passive motion machine

Pediatric evaluation of disability inventory (PEDI): Comprehensive, clinical assessment tool used to assess functional capabilities (self care, mobility and social function) and performance in children with disability

Physician rating scale (PRS): Scale used to measure gait pattern and range of motion

Ptosis: A drooping of upper eyelid (as from paralysis of oculomotor nerve)

Quadriplegia: Paralysis of all four limbs

Range of motion (ROM): Range, measured in degrees of a circle, through which joint can be extended and flexed

Rigidity: Continuous involuntary sustained muscle contraction

Spasticity (see also Spasm): Condition described by rate-dependent increase in tone and exaggerated deep tendon reflexes

Spasm (see also Spasticity): An involuntary contraction of muscle or group of muscles

Strabismus: Misalignment of visual axes of eyes

Tardieu scale: Scale used to measure velocity-dependent component of hypertonia (i.e., muscle spasticity)

Tone intensity: Magnitude or degree of muscle resistance to passive elongation or stretch

Torticollis (see also Cervical dystonia): A contracted state of cervical muscles, producing twisting of neck and unnatural position of head

Video gait analysis (VGA): Visual, analytical tool used to evaluate structural movement of entire body during gait cycle

Vulpe assessment battery (VAB): A comprehensive, process-oriented, criterion-referenced assessment of children's functional abilities

1 INTRODUCTION

1.1 Background

Spasticity is a symptom that can cause disability in affected patients. It is a form of muscular hypertonicity characterized by a rate-dependent increase in tone.^{1,2} Clinically, it is an increased resistance to passive movements that characteristically gives way suddenly as the passive stretch is continued. It may interfere with voluntary movement and affect the activities of daily living such as dressing, eating and walking.³ The rationale behind treating spasticity is to decrease muscle tone; alleviate distressing symptoms; improve motor function; or prevent or reduce the complications associated with muscle hypertonia, for example, contractures.^{2,3}

1.2 Current Treatments for Spasticity

Pharmacologic and non-pharmacologic treatments are used to treat spasticity in patients. Oral antispastic medications such as dantrolene (Dantrium[®]), baclofen (Liorseal[®]) and tizanidine (Zanaflex[®]) are commonly used. These drugs have a non-selective effect and can be a benefit to those with generalized spasticity. Systemic side effects, such as sedation and generalized weakness, may limit their use. The possibility of tolerance may limit its long-term use. Increasing the dosage or changing to another agent with a different mechanism of action may provide long-term symptom relief.³ Other drugs that may be used to treat spasticity include benzodiazepines, clonidine and gabapentin.

Local anesthetics and nerve-blocking agents are injected locally to relieve spasticity.⁴ Local anesthetics, such as lidocaine and bupivacaine, reversibly block conduction when applied to nerve tissue in appropriate concentrations.⁴ The use of these agents is associated with a risk of central nervous system (CNS) and cardiovascular (CV) toxicity.⁴ Nerve-blocking agents, such as alcohol and phenol, can reduce spasticity by chemically destroying the nerve fibres. While they are commonly used for lower limb spasticity, there is a risk of sensory impairment when used on the upper limbs.⁴

Non-pharmacologic treatment such as physical and occupational therapy is often used with pharmacologic therapy. After tone is decreased with pharmacologic agents, the therapist can focus on functional treatment goals and implement interventions effectively. The therapist can also evaluate a patient's progression during treatment. Surgery may be performed to relieve spasticity.

Range of motion (ROM) exercises are an essential component of spasticity management to prevent fixed muscle shortening or contracture. Physical therapists may use splinting, serial casting or orthosis that allow for prolonged static stretching of muscles. Functional electrical stimulation (FES) is provided through small electrodes placed on the skin. FES can be used to stimulate a weakened muscle during a specific phase of a functional activity, apply stimulation to opposing muscles or improve muscle activity while performing a functional task.⁵

1.3 Botulinum Toxin A

Botulinum toxin is produced by the anaerobic bacterium *Clostridium botulinum*.⁶ It inhibits the release of acetylcholine from neurons at the neuromuscular junction, resulting in muscle relaxation.⁶ Among serotypes A to G of botulinum toxin,⁶ botulinum toxin A (BTX-A) is the one in routine use.

BTX-A is commercially available as a purified compound in two products: Dysport[®] (Ipsen) and Botox[®] (Allergan).^{7,8} Dysport[®], which is mainly available in Europe, is distributed by Speywood Pharmaceuticals in England, a subsidiary of Beaufour Ipsen of France. Botox[®] is available in North America and most other markets.⁸ The two formulations differ in potency and different dose ratios of Botox to Dysport are used depending on the type of dystonia.

BTX-A is injected into affected muscles. The dose is determined on an individual basis, but is generally related to the muscle being injected. Factors such as susceptibility to toxin or pre-existing weakness must be considered. The pharmacologic effects of BTX-A injection usually last two to four months.⁷ Clinical effects may last longer when other pharmacologic or non-pharmacologic treatments are also used.⁶ Repeat doses may be required at regular intervals. The time between doses may vary among patients and may depend on tolerance due to the formation of neutralizing antibodies. Clinical observation of abnormal movement or electromyography (especially for smaller muscles) may help in the identification of the affected muscle.

The adverse effects experienced with treatment may also be attributed to BTX-A. The most common local adverse effect is transient weakness of adjacent muscles. It may be expressed as dysphagia when BTX-A is used for cervical dystonia or ptosis when used for blepharospasm. Systemic adverse events, which are rare, include transient flu-like symptoms, anaphylaxis and excessive fatigue. Patients who are pregnant or breastfeeding; or those with significant peripheral nerve or muscle disease, such as myasthenia gravis or Lambert-Eaton syndrome, should avoid BTX-A treatment. Patients who are receiving antibiotics, anesthetics or other medications that may affect neuromuscular transmission should be treated cautiously.⁹

Botox[®] is approved in Canada as therapy for the following indications:¹⁰

- subjective symptoms and objective signs of cervical dystonia (spasmodic torticollis) in adults
- blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients ≥ 12 years of age
- strabismus in patients ≥ 12 years of age
- dynamic equinus foot deformity due to spasticity in pediatric cerebral palsy patients ≥ 2 years of age
- hyperhidrosis of the axilla
- focal spasticity, including upper limb spasticity associated with stroke in adults.

1.4 Diseases in which Spasticity is a Common Symptom

In several diseases, the central motor pathway of the central nervous system (CNS) is damaged, resulting in decreased selective motor control and abnormal patterns of muscle activity or spasticity. Focal increase in tone and spasm may result in pain, lead to difficulty with personal hygiene and hinder self care. Minimizing spasticity may enhance the patient's ability to relieve symptoms and achieve specific passive or functional goals.³

A cerebral vascular accident (CVA) is a vascular lesion secondary to ischemia or hemorrhage.¹¹ The terms "CVA" and "stroke" are often used interchangeably. Cerebral ischemia is caused by reduced blood flow, which results in infarction or the death of brain tissue.¹¹ Cerebral hemorrhage is caused by bleeding in the brain tissue due to the rupture of an artery. In either case, the damage to the CNS commonly results in neuromotor dysfunction, including hemiparesis and spasticity. There is a lack of consensus regarding the number of patients developing spasticity and the relationship between spasticity and disabilities after acute stroke.⁹

Cerebral palsy (CP) is a disorder of movement and posture that results from a non-progressive lesion or injury of the immature brain.¹¹ It is classified according to the extremities involved, the characteristics of neurologic dysfunction and gross motor function. The clinical manifestations often differ according to gestational age at birth, chronological age and the CNS lesion. The incidence rate of CP is approximately two to three per 1,000 births; its prevalence rate is 1.5 to two per 1,000 live births.¹¹ The effects of CP can vary from awkwardness in hand control to no muscle control.

With the increased use of BTX-A and as the population being treated with BTX-A expands, the evidence regarding its efficacy and safety should be reviewed.

2 OBJECTIVES

Our primary objectives, which were identified in a research protocol that was written a priori, were to determine if therapy with BTX-A was:

- effective in reducing focal spasticity in patients with upper or lower limb spasticity compared with pharmacologic and non-pharmacologic therapies
- safe when used to reduce focal spasticity in patients with upper or lower limb spasticity compared with pharmacologic and non-pharmacologic therapies.

3 METHODS

A preliminary search of the medical literature revealed that BTX-A had been used in clinical trials to treat spasticity in a variety of patients. As a result, the review was done without limits on the disease involved.

3.1 Literature Search Strategy

Published literature was identified by first searching several databases (Appendix 1). Where possible, retrieval was limited to the human population and there were no language restrictions. BIOSIS Previews[®], EMBASE[®], MEDLINE[®], PASCAL and ToxFile were searched on DIALOG[®], with regular updates scheduled throughout the project on all databases except ToxFile. Parallel searches were performed and updated in PubMed and The Cochrane Library. A separate search was undertaken on DIALOG[®] to identify articles that were not captured using the clinical trial filter.

Grey literature was obtained by searching health technology assessment and related agencies' web sites and their associated databases. Clinical registries were searched for information on current or completed trials. Google[™] and other Internet search engines were used to identify web-based information. We hand searched of the bibliographies and abstracts of retrieved reports; and contacted appropriate experts and agencies.

Allergan and Ipsen were invited to contribute published and unpublished literature regarding their products. The authors of trials were also contacted to contribute information where necessary.

3.2 Eligibility Criteria

The following factors were used when considering studies for this review:

- participants: patients with upper or lower extremity spasticity
- intervention: all commercially available BTX-A of any dosage or duration
- comparator: any pharmacologic or non-pharmacologic intervention (e.g., casts, splints, electrostimulation) used for spasticity
- outcome measures: the primary outcome measure was muscle tone; secondary outcomes included ROM (passive and active), results of motion analysis, function or disability, pain, quality of life and adverse events
- study design: randomized controlled trials (RCTs).

3.3 Selection Process

3.3.1 Article selection

Two reviewers (KG and LM) independently reviewed citations from the literature search. After a review of titles and abstracts, only potentially relevant citations were retained. In case of doubt from either reviewer, the full text was retrieved to gather further information. Relevant review articles were also retrieved and their references manually searched for further trials. These were used to prepare background information.

3.3.2 Selection of relevant studies

Once the full text of all potentially relevant trials was acquired, two reviewers (KG and LM) independently made the final selection of those to be included using inclusion and exclusion criteria and a standard form (Appendix 2). Disagreement regarding the inclusion of a study was resolved by consensus. An agreed-upon third party (AM) resolved any persistent differences.

3.4 Data Analysis

3.4.1 Assessment of quality

The quality of the included studies was assessed independently by two reviewers (KG and LM) using the Jadad scale (Appendix 3) and assessing allocation concealment (adequate, inadequate, or unclear). Because of the low inter-rater reliability that can occur when using the Jadad scale, a calibration exercise with 10 randomized trial reports chosen by the information specialist was conducted before the assessment of the relevant trials included in this review. Quality assessment was undertaken to describe heterogeneity among trials.

3.4.2 Data abstraction

Two reviewers (KG and LM) used a standard form to perform data abstraction (Appendix 4). Any missing information (for example, number of patients, standard deviation) was sought from the primary author(s) of the study. Information from each trial was collected using a separate form for each outcome. Any disagreements were resolved by consensus.

3.4.3 Statistical analysis

Statistical reporting and meta-analysis were done using intention-to-treat (ITT) data whenever possible. Meta-analysis was performed when enough quantitative data were provided and trials were sufficiently similar. Binary data were expressed as risk differences (RD), while continuous outcomes were described as weighted mean differences (WMD). Point estimates were accompanied by a precision estimate using 95% confidence intervals (CI).

MetaView 4.1 is used to calculate pooled results. MetaView uses DerSimonian and Laird random effects and Mantel-Haenszel fixed effects models for combining dichotomous outcomes. DerSimonian and Laird random and inverse variance fixed effects models are used for combining continuous outcomes.

The statistical heterogeneity across trials is assessed by performing a chi-square test procedure using MetaView. A p value of <0.1 is used to indicate the presence of significant statistical heterogeneity. A funnel plot is used, where possible, as an aid to detect publication bias; asymmetrical plots suggest that bias can pose a threat to the validity of a meta-analysis.

4 RESULTS

4.1 Quantity of Research Available

The literature search was conducted on April 1, 2002 and updated until April 30, 2004. The electronic search was divided into two searches; one included an RCT filter and one did not. The search without the RCT filter captured review articles and articles for manual searching.

The RCT electronic DIALOG[®] search yielded 92 unique citations. Of these, 42 were considered potentially relevant [κ score (κ)=0.772 (95% CI=0.639; 0.906)]. A total of 36 citations were identified through the DIALOG[®] alert system, of which three were considered potentially relevant. We identified 12 citations in the PubMed search, but none was considered potentially relevant. In total, 45 citations were potentially relevant. Nine additional potentially relevant citations were identified through manual searching of retrieved articles.

Two reviewers (KG and LM) applied a priori eligibility criteria to the potentially relevant citations. As a result, 18 citations were excluded: 11 review articles, two non-RCTs, three trials without controls and two for other reasons (Appendix 5). A total of 33 unique RCTs reported in 37 citations (four duplicates) were identified for inclusion in this review (κ =1.0).

A flow chart of the included trials, the trial characteristics and trial findings are summarized in Appendices 6, 7 and 8 respectively.

4.2 Description of Outcomes Measures

Various outcome measures have been used to quantify the effect of BTX-A on spasticity (Appendix 9). Among the scales used in measuring muscle tone, the Ashworth scale, the modified Ashworth scale (MAS) and the expanded Ashworth scale (EAS) are often used (Appendix 10). ROM can be categorized as passive or active. It is commonly measured using a goniometer, which measures the change in movement in degrees. Motion analysis or gait analysis identifies the abnormal movements of muscles and joints as the body moves. A

patient's gait or movement can be recorded using video gait analysis (VGA) to allow analysis in slow motion or comparison over time. Several trial-specific scales have been used to quantify a physician's, caregiver's or patient's impression of improvement, quality of life or pain.

4.3 BTX-A for Upper Extremity Spasticity in Patients Post-stroke

We identified nine RCTs (consisting of six trial reports¹²⁻¹⁷ and three published abstracts¹⁸⁻²⁰) (Appendix 7). Four studies used Dysport¹²⁻¹⁵ and five studies used Botox.¹⁶⁻²⁰ Eight studies compared various doses of BTX-A to placebo, while one compared BTX-A, with or without electrical stimulation, to placebo.¹⁵ The quality scores of the trials ranged from two to five, with a mean score of 3.1. Follow-up times ranged between two and 16 weeks, with a mean duration of 15.1 weeks. Seven of the nine trials did not describe the allocation of patients clearly; the remaining two trials described allocation adequately. All the included trials were randomized, controlled and double-blinded except for a four-armed trial by Hesse *et al.* that compared BTX-A with or without electrical stimulation, to placebo with or without electrical stimulation.

Patients included in the trials had experienced a stroke at least three to 12 months earlier and were experiencing spasticity in the upper limb (as measured by the modified Ashworth score or Ashworth score or expanded Ashworth score of two to three). The trial sample size ranged from 24 to 122 patients (total number of patients=596).

Nine trials reported on muscle tone, five reported on passive range of motion (PROM), four on active range of motion (AROM), five on pain, eight on patient's, caregiver's or physician's assessment of function and disability and nine on adverse events. There was no information on motion analysis or quality of life in any of the included trials.

4.3.1 Muscle tone

All nine RCTs reported on muscle tone.¹²⁻²⁰ Four trials measured muscle tone using the MAS, three used the Ashworth scale and two used the EAS. The MAS measured tone on a scale of zero to five, whereas the older Ashworth scale measured tone on a scale of zero to four (Appendix 10). The two trials that used the EAS were described in abstracts where the scale was not defined. Lower scores on these scales correspond with decreased tone.

a) MAS

The trial by Hesse *et al.* evaluated patients receiving Dysport 1,000 U with or without electrical stimulation and placebo at two, six and 12 weeks post-injection. For comparison, the Dysport alone (n=6) and the placebo (n=6) groups were evaluated. Muscle tone was measured at the elbow, wrist and finger, using the MAS. The mean difference from baseline was greater in the Dysport alone group compared with placebo. For the elbow, the MAS scores were -0.5 versus 0.0 at week 2, -0.5 versus 0.16 at week 6 and -0.17 versus 0.16 at week 12. For the wrist, the MAS scores were -0.34 versus -0.16 at week 2, -0.34 versus -0.33 at week 6 and -0.17 versus -0.16 at week 12; and for the finger, -0.67 versus 0.0 at week 2, -0.67 versus -0.16 at week 6

and -0.50 versus 0.17 at week 12 for the Dysport and placebo groups respectively. It was not reported whether the improvement demonstrated in the Dysport group was significantly different from that with placebo.

In the trial by Bhakta *et al.*, median MAS scores at the finger were significantly lower in the treatment group at week 2 (-2 versus 0, $p < 0.001$), week 6 (-1.5 versus 0, $p < 0.001$) and week 12 (-1.0 versus 0, $p < 0.006$) compared with placebo. Median MAS scores at the elbow were significantly lower in the treatment group compared with placebo only at week 2 (-1.0 versus 0, $p < 0.002$).

In two trials that were conducted by Bakheit *et al.*, the magnitude of benefit was examined with an area under the curve analysis. In the 2000 study, muscle tone was measured at the elbow, wrist and fingers at 16 weeks using the MAS. The mean change from baseline was statistically significant for all Dysport doses at the elbow (-16.2 versus -3.2 for 500 U, $p = 0.002$; -15.0 versus -3.2 for 1,000 U, $p = 0.006$; -14.2 versus -3.2 for 1,500 U, $p = 0.013$) and wrist (-17.1 versus -6.3 for 500 U, $p = 0.028$; -20.7 versus -6.3 for 1,000 U, $p = 0.004$; -18.5 versus -6.3 for 1,500 U, $p = 0.017$) compared with placebo. Only the mean change from baseline for the 1,000 U Dysport dose was significant at the fingers (-16.3 versus -6.3, $p = 0.044$).

The 2001 trial by Bakheit *et al.* compared muscle tone at the elbow, wrist and finger, at 16 weeks, using the MAS. The mean change from baseline was significant at the wrist and finger compared with placebo, -19.8 versus -9.1, $p = 0.004$; and -16.6 versus -9.9, $p = 0.001$ respectively.

b) Ashworth

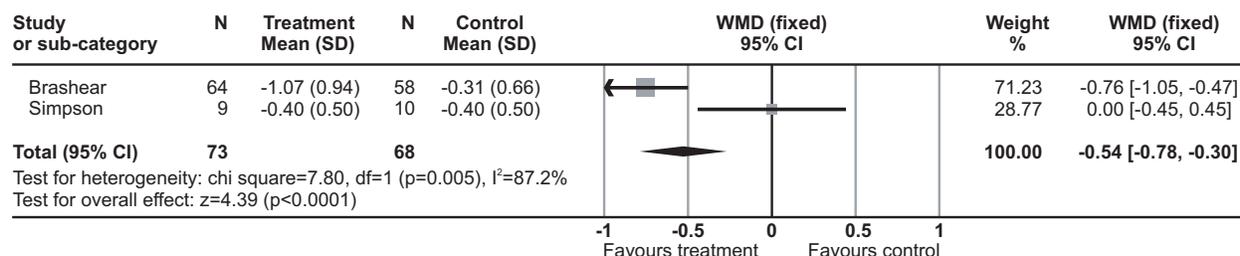
The O'Brien *et al.* trial compared muscle tone using the Ashworth scale. Patients treated with 300 U Botox experienced a decrease in wrist flexor tone at weeks 2, 4 and 6 and a decrease in elbow flexor tone at weeks 2 and 4. Whether this decrease was significantly different from baseline was not reported.

A trial by Simpson *et al.* measured muscle tone at the elbow and wrist using the Ashworth scale at weeks 2, 4, 6, 10 and 16. Patients receiving 300 U Botox experienced a significant decrease in Ashworth score at the elbow and wrist at weeks 2 and 4, compared with placebo ($p < 0.05$). The 300 U dose and the 75 U dose also produced significant decreases at the wrist at week 6 compared with placebo ($p < 0.05$).

The trial by Brashear *et al.* measured muscle tone at the wrist, finger and thumb at weeks 6 and 12 using the Ashworth scale. A response to treatment was defined as being ≥ 1 point improvement from baseline. A significant decrease in the Ashworth score in the Botox group compared with placebo was reported at the wrist (-1.66 versus 0.48 in week 6, $p < 0.001$; -1.07 versus -0.31 in week 12, $p < 0.001$) and finger (-1.34 versus -0.32 in week 6, $p < 0.001$; -0.78 versus -0.12 in week 12, $p < 0.001$). There was a significant decrease at the thumb only at week 12 (-0.92 versus -0.31, $p = 0.02$).

When the week 16 wrist data from the 300 U dose group in the Simpson trial were combined with the week 12 wrist data from the Brashear trial, a statistically significant difference was calculated (-0.54, 95% CI: -0.78 to -0.30).

Figure 1: Effect of BTX-A on muscle tone using Ashworth scale at wrist in patients with stroke



c) EAS

In the trial by Childers *et al.*, the mean decrease in EAS for wrist flexors was greater than that of placebo for all Botox groups through week 12. The 360 U group demonstrated the greatest reduction in tone for the longest duration. Responses at the elbow and finger flexors demonstrated similar patterns. No qualitative information was provided.

In the trial by de Beyl *et al.*, muscle tone was significantly improved at the wrist in the 360 U dose group at weeks 1 (p<0.001), 4 (p<0.0018) and 6 (p<0.005); and at the elbow at week 4 (p<0.003) compared with placebo. Muscle tone was not significantly changed in the 180 U and 90 U dose groups. The actual scores were not reported.

Only the 2000 and 2001 trials by Bakheit could be combined. Since the Bakheit 2000 trial was a dose-ranging trial, only the Dysport 1,000 U group was combined with the results from Bakheit 2001 and compared to placebo. At 16 weeks, a statistically significant improvement at the elbow in the treatment group compared with placebo was detected by meta-analysis, WMD=-4.65 (95% CI: -9.03 to -0.28). Statistical heterogeneity was also detected. When a random effects model was used to combine these results, the CI overlapped the null, suggesting no statistical significance, -6.28 (95% CI: -16.02 to 3.47). Statistically significant improvements were seen at the wrist and fingers. At the wrist, the mean difference compared to placebo was -11.73 (95% CI: -16.72 to -6.74) and at the fingers, the mean difference compared to placebo was -7.87 (95% CI: -13.49 to -2.24).

Figure 2: Effect of BTX-A on muscle tone using expanded Ashworth scale at elbow in patients with stroke (random effects model)

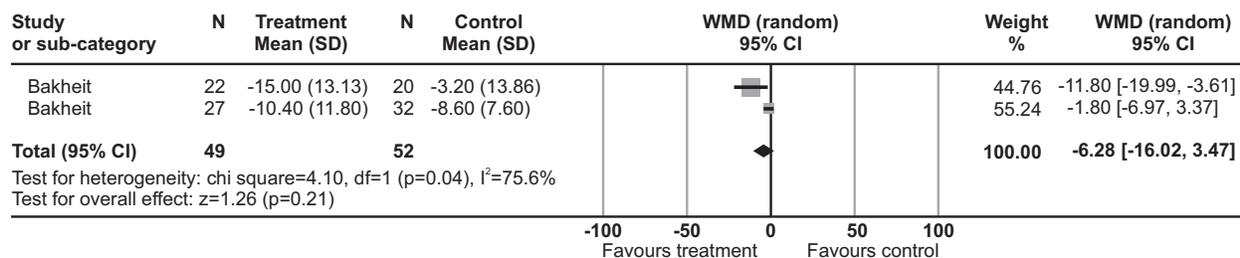


Figure 3: Effect of BTX-A on muscle tone using expanded Ashworth scale at elbow in patients with stroke (fixed effects model)

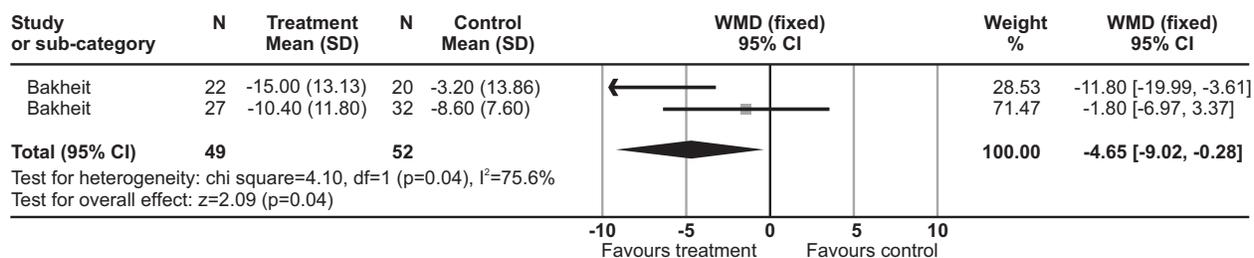


Figure 4: Effect of BTX-A on muscle tone using expanded Ashworth scale at wrist in patients with stroke

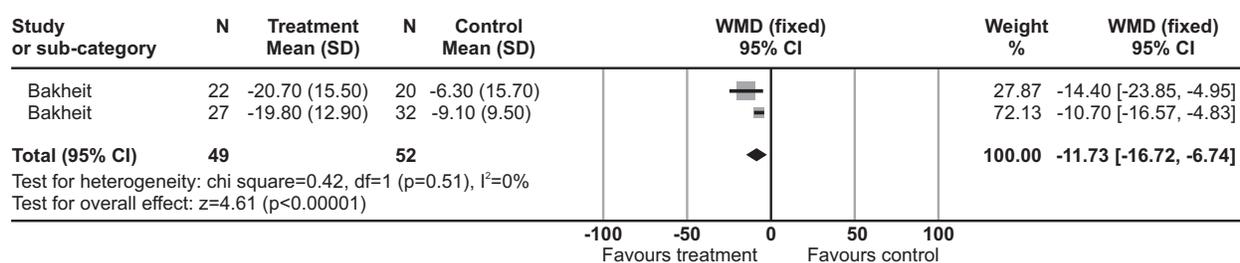
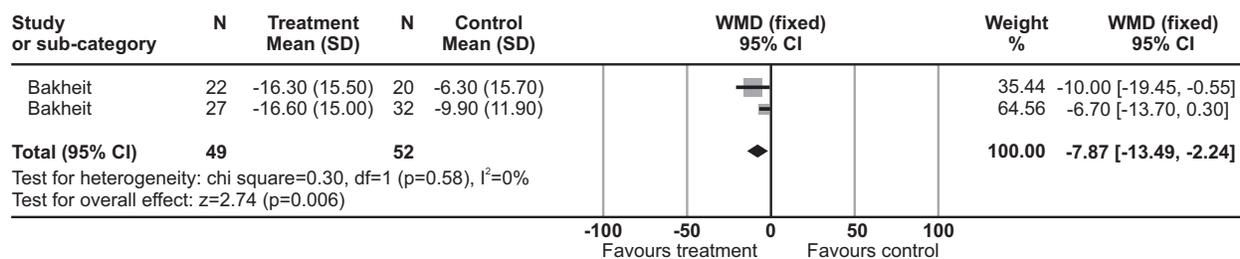


Figure 5: Effect of BTX-A on muscle tone using expanded Ashworth scale at finger in patients with stroke



4.3.2 Passive Range of Motion (PROM)

Of the nine included trials, four included information on PROM.^{12-15,18}

In the trial by Bhakta *et al.*, PROM was measured at the elbow and wrist. Passive elbow extension was recorded as zero if full extension was possible (positive values indicating flexion deformity). There were no significant differences in PROM at the elbow or shoulder between the groups. There was however, a significant improvement in PROM at the wrist dorsiflexion; median difference between treatment and placebo groups=+17° (p=0.006) at week 6.

The trial by de Beyl *et al.* reported a significant improvement in PROM at the wrist and elbow at all Botox doses, but no quantitative data were provided in the abstract.

Bakheit *et al.* (2000) measured PROM at the wrist and elbow at week 4. The mean change from baseline at the elbow and wrist was numerically greater in all Dysport groups except the 1,000 U dose group at the elbow, compared with placebo. These differences were not statistically significant from placebo.

The second trial by Bakheit *et al.* (2001) measured PROM at the wrist and elbow at weeks 4 and 16. At week 4, the mean change from baseline was not statistically different from placebo at the wrist (25.7° versus 17.4°, p=0.09) and elbow (10.3° versus 3.5°, p=0.18). The difference became significant at the elbow at week 16 (163.2° versus 55.9°, p=0.036). No 16-week data were provided for the wrist.

Of the four trials that reported on PROM, two studies provided data suitable for meta-analysis. Bakheit 2000 and 2001 measured PROM at the wrist and elbow at four weeks. A meta-analysis of the mean difference at the wrist and elbow was found to favour treatment, but it was not statistically significant. The weighted mean difference (WMD) in PROM at the elbow was 2.58° (95% CI: -6.37 to 11.54) and at the wrist was 9.00° (95% CI: -0.28 to 18.28).

Figure 6: Effect of BTX-A on PROM at elbow in patients with stroke

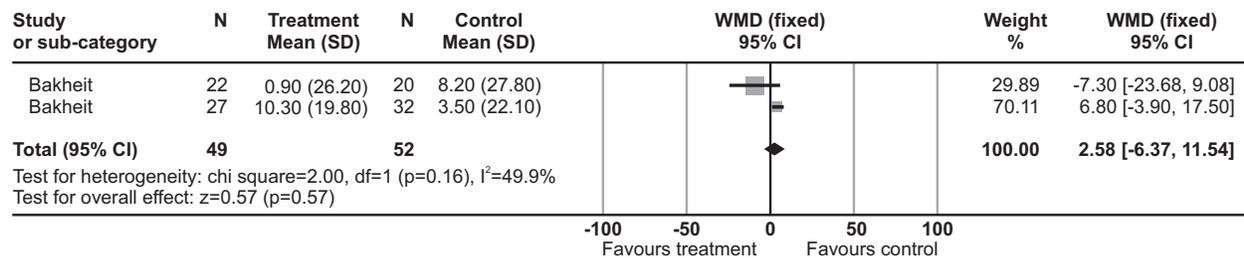
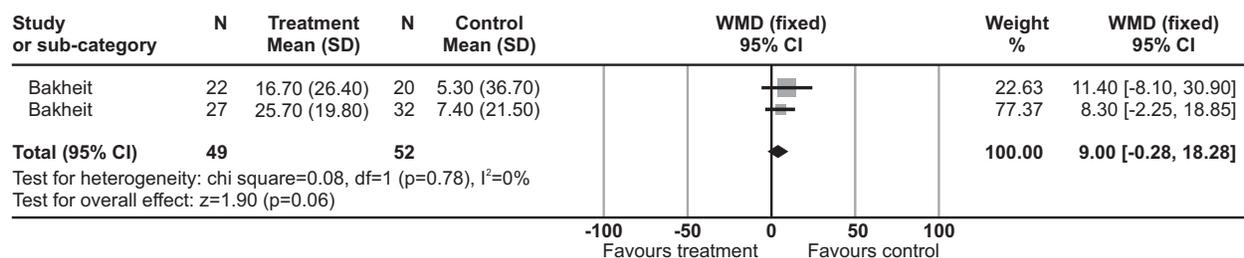


Figure 7: Effect of BTX-A on PROM at wrist in patients with stroke



4.3.3 Active Range of Motion (AROM)

Of the nine included trials, four included information on AROM.^{12-14,18}

In the trial by de Beyl *et al.*, AROM at the elbow was significantly improved at week 6 for the 360 U dose group; at weeks 1, 4, 6 and 12 for the 180 U dose group; and at weeks 1, 6 and 12 for the 90 U dose group. No quantitative data were provided.

The trial by Bhakta and the two trials by Bakheit did not report any significant differences with BTX-A treatment compared to placebo.

When the results from the Bakheit 2000 and 2001 trials were combined by meta-analysis, a statistically significant difference could not be detected between the BTX-A groups and placebo for the elbow or wrist.

Figure 8: Effect of BTX-A on AROM at elbow in patients with stroke

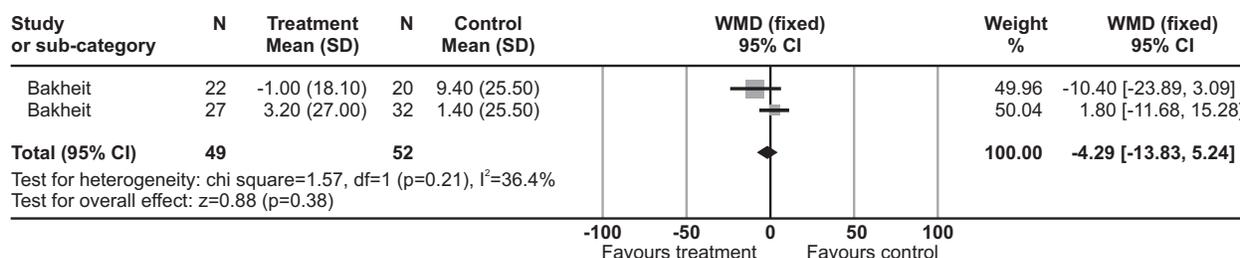
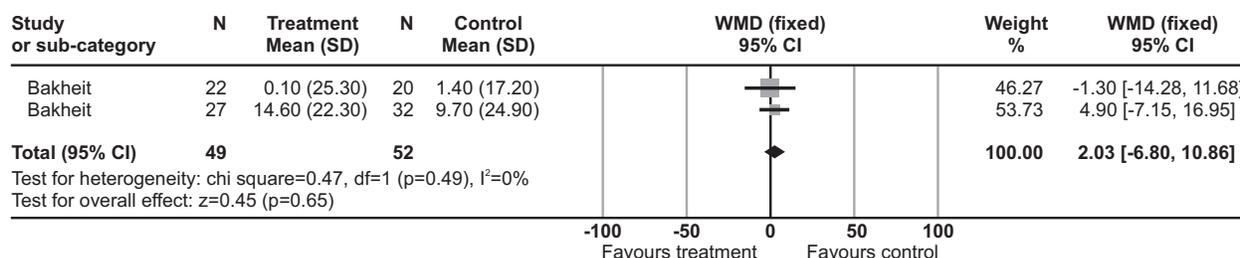


Figure 9: Effect of BTX-A on AROM at wrist in patients with stroke



4.3.4 Pain

Five trials reported pain as an outcome measure.¹²⁻¹⁶ No trial described the type or severity of pain (only the incidence was reported).

The trial by Simpson *et al.* reported no significant differences in pain assessment between the treatment group and the placebo group. No quantitative data were provided to describe how the assessment was performed.

Hesse *et al.*, used a global pain assessment score (zero to three), but quantitative analysis was not provided, as most patients did not suffer from pain.

There were no statistically significant differences in pain between the study groups in the trial by Bhatka *et al.* In the week preceding intervention, 65% of the patients reported arm pain. Arm pain was not improved (no change in median scores) at week 6.

Both trials by Bakheit measured muscle pain using a four-point scale (0=no pain, 3=severe pain) and both trials reported no statistically significant differences between the study groups.

4.3.5 Patient's, caregiver's or physician's assessment of function and disability

In the Bakheit 2000 trial, patients and caregivers made a subjective evaluation of the effects of treatment on the ease (or difficulty) of cleaning the palm, cutting fingernails and putting an arm through a sleeve. More patients showed improvement at four weeks in the Dysport group compared with placebo. The same three functions were evaluated in the Bakheit 2001 trial, which reported that the activities were less difficult four weeks after Dysport treatment. Furthermore, patients and investigators rated the global assessment of benefit at the end of the trial as “much improved” or had “some improvement” in the Dysport group compared with placebo.

In the Brashear *et al.* trial, functional disability was measured by investigators using a four-point disability assessment scale. A score of 0 indicated no disability, 1=mild disability, 2=moderate disability and 3=severe disability. Four areas of disability were assessed: hygiene, dressing, limb position and pain; one area was selected as the primary target of treatment. Most patients selected dressing (32%), limb position (30%) and hygiene (26%) over pain (12%). At 12 weeks, patients treated with Botox had a greater improvement in the principal target compared with placebo (-0.46 versus -0.88, $p=0.02$). When all the areas of disability were evaluated, more Botox-treated patients (88%) had a ≥ 1 point improvement on the disability assessment scale compared with those receiving placebo (53%), $p=0.007$. At 12 weeks, the scores for the physicians', patients' and caregivers' global assessment were significantly higher in the Botox-treated group (0.5 versus 1.09 for physicians, $p<0.001$, 0.48 versus 1.05 for patients and caregivers, $p=0.002$).

Hesse *et al.* reported the difficulties encountered by patients (or observed by caregivers) during three activities of daily living (cleaning the palm, cutting fingernails and putting the arm through a sleeve). It was not reported whether significant differences existed between patients treated with Dysport and placebo.

Simpson *et al.* measured physicians' and patients' global assessment of response on an eight-point scale (-4=severe worsening and +4=abolishment of symptoms). Statistically significant differences in global assessments by the physicians and patients were reported at four and six weeks ($p\leq 0.05$) at the 75 U and 300 U doses, but not for the 150 U dose group.

Patients completed the rating of disability and caregivers completed the rating of caregiver burden using a five-point Likert scale in the Bhakta *et al.* trial. Significant differences between the Dysport and placebo groups in patient disability were reported at week 2 ($p=0.004$) and week 6 ($p=0.016$), but not at week 12 ($p=0.055$). Significant differences in caregiver burden between Dysport and placebo groups were reported at week 2 ($p=0.011$), week 6 ($p=0.005$) and week 12 ($p=0.027$).

The trial by O'Brien reported a significant improvement in the physicians' and patients' global assessment of spasticity with Botox at weeks 4 and 6. The trial by Childers *et al.* reported improvement in the physicians' global assessment with Botox. No qualitative data were reported in either trial.

4.3.6 Adverse events

All the trials reported adverse events, but only three trials reported data in a manner suitable for the pooling of results to determine an overall effect.

O'Brien *et al.* reported no drug-related, severe, irreversible or unexpected adverse events.

The trial by Simpson *et al.* reported three serious adverse events in the treatment group: hypothyroidism, visceral lymphoma and pain due to spasticity. Other adverse events experienced by the study participants were transient global amnesia; finger twitch; rash; soreness and pain at the injection site; and bladder instability. There were no significant differences in the frequency of adverse events. The incidence of adverse events in the placebo group was not reported. Hesse *et al.* reported that the treatment was well tolerated by all patients and that no study-related serious adverse events were observed. The trial by Childers *et al.* also reported no serious adverse events related to BTX-A. No quantitative data were provided in either abstract.

DeBeyl *et al.* reported depression as the only serious adverse event that was possibly related to treatment. No additional details were provided regarding adverse events in either group.

The trial by Brashear *et al.* reported adverse events that affected four or more patients or their caregivers, not the overall incidence of adverse events. No significant differences in the incidence of adverse effects were reported between the study groups. Common adverse events in both groups included lack of coordination (13% versus 5%), infection (10% versus 5%) and pain (6% versus 8% in the placebo and treatment groups respectively).

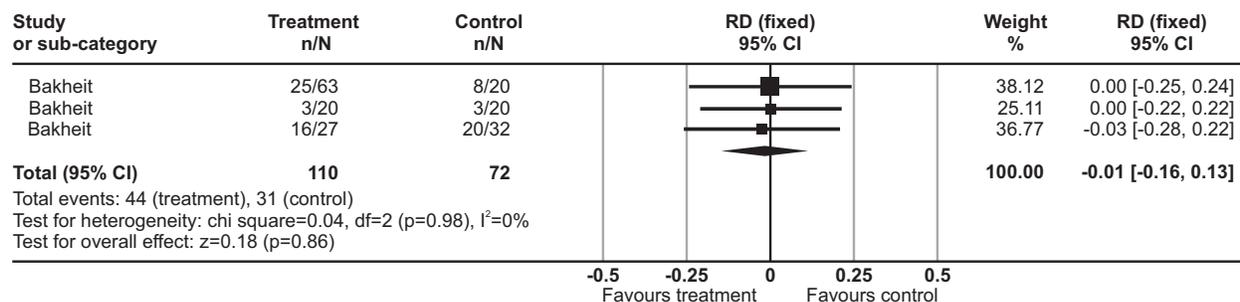
In the trial by Bakheit *et al.*, 33 patients reported adverse events: 13 in the 500 U dose group, four in the 1,000 U dose group, eight in the 1,500 U dose group and eight in the placebo group. In the treatment group, the most frequently reported adverse events included urinary tract infection and respiratory tract infection (n=6), seizures (n=5) and accidental injury (n=5). Other adverse events reported by the treatment group included rashes (n=6) and flu-like symptoms (n=3). The types of adverse events experienced by the control group were not described.

The later trial by Bakheit *et al.* reported that 16 patients (59.3%) in the treatment group and 20 patients (62.5%) in the control group experienced adverse events. Three patients in both groups reported accidental injury and three patients in both groups reported urinary tract infection and respiratory infection. In the treatment group, other adverse events reported as “probably related” to the study medication were fatigue, tiredness and pain after injection. There was no statistically significant difference between the two groups.

In the trial by Bhakta *et al.*, three patients in each group reported adverse events. In the BTX-A group, two patients reported self-limiting arm pain in the first week of injection and one patient reported worsening of muscle spasm. In the control group, one patient developed herpes labialis one week post-injection, one patient experienced two transient ischemic attacks 12 days post-injection and one patient had an exacerbation of cardiac failure after four weeks of treatment.

Three of the trials reported adverse events in a manner appropriate for meta-analysis.¹²⁻¹⁴ The trials by Bakheit lasted 16 weeks and the trial by Bhakta lasted 12 weeks. When the results of these three studies are pooled, 1% fewer patients experienced adverse events in the treatment group, 0.01 (95% CI: -0.16 to 0.13), but this difference was not statistically significant.

Figure 10: Incidence of adverse events with BTX-A treatment in patients with stroke



4.4 Use of BTX-A for Lower Extremity Spasticity in Patients Post-stroke

Three trials that were reported in four publications were included in this section of the review.²¹⁻²⁴ The Kirazli and On trial compared Botox to 5% phenol, whereas Johnson compared Dysport, FES and physiotherapy to physiotherapy alone. The Pittock *et al.* trial compared varying doses of Dysport with placebo. All trials lasted 12 weeks. Quality scores ranged from 2 to 5, with a mean score of 3.3 (Appendix 7).

Patients in the trials had experienced a stroke in the previous six to 12 months. Kirazli and On characterized the degree of spasticity using the Ashworth scale (>3 at ankle flexor and ankle invertor) in 20 patients. Johnson characterized spasticity according to the patient’s degree of mobility using the Hauser ambulation index, degree of calf stretch and calf activation in 21 patients. The trial by Pittock *et al.* included 221 patients with hemiparesis with spastic equinovarus deformity of the ankle preventing full ankle dorsiflexion.

Kirazli and On, and Pittock reported on muscle tone and adverse events. Johnson and Pittock reported on gait analysis. Only Pittock reported on patients’, caregivers’ and physicians’ assessment of function and disability, while the Kirazli and On trial was the only one to report on ROM. Information on quality of life was excluded in all trials.

4.4.1 Muscle tone

Muscle tone was measured using the Ashworth scale at two, four, eight and 12 weeks in the Kirazli and On trial. The mean change (decreases) from baseline in Ashworth scores with ankle dorsiflexion was significantly different from phenol at week 2 (1.5 versus 0.7, p<0.05) and week 4 (1.4 versus 0.7, p<0.05). Similarly, the mean change (decreases) from baseline with ankle eversion were significantly different at week 2 (1.2 versus 0.4, p<0.05) and week 4 (1.2 versus 0.5, p<0.05).

At four weeks, each treatment group in the Pittock *et al.* trial demonstrated statistically significant differences compared with placebo (500 U: p=0.0093, 1,000 U: p=0.0002, 1,500 U: p=0.0116). At weeks 8 and 12, only the 1,500 U group demonstrated a significant difference compared with placebo (p=0.0170 and p=0.0188 respectively).

4.4.2 PROM

PROM was measured as the number of patients who experienced improvement, defined in the Kirazli and On trial as a goniometer measurement change $>5^{\circ}$ between assessments. More patients in the treatment group experienced improvement in PROM compared with patients receiving phenol (75% versus 62.5% respectively). The mean gain in PROM was 21.7° , compared with 18.2° in the phenol group. It is not reported whether the improvement observed in the treatment group was significantly different from the phenol group.

4.4.3 AROM

Only the Kirazli and On trial discussed AROM. Similar to PROM, more patients in the treatment group experienced improvement in AROM compared to those receiving phenol (60% versus 50% respectively). The mean gain in AROM was 20.2° in the treatment group and 17° in the phenol group.

4.4.4 Motion and gait analysis

The trial by Johnson *et al.* compared walking speed in a control group receiving only physiotherapy and a treatment group receiving physiotherapy and BTX-A. The median walking speed was found to be significantly greater in the treatment group ($p=0.04$).

Pittock *et al.* measured walking speed (distance covered during a two-minute test), step rate and step length. There were no statistically significant differences between groups in any outcome measure.

4.4.5 Patient's, caregiver's or physician's assessment of function or disability

In all treatment groups in the Pittock *et al.* trial, more patients and investigators considered the patient's condition was improved or much improved compared with those who thought it was the same or worse. More patients and investigators said that they were likely to or would definitely use the treatment again compared with those who said that they would be unlikely to or would not. There were no statistically significant differences between the overall assessments made by the patients or the investigator.

4.4.6 Pain

Pain was measured at the knee, ankle or foot in the Pittock *et al.* trial. At eight weeks, there was a statistically significant difference between groups treated with Dysport 1,000 U ($p<0.01$) and Dysport 1,500 U ($p<0.05$) compared with placebo.

4.4.7 Adverse events

The Kirazli and On trial reported adverse events, but it was only reported in the Kirazli publication. Two patients experienced a mild discomfort from the BTX-A injection. In the first week, however, 30% of patients in the phenol group developed dysesthesia (impairment of sensation) that lasted two to four weeks.

The Pittock *et al.* trial reported that 29%, 25%, 33% and 29% of patients experienced an adverse event in the 500 U, 1,000 U, 1,500 U and placebo groups respectively. Severe adverse events were reported in two patients receiving 500 U (one had pharyngitis, one had dysphagia), three patients in the 1,000 U group (one had headache, one experienced somnolence, one experienced dizziness), five in the 1,500 U group (two experienced pain, one had asthenia, one experienced somnolence, one had abnormal gait) and five in the placebo group (one experienced pain, one had edema, one had paresthesia, one had hypertonia, one had pancreatitis). The remaining mild to moderate adverse events that occurred in >5% of patients included pain, asthenia, convulsion and myasthenia.

4.5 Use of BTX-A for Upper Extremity Spasticity in Patients with Cerebral Palsy

The literature search identified two unique trials involving the use of BTX-A in patients with CP and upper extremity spasticity. The study by Corry *et al.*²⁵ was a randomized double-blind, placebo-controlled trial involving 14 patients with CP. The trial lasted 12 weeks and its Jadad score was 3. The study by Fehlings *et al.*²⁶ was a randomized, single-blind study involving 30 patients with CP. It lasted 24 weeks and its quality score was 2. Allocation concealment was unclear in both trials (Appendix 7).

Both trials included children with CP. The patients in the Corry *et al.* trial exhibited a dynamic component to their tone. Fehlings *et al.* used an MAS ≥ 2 at the elbow, wrist or thumb as an eligibility criterion. Corry *et al.* compared Botox and Dysport to placebo, whereas Fehlings *et al.* compared Botox and occupational therapy to occupational therapy alone.

Both trials included information on muscle tone, range of motion and adverse events. The trial by Corry *et al.* also measured patients' and parents' assessment of disability and function. Fehlings *et al.* used functional outcome measures including the quality of upper extremity skills test (QUEST) and the pediatric evaluation of disability inventory (PEDI). Pain and quality of life were not evaluated in either trial.

4.5.1 Muscle tone

The study by Corry *et al.* measured tone at the elbow, wrist and thumb using the Ashworth scale. At week 2, elbow tone was significantly improved (-1 versus 0, $p=0.01$) compared with placebo. This improvement was not demonstrated at week 12. Wrist tone was significantly improved compared with placebo at weeks 2 and 12 (-1 versus 0, $p=0.003$ and 1 versus 0, 0.001 respectively). There was no improvement in tone at the thumb compared to placebo at weeks 2 or 12.

The study by Fehlings *et al.* recorded tone intensity at the elbow, forearm, wrist and thumb using the modified Ashworth scale (MAS). Both groups showed a decline in spasticity throughout the study. The group injected with BTX-A showed a greater decline, but the overall differences between the BTX-A and control group were not statistically different.

4.5.2 AROM

Corry *et al.* measured AROM at the elbow, wrist and thumb. A significantly greater median change in elbow and thumb extension was reported at two weeks ($p=0.026$ and 0.036 respectively), but not at 12 weeks. There was no difference observed in wrist extension, thumb abduction or metacarpophalangeal extension at two or 12 weeks.

4.5.3 Patient's, caregiver's or physician's assessment of function and disability

The Corry *et al.* study measured patients' or parents' opinion of change at two and 12 weeks using a five category scale: very much better, much better, better, no change or worse. At two and 12 weeks, more patients in the treatment group reported an improvement compared with those in the placebo group. Whether the two groups were statistically different was not reported.

In the Fehlings *et al.* study, the primary outcome measure used was the quality of upper extremity skills test (QUEST). The evaluation revealed improvement in the BTX-A group over the control group at one, three and six months, but reached statistical significance at one month ($p=0.039$). The caregiver completed the self-care domain of the PEDI score to assess the child's activities of daily living. The mean change from baseline was significantly greater in the treatment group compared with the placebo group at all follow-up visits. The overall difference between the two groups was significant ($p=0.04$).

4.5.4 Adverse events

In the Corry *et al.* study, locally excessive weakness made the coin transfer exercise worse in two of 14 patients. One patient in the placebo group was described as becoming temporarily hypertonic, irritable, feverish and poorly cooperative at 48 hours.

In the Fehlings *et al.* study, one patient in the treatment group experienced a temporary decreased grip strength lasting two weeks. No other adverse events were reported.

4.6 Use of BTX-A for Lower Extremity Spasticity in Patients with Cerebral Palsy

Thirteen RCTs reported in 16 publications met the eligibility criteria and were included in the analysis.²⁷⁻⁴² Of the 13 trials, nine involved Botox,^{28-30,32-35,39,42} three involved Dyport^{27,40,41} and one included both Botox and Dysport.³¹ All the trials involving Dysport were compared to placebo, whereas the trials involving Botox were compared against placebo, casting or physiotherapy. Ten of the 13 trials were presented as full publications and three were presented in abstract form. The quality scores ranged from one to four, with a mean score of 2.5. The follow-up ranged from six weeks to one year with a mean of 18.9 weeks (Appendix 7). Among the 13 trials included in this section, two reported on muscle tone, six reported on PROM, three reported on AROM, five reported on motion analysis and gait analysis, seven reported on patients' caregivers' or physicians' assessment of function and disability, two reported on pain and five reported on adverse events. There were no trials reporting on quality of life.

4.6.1 Muscle tone

Muscle tone was reported in the Corry *et al.* trial. Calf tone was measured using the Ashworth score at weeks 2 and 12. At week 2, calf tone was significantly decreased compared with baseline ($p=0.0001$) in the treatment group. This effect was decreased by week 12 ($p=0.07$). There were no significant differences from baseline at weeks 2 or 12 in the group with casts. It was not reported whether the changes from baseline demonstrated by the BTX-A treated group were significantly different from placebo.

In the crossover trial by Reddihough *et al.*, a significant decrease in MAS was demonstrated at the left hip adductors and left calf at six months ($p<0.05$). However, scores were only obtained from eight of the 49 patients.

In the trial by Flett *et al.*, patients received one course of BTX-A or a course of fixed plaster casting for four weeks (2x2 weeks). Both intervention arms received night plasters simultaneously in time for the first follow-up evaluations at two months. There were no significant differences in MAS between BTX-A and fixed plaster casting at two, four and six months.

4.6.2 PROM

The trial by Sutherland *et al.* measured PROM at the ankle joints. There were no significant changes from baseline in the treatment group or placebo group in passive ankle dorsiflexion with the knee extended or flexed. There was, however, increased PROM at the ankle in the BTX-A group and a loss of range in the placebo group when range was measured with the knee flexed. With the knee flexed, PROM increased by a mean of 1.3° in the treatment group compared with a mean loss of 5.4° in the placebo group. With the knee extended, the loss of range was less in the BTX-A group. Both groups reported a mean loss in PROM of 0.56° and 6.3° respectively. It was not reported whether these differences were significant.

Corry *et al.* measured passive ankle dorsiflexion with the knee extended and flexed at weeks 2 and 12. With the knee extended, the changes from baseline in both groups were similar at week 2. There was a significant change at week 12 ($p=0.01$) in the BTX-A treatment group, but not in the casted group ($p=0.15$). The changes in dorsiflexion with the knee extended in both groups were not significantly different from each other at weeks 2 and 12. With the knee flexed, the treatment group demonstrated significant differences from baseline at weeks 2 and 12 ($p=0.008$ and $p=0.003$ respectively). The casted group demonstrated a significant difference from baseline only at week 2 ($p=0.02$). It was not reported whether these differences were significantly different from each other.

The trial by Koman *et al.* (2000) reported no significant differences in passive ankle dorsiflexion between the Botox and placebo groups. Quantitative data on this outcome were not reported.

In the Uhbi *et al.* trial, there were no significant differences in the mean change from baseline in the passive ankle dorsiflexion between the treatment and placebo groups at weeks 2, 6, and 12.

The trial by Baker *et al.* measured passive ankle dorsiflexion with the knee extended and flexed at weeks 4, 8 and 16. There was a significant difference in the mean change from baseline between the Dysport 30 U/kg group and placebo in the passive ankle dorsiflexion with the knee extended (-0.6° versus 2.6° , $p<0.05$) and the knee flexed (-1.0° versus 4.4° , $p<0.05$) at week 4. There were no significant differences in the other measures.

Reddihough *et al.* measured ankle dorsiflexion with the knee extended and flexed. At three months, ankle dorsiflexion with the knee extended was significantly increased in the BTX-A phase (mean change: 1.36° versus -7.27° , $p<0.05$). At six months, ankle dorsiflexion with the knee flexed was significantly increased in the BTX-A phase (mean change: 5.44° versus -3.09° , $p<0.01$), where a negative measurement corresponds to a decline from baseline.

No significant differences in PROM between BTX-A and fixed plaster casting were reported at two, four and six months by Flett *et al.*

The reporting of data did not allow for meta-analysis of this outcome.

4.6.3 AROM

The study by Sutherland *et al.* measured dynamic ankle dorsiflexion at 10% of the gait cycle. This measurement was thought to provide indirect information about the compliance of the ankle plantar flexor muscles shortly after foot contact. The subject was classified as “improved” if the difference was $>3^{\circ}$. The mean change in dorsiflexion at 10% of the gait cycle was greater in the Botox group compared with placebo. This study also evaluated passive ankle dorsiflexion by measuring the amount of dorsiflexion in stance and swing phases. The peak dorsiflexion in stance and swing were significantly greater in the BTX-A group compared with baseline (stance, 12.5 versus -3.6 and swing, 6.2 versus -3.8 , $p=0.006$ for both measures).

Koman *et al.* (2000) measured active ankle dorsiflexion with the knee flexed. The mean change from baseline was significantly greater in the Botox group compared with the control group at weeks 4 and 12 ($p<0.05$).

The study by Love *et al.* measured dynamic muscle range using the modified Tardieu scale. Dynamic range of movement is the angle at which first catch is felt during a fast velocity movement. The improvement demonstrated by the Botox group was significantly greater from placebo at three and six months ($p<0.001$ and $p=0.017$ respectively).

4.6.4 Motion analysis and gait analysis

The 1994 trial by Koman *et al.* reported that 33% of patients receiving placebo had an improved gait versus 83% of patients in the treatment group. It was not reported whether this difference was significantly different from each other.

The 2000 trial by Koman *et al.* used a modified physician rating scale (PRS) to measure dynamic gait pattern during walking. It included a composite of scores of gait pattern, hindfoot (ankle) position, hindfoot position, degree of crouch and speed of gait. The mean change from baseline

in the modified PRS score was significantly greater in the BTX-A group compared with the placebo group at all visits ($p=0.041$ at week 2, $p=0.019$ at week 4, $p=0.003$ at week 8, $p=0.016$ at week 12).

The trial by Corry *et al.* measured gait using the ankle at foot initial contact, maximal dorsiflexion in stance, maximal plantarflexion and ankle range. At two weeks, there were no statistically significant differences in any of the outcomes between the BTX-A group and casted group. At 12 weeks, statistically significant differences were found for the maximal dorsiflexion in stance (6.9 versus -1.7, $p=0.04$) and the maximal plantarflexion (-12.2 versus -33.3, $p=0.01$) demonstrating improved ankle dorsiflexion in the BTX-A group.

Uhbi *et al.* measured video gait analysis (VGA) at weeks 2, 6 and 12. A change of one grade on this scale was considered clinically significant. No statistically significant differences between the BTX-A and placebo groups were reported at two weeks. Among patients, 48% of those in the BTX-A group and 17% of those in the placebo group reported improvement at six weeks ($p=0.02$). At week 12, 50% of patients in the BTX-A group and 11% of those in the placebo group reported improvement ($p=0.003$). Uhbi *et al.* also measured physician-rated gross motor function measure (GMFM) scores. A change of $\geq 6\%$ in the GMFM score was considered to be clinically significant. There were no significant differences between the BTX-A group and the placebo group at weeks 2 and 6. The BTX-A group demonstrated a clinically significant improvement over placebo at 12 weeks ($p=0.04$). Of patients in the BTX-A group, 37% demonstrated a clinically significant improvement from baseline compared with 7% in the placebo group. The mean improvement in the BTX-A group was 9.7% at 12 weeks.

Boyd *et al.* reported GMFM scores (total GMFM, GMFM goal scores and GMFM-66) as reported by a physiotherapist. The BTX-A treated group were not significantly different from the placebo group at 12 months for all three GMFM scores.

Baker *et al.* measured an overall GMFM score as a percentage of the maximum score possible (100%) at weeks 4 and 16. There were no statistically significant differences between the groups.

In the Reddihough *et al.* trial, there were no significant differences in GMFM between the treatment and control phases at three or six months.

The VGA of initial foot contact was performed in the Kanovsky *et al.* trial at weeks 4 and 16. A significant difference in the number of patients improved was noted at 16 weeks (38% versus 20%, $p=0.04$ for the BTX-A and control groups respectively). There was also progressive improvement in GMFM in both groups, but they were not statistically significant.

Differences in GMFM, PRS for VGA and global scoring scale for VGA were not statistically significant between BTX-A treatment and fixed plaster casting in the trial by Flett *et al.* at two, four and six months.

4.6.5 Patient's, caregiver's or physician's assessment of function or disability

Koman (1994) *et al.* reported a greater increase on the PRS in the treatment group compared with control (an average improvement of 3.1 versus 2.3) on a scale of zero to 14 (a maximal score of 14 would indicate normal gait for that extremity). In the assessment by parents and

guardians, it was also reported that there was greater improvement in the treatment group compared with the control group (66% versus 33%). One patient in the treatment group had a fixed contracture that did not improve. One patient had excessive physical therapy and experienced short-term improvement.

Baker also measured subjective assessments of benefit reported by parents and investigators at weeks 4, 8 and 16. Assessment was categorized as good, minimal, no or worsened response to treatment. A statistically greater number of parents and investigators considered 30 U/kg of Dysport to provide good functional response compared with placebo, $p < 0.01$ and $p < 0.05$ respectively.

Significantly more parents in the Reddihough *et al.* trial thought that BTX-A treatment was of benefit to their child's ability at three and six months ($p < 0.05$ for both) as determined using a short questionnaire. Most parents rated the benefit of BTX-A treatment as good, very good or excellent. The Vulpe assessment battery (VAB), which was used to study upper limb skills during activities of daily living such as dressing, feeding and play, was included because it has been claimed that reduced spasticity in the lower limb can affect the upper limbs. Overall, the VAB results revealed a trend for the BTX-A phase to perform better than the control phase. The fine motor component of the VAB demonstrated a significant difference ($p < 0.05$).

In the Kanovsky *et al.* trial, parental and investigator subjective functional assessments (SFA) were made at weeks 4, 8 and 12. More patients and investigators reported a good response after BTX-A treatment compared with placebo at weeks 4 and 8 (parent, 50% versus 46% in week 4, 58% versus 39% in week 8; investigator, 58% versus 42% in week 4, 54% versus 27% in week 8, in the BTX-A and placebo-treated patients respectively). There were no obvious differences between the groups at week 16.

4.6.6 Pain

Barwood *et al.* measured pain after adductor-release surgery to treat or prevent hip dislocation in children with spastic CP with or without pre-treatment with Botox. Pain scores were assessed hourly by nursing staff and every eight hours by two other observers. A validated observational pediatric pain category rating scale was used, where 0=no pain and 3=severe pain. The pain scores rated by the nursing staff, parents and the trial coordinator were averaged to give a total score. Pain scores recorded at 24 and 48 hours were significantly different in the BTX-A and placebo groups; the mean differences were 2.2 ($p < 0.02$) and 3.7 ($p < 0.001$) respectively. A significant reduction in mean duration of hospital stay was also noted (33%, $p < 0.003$).

4.6.7 Adverse events

The 1994 trial by Koman *et al.* reported that 50% of patients in the treatment and placebo group experienced soreness at the injection site. Two patients in the control group experienced unsteadiness, one patient experienced fatigue and one patient experienced headache. The local side effects generally lasted one to two days. Neither group had generalized or systemic complications. While several types of adverse events were reported, it was unclear how many patients in the placebo group experienced adverse events.

The adverse events reported in the Koman *et al.* trial in 2000 were rated as probably, possibly or remotely treatment-related. All the adverse events were rated as mild to moderate and there were no withdrawals due to adverse events. In the BTX-A group, 17% of patients experienced adverse events compared with 4% of patients in the placebo group. It was not reported whether the difference was significantly different.

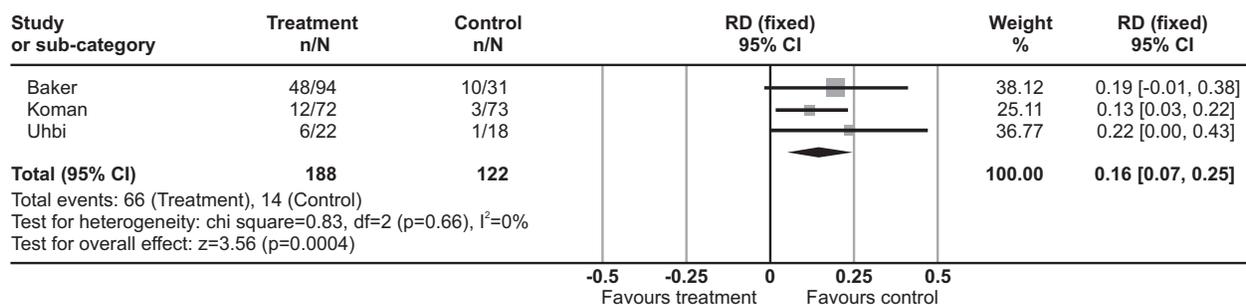
Ubhi *et al.* reported more adverse events in the treatment group compared with placebo. All adverse events were self-limiting and the number of events was small. Two patients in the treatment group experienced post-injection calf pain, two patients experienced an increased frequency in falls, one person had a seizure and another patient experienced wheeziness. One patient in the placebo group vomited after the injection.

In the trial by Baker *et al.*, 48 of 94 (51%) of Dysport-treated patients reported adverse events compared with 10 of 31 (32%) in the placebo group. There were no statistically significant differences between the placebo and any Dysport group.

In the Reddihough *et al.* trial, patients were asked if their child experienced a complication or side effect from the BTX-A injection. At three months, 19% (4/21) of parents reported adverse events. At six months, 26% (6/23) reported adverse events. The adverse events reported included incontinence (n=4), short-term muscle weakness (n=4) and non-specific complaints such as “out of sorts” and “sick and sore” (n=2). When they were asked about pain at three months, 30% (7/23) of parents reported that their child experienced some pain. At six months, 17% (4/23) of parents reported that their child experienced pain with BTX-A treatment.

When the results from three trials were pooled, patients receiving BTX-A experienced significantly more adverse events than those receiving placebo with a risk difference=0.16 (95% CI: 0.07 to 0.25).

Figure 11: Incidence of adverse events with BTX-A treatment in patients with cerebral palsy



4.7 Use of BTX-A for Lower Extremity Spasticity in Patients with Multiple Sclerosis

Two RCTs described in three publications met the eligibility criteria and were included.⁴³⁻⁴⁵ Both trials investigated the use of BTX-A for lower limb spasticity in patients with multiple sclerosis (MS). The quality of the trials ranged from four to five on the Jadad scale with a mean quality score of 4.5. The duration of follow-up was 12 weeks in both trials (Appendix 7).

The trial by Snow *et al.* compared Botox 400 U to placebo, whereas the trial by Hyman *et al.* was a dose-ranging trial comparing Dysport 500 U, 1,000 U and 1,500 U to placebo. Both trials included patients with stable MS whose spasticity interfered with the activities of daily living. The trial by Snow *et al.* reported on muscle tone, whereas the Hyman *et al.* trial reported on muscle tone; PROM; AROM; physicians', caregivers' or patients' assessment of function and disability and adverse events. Neither trial reported on gait analysis or quality of life.

4.7.1 Muscle tone

The trial by Hyman *et al.* measured MAS at week 4. The MAS calculated for both legs was a composite measure of muscle tone and spasm frequency. Median scores in the Dysport 500 U, 1,000 U and 1,500 U groups were 4.0, 12.0 and 8.0 respectively, compared to a median score of 8.0 in the placebo group. It was not reported whether these changes were significantly different from those with placebo. The change in the BTX-A group was due to improvements in tone and spasm frequency, whereas the improvements in the placebo group were mainly due to reduction in spasm frequency only.

In the trial by Snow *et al.*, the effect on spasticity was determined by using a score that included the Ashworth scale, which was modified for the adductors. It was a composite measure of the degree of muscle tone and the spasm frequency. There was a significant reduction in the spasticity score at six weeks. This was mainly attributed to a reduction in the muscle tone (mean 2.6 ± 0.98 to 1.4 ± 0.98 , $p=0.008$).

Due to the difference in the reporting of muscle tone, the results of the trials could not be combined.

4.7.2 PROM

The trial by Hyman *et al.* measured passive hip abduction at week 4. All three Dysport groups demonstrated a greater mean change from baseline compared with placebo. The greatest difference was with the Dysport 1,000 U group. It was not reported whether these differences were significantly different from those with placebo.

4.7.3 AROM

Active hip abduction was measured in the Hyman *et al.* trial as the number of patients who improved. One patient in each of the 500 U and 1,000 U Dysport groups and two patients in each of the 1,500 U Dysport and placebo groups experienced improvement at week 4. It was not reported whether these differences were significantly different from those with placebo.

4.7.4 Patient's, caregiver's or physician's assessment of function and disability

The patients and investigators in the Hyman *et al.* trial were asked to rate the response to treatment on a five-point scale (excellent, good, fair, poor, no benefit). Overall opinions of a positive response (excellent, good or fair) to treatment were reported at four weeks. Among investigators, 67%, 48% and 36% in the 500 U, 1,000 U and 1,500 U Dysport groups reported a

positive response compared to 44% in the placebo group. Among patients, 62%, 53% and 47% in the 500 U, 1,000 U and 1,500 U Dysport groups reported a positive response compared to 44% in the placebo group. It was not reported if the differences were significant.

4.7.5 Pain

Hyman *et al.* reported the number of patients who were free of upper leg pain at week 4. Among patients, 61%, 41% and 65% in the 500 U, 1,000 U and 1,500 U Dysport groups were pain-free compared to 67% in the placebo group. No significant differences were reported.

4.7.6 Adverse events

The Hyman *et al.* study reported that 32/58 patients (55%) experienced an adverse event compared to 10/16 patients (63%) in the placebo group. The most frequent adverse events reported in all the Dysport groups were hypertonia (new or worsening spasticity) of injected or non-injected muscles (22%) and weakness of non-injected muscles (14%). The types of adverse events were similar for the placebo group with the exception of muscle weakness. Twice as many adverse events per patient were reported by the 1,500 U Dysport group compared with the 500 U and 1,000 U Dysport groups. The mean number of adverse events per patient was 2.7, 1.2 and 1.1 for the 1,500 U, 500 U and 1,000 U Dysport groups respectively. Six patients experienced serious adverse events, including two patients receiving Dysport and four patients receiving placebo.

One patient in the placebo group of the Snow *et al.* trial reported left-sided numbness and hemiparesis. Overall adverse events were not reported.

4.8 Use of BTX-A for Upper or Lower Limb Spasticity in Various Disorders

Four trials investigating BTX-A use in various disorders were identified in this systematic review. A qualitative description of the included trials is presented in Appendix 7. Four RCTs, described in four reports and an abstract, evaluated the efficacy of BTX-A for limb spasticity in patients with various disorders.⁴⁶⁻⁵⁰ Botox was used in two studies^{46,49,50} and Dysport was used in two studies.^{47,48} The RCTs were assessed to be of moderate quality (mean 3, range 2 to 4), using the Jadad scale. The trial duration ranged from two weeks to 12 weeks. Allocation was adequately concealed in three of four trials.^{46,47,49} Two of the four trials acknowledged support from manufacturers.^{47,48} Trial designs included two crossover studies,^{46,47} one dose-ranging study⁴⁸ and a parallel group trial.⁴⁹

4.8.1 Crossover studies

Grazko *et al.* performed a crossover trial to evaluate the effects of Botox versus saline in 12 patients with spasticity and eight patients with rigidity. For spasticity, diagnoses included stroke, multiple sclerosis, trauma and perinatal hypoxia; two patients were taking baclofen. The amount of Botox used was based on muscle size, with a total dose range of 25 U to 250 U per session for the spasticity group. Eight patients were injected in the lower extremities and four patients received injections in the upper limb muscles. Patients were evaluated at baseline and two weeks post-injection. If there was no improvement at the first assessment, the patient received the other treatment. As a result, the trial was considered to be a crossover for some patients. Several patients had repeat injections. Follow-up was maintained until muscle scores returned to baseline, with a maximum duration of four months.

Improvement in tone by ≥ 2 grades on the MAS was considered to be clinically significant. This was achieved by all patients with spasticity. The duration of follow-up ranged between one to four months. Five patients with severe painful spasms also noted a significant decrease in the number and intensity of the spasms. No systemic side effects were reported.

Burbaud *et al.* investigated the effectiveness of Dysport for ankle plantar flexor and foot invertor spasticity in patients with hemiparesis. Diagnoses included 19 cases of stroke and four cases of traumatic hemiparesis. The patients were examined at baseline; and after one, three and four months. Patients were randomly injected with Dysport or placebo at zero and three months. A constant total dose of 1,000 U Dysport was injected among various muscles according to their contribution to spasticity. Clinical outcomes were compared one month after Dysport and placebo injections. Data from the two groups who received placebo or Dysport at day 0 were studied separately. The data from both groups were pooled to evaluate the clinical effects in the population.

A significant difference ($p < 0.0001$) was found at 30 days for the Ashworth scores of ankle extension, inversion and active dorsiflexion. Differences in ankle scores were still significant at days 90 and 120 for extension and inversion respectively. Ashworth scores for active dorsiflexion were not significantly different at 90 or 120 days. The video score, which measured gait velocity, was significantly higher after Dysport injection and an improvement in the Fugl-Meyer score was noted. Eight of 22 patients demonstrated a velocity change > 7 cm/s after Dysport injection. While no general or local side effects were reported, three patients noted local pain at the injection site.

4.8.2 Dose-response study

Smith *et al.* assessed the dose-response relationships of BTX-A in upper limb spasticity that was associated with stroke or head injury. Diagnoses included 18 cases of stroke and three cases of head injury. Patients continued to receive physiotherapy and were randomized to receive saline; or 500 U, 1,000 U or 1,500 U of Dysport by intramuscular injection. Dosage and the range of muscles injected were based on the distribution of spasticity. Two-thirds of the randomized dose was injected above the elbow and the remainder was injected below the elbow. Assessments were made at baseline; and at two, six and 12 weeks. After 12 weeks, randomization was broken; three stroke and one brain injury patient originally allocated to placebo were re-

randomized to active treatment and reassessed, resulting in the double counting of patients. Analysis was based on combined and individual dose treatment.

At six weeks, the 500 U Dysport group demonstrated a significant decrease in MAS at the wrist compared with placebo. Also, the 1500 U Dysport group demonstrated a significant increase in PROM at the elbow compared with placebo. At week 6, the PROM at the wrist and MAS at the wrist and fingers were significantly different when the combined dose was compared with placebo. No significant changes were noted in AROM.

At 12 weeks, there was no significant difference between any of the treatment groups and placebo, except for a small significant increase in PROM at the elbow ($p < 0.05$) in patients receiving 1,500 U of Dysport.

While dose-related improvements in spasticity at the elbow and wrists were observed in hemiplegic stroke and brain-injured patients, no clinically significant increased duration of effect was found with increasing dose. No overall benefit was found in disability in severely affected upper limbs.

Dysport was well tolerated. One patient reported hip pain and one patient had flu-like symptoms for two days post-injection. One patient receiving 1,000 U of Dysport complained of the occasional tendency for a limb to get caught in the spokes of the wheelchair.

4.8.3 Parallel group trial

The effectiveness of Botox for managing focal hypertonia in adults was evaluated in a published trial by Richardson *et al.* and an abstract by Thompson *et al.*⁴⁹ Diagnoses included stroke, head injury, spinal cord injury, tumour, cerebral palsy and anoxic brain damage. Patients were stratified into those who presented with upper limb spasticity ($n=32$) and those with lower limb spasticity ($n=20$). Patients were randomized to receive Botox or saline placebo and continued other previously established treatments during the study. Botox was administered to 16 patients with upper limb spasticity and 11 patients with lower limb spasticity. Other patients received placebo. Assessments were made at baseline; and at three, six, nine and 12 weeks post-injection. For each variable, an aggregate score for the treatment period was calculated as the sum of the raw scores for weeks 3 to 12 inclusive.

On the Ashworth scale, aggregate outcome scores were significantly better in the treatment group than the placebo group ($p < 0.02$). An improvement in Ashworth score was noted between groups at baseline and week 3, with the treatment group showing greater improvement. For the ROM index, aggregate outcome scores showed change in both groups, but were significantly better in the treatment group compared with the placebo group ($p < 0.03$). Patients' or caregivers' self-rating of problem severity showed improvement in response to treatment. There was no group difference in aggregated outcome scores for the gross motor function score of the Rivermead motor assessment scale.

For the 32 patients with upper limb dysfunction, the scores of the treatment group had no effect on the aggregated outcome score. The aggregated outcome scores for the 20 patients with lower limb spasticity were significantly better for the treated than for the placebo group.

Compared with placebo, BTX-A treatment produced significantly greater improvements in Ashworth ratings and self-rated problem scores. Gross motor function of the upper limb and timed 10-metre walk data of lower limb patients did not show significant treatment effects. No side effects were recorded by any of the patients. Four patients noted pain at the time of injection.

5 DISCUSSION

Our review revealed that BTX-A had been investigated for the treatment of spasticity in a variety of diseases. A total of 33 RCTs were included in our review. Most of the trials were conducted in patients with stroke and upper limb spasticity (n=9) and in patients with CP and lower limb spasticity (n=13). In a few trials (n=6), BTX-A was investigated for use in spasticity in patients with multiple sclerosis (MS), traumatic brain injury and spinal cord injury. Sample sizes in stroke trials ranged from 20 to 221 patients, 10 to 145 patients in CP trials and 12 to 23 patients in MS trials.

The Jadad scale for randomized, double-blind trials is used to assess quality. Quality scores according to the Jadad scale vary (high=4 trials, moderate=16 trials, low=13 trials). This scale may not have accurately reflected the quality of some trials. The use of a summary score to rate quality can be problematic. The Jadad score is used to rate randomization, double-blinding and withdrawals. It is preferable to examine the individual components of methodological quality separately.⁵¹ Some included trials are single-blinded,^{23,26,30,31,35} thus they can only receive a maximum score of three. Several other trials are reported in abstracts and are also rated as low quality. This is not unusual as authors are often limited by word count or space in abstracts. Despite the low scores of some trials, they provide important clinical information for patient management.

Differences between the trials make comparison difficult. BTX-A is compared to different treatments such as placebo, physiotherapy, casting and orthosis. There is a lack of comparison to current pharmacologic treatments. This limits the conclusions regarding its comparative efficacy. BTX-A differs from most other pharmacological treatments in that it is administered directly into the affected muscles allowing focal treatment (i.e., specific targeting of spastic muscles) as opposed to generalized treatment of spasticity. Also, the dose, location and frequency of injection differ among trials, based on patients' requirements. Additional anti-spasticity medications are used in some trials and not in others. A variety of therapies limit the ability to compare trial results.

Muscle tone and ROM are commonly reported in the trials, but are not necessarily the most important outcome. Reduction in muscle tone using Ashworth scale and improvement in joint motion is often achieved, but whether these objective improvements translate into functional ability has been more difficult to establish for spasticity.⁹ Therefore, the studies that include functional outcome measures require careful clinical consideration. Furthermore, although the reliability and validity of the Ashworth and modified Ashworth scale have been explored

(Appendix 10), there is incomplete evidence that these scales reflect spasticity. The lower grades on the MAS may not provide a valid measure of spasticity.⁵² These scales are ordinal and trial investigators may have used an inappropriate statistical test.⁵³

Although inadequately captured in this review, goal-focused patient-specific outcomes are appropriate to measure clinically meaningful improvements in these diverse populations. Important goals may include increasing the use or function of an upper extremity, improving brace fit, preventing contracture, decreasing pain and increasing ease of care. The goals are patient-specific, as each clinical case is unique and each patient and family may have different priorities. A difficulty in using goal-focused outcomes is that they must be sensitive and specific enough to capture the clinical changes in each case, yet general enough to standardize and combine data.

Although most studies included in our report do not use goal-focused scales as a primary outcome measure, they are utilized in some trials.^{12,17,27,33} The RCT conducted by Brashear *et al.* incorporates the use of a goal-focused tool (disability assessment scale) in a large, multi-centre RCT. Others studies have incorporated functional outcome measures such as the quality of upper extremity skills test (QUEST) used by Fehlings *et al.*, gait analysis or the pain scales. These trials have built on the experience and knowledge accumulated in previous trials. With the growing acceptance of these scales, they may be incorporated into future clinical trials.

Several dose-ranging trials have been conducted,^{12,16,18-20,24,40,43} but a dose-response relationship is not always evident. The dose used is patient- and muscle-specific and may depend on several factors, including the number of muscles to be injected, the number and location of neuromuscular junctions in the muscles, severity of spasticity and the patient-specific goal to be attained. An increased dose does not always lead to an increased incidence of adverse events in the trials.

BTX-A injections were generally well tolerated. Few studies reported a significant difference in adverse events. Most adverse events were local. Pain and soreness at the injection site, which were commonly reported across all trials, were often mild and temporary. Weakness was also reported and may be attributed to an extension of the pharmacology of BTX-A. Weakness may have contributed to reports of lack of coordination, abnormal gait, unsteadiness or accidental injury. There were no reports of severe weakness. Systemic adverse events were rare. Some trials reported infection (urinary tract infection, respiratory tract infection) and flu-like symptoms. Severe adverse events were rarely reported. They included hypothyroidism, lymphoma, pain and depression. It was unclear, however, whether these adverse events were drug-related.

The conditions associated with spasticity are mostly long-term and have extensive neurological involvement, causing limitations in function and activities of daily living. The trials identified in this report are short-term, ranging from six to 24 weeks; one trial lasted 12 months. Thus, the long-term effects of repeated BTX-A injection such as the prevention of fixed contractures, prevention of surgical intervention and long-term improvement in gait or upper extremity function require further analysis. Such studies are difficult to design and expensive to conduct. Most of the trials involve small numbers of patients and may be underpowered. It is difficult to determine the most appropriate size, as there are many variables to consider, for example, the

incidence of spasticity in patients with CP or stroke, as these values are poorly described in the literature. In certain cases (e.g., CP), obtaining a large sample size is difficult and physicians find that the smaller trials provide valuable information. In these cases, the combination of results would produce a better sense of effect size.

Issues such as the variability in outcome measures and missing statistical data prevent the pooling of results. For example, our primary outcome, muscle tone, is reported using the Ashworth scale, the modified Ashworth scale or the expanded Ashworth scale. Although they are similar, these scales cannot be combined to give an overall effect size. Another difficulty is obtaining useful data for meta-analysis (i.e., mean difference from baseline and standard deviation). Some trials use median and range or inter-quartile range. In most cases, the results of only two or three trials, sometimes by the same author, can be combined. In the section describing the evidence of BTX-A in patients with stroke and upper limb spasticity, most outcomes can only be pooled from the two trials by Bakheit. The small number of trials included in the meta-analysis limit the robustness of the outcome.

BTX-A is one tool available for the treatment of spasticity. Unlike many other pharmacologic treatment options, its use means that the muscles with increased tone can be directly targeted. Multiple intramuscular injections are needed, so consideration must be given to the control of discomfort during the procedure. Depending on the technique used, young children may require sedation or anesthesia. Depending on the severity of spasticity, the muscles involved and the goals of the injection, patients may require one to several vials of Botox per session. The average cost per vial (100 U/vial) in Canada is \$357.⁵⁴ As a result, appropriate candidates for this treatment should be chosen carefully. Physicians, caregivers and patients should be aware of the evidence supporting its use and its limitations. Further research on longer term functional outcomes in patients with spasticity should be conducted. Until then, attention to appropriate patient selection and patient-specific goal-focused outcomes is recommended.

6 CONCLUSION

BTX-A treatment results in decreased muscle tone across most trials and diseases. Increased range of motion, improved gait and improved function are shown in many studies, but statistical significance is not always reached. The variability in results across studies may be due to the variety of disorders studied, the unique expressions of disease state in each clinical condition and the differences in study designs and outcomes measures used. Combining results to improve clarity is seldom possible. The adverse events reported in most studies are low in number and often temporary. Improved methods of reporting would, however, allow more robust conclusions about the comparative safety of BTX-A. Long-term patient-specific goal-focused outcomes are needed to further define the clinically meaningful improvements in therapeutic outcomes.

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Appendix 1: Botulinum Toxin Type A - Search Strategy

?	Truncation symbol, one character only
*	Truncation symbol, any number of characters
n	Near/next (i.e., terms are near/next to one another, any order)
“ ”	Phrase
l	Link (i.e., to subheading)
ti	Title
ab	Abstract
au	Author
de	Descriptor
dt	Publication type
tn	Trade name
mn	Manufacturer name
nd	Device name
md	Device manufacturer
rn	Registry number (i.e., CAS)
tw	Text word

DATABASES	LIMITS	KEYWORDS/DESCRIPTOR
DIALOG® BIOSIS Previews® EMBASE® MEDLINE® PASCAL ToxFile	Human (BIOSIS, EMBASE®, MEDLINE® and ToxFile only)	BIOSIS: botulinum toxin/de EMBASE: botulinum toxin a/de OR tn=botox OR tn=dysport OR tn=oculium MEDLINE/ToxFile: botulinum toxin type a/de All databases: botox OR BTX-A OR “BTX A” OR BtxA OR dysport OR oculinum OR “botulinum toxin type a” OR “botulinum toxin a” AND BIOSIS: spasticity/de EMBASE: spasticity!/de MEDLINE/ToxFile: muscle spasticity/de

		<p>PASCAL: spasticity/de</p> <p>All databases: (muscle* OR musculoskeletal OR limb OR limbs)(3n)(spasm* OR spastic*) OR spasticit*</p> <p>AND</p> <p>EMBASE: arm!/de OR leg!/de OR arm muscle/de OR hand muscle/de OR leg muscle/de OR biceps brachii muscle/de OR quadriceps femoris muscle/de OR gastrocnemius muscle/de OR extensor digitorum longus muscle/de OR soleus muscle/de</p> <p>MEDLINE/ToxFile: arm!/de OR leg!/de</p> <p>All databases: elbow OR elbows OR forearm OR forearms OR finger OR fingers OR thumb OR thumbs OR shoulder OR shoulders OR hand OR hands OR wrist OR wrists OR arm OR arms OR thenal OR thenals OR thenar OR “upper extremit*” OR “upper limb*” OR leg OR legs OR foot OR feet OR ankle OR ankles OR metatars* OR toe OR toes OR hallux OR heel OR heels OR hip OR hips OR knee OR knees OR thigh OR thighs OR “lower extremit*” OR “lower limb*” OR forefoot OR forefeet OR bicep OR biceps OR quadriceps* OR hamstring* OR gastrocsoleus or gastrocnemius OR “extensor hallucis” OR hip(2n)adductor*</p> <p>AND</p> <p>EMBASE: major clinical study/de OR prospective study/de OR multicenter study/de OR controlled study!/de OR randomized controlled trial/de OR drug comparison!/de OR evidence based medicine!/de</p>
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		<p>BIOSIS: multicenter study/de OR randomized controlled trial/de OR randomized clinical trial/de OR randomized trial/de OR evidence-based medicine/de OR meta-analysis/de OR prospective study/de</p> <p>MEDLINE/ToxFile: controlled clinical trials!/de OR epidemiologic research design!/de OR comparative study/de OR follow-up studies/de OR prospective studies/de OR dt=meta-analysis OR dt=multicenter study OR dt=randomized controlled trial OR dt=controlled clinical trial</p> <p>All databases: random* OR “single (blind* OR dumm* OR mask*)” OR “double (blind* OR dumm* OR mask*)” OR “triple (blind* OR dumm* OR mask*)” OR “treble (blind* OR dumm* OR mask*)” OR placebo* OR “meta analy*” OR metaanaly* OR “quantitative* (review* OR overview*)” OR “systematic* (review* OR overview*)” OR “methodologic* (review* OR overview*)” OR “control* (study OR studies OR trial*)” OR RCT? OR “control* clinical (study OR studies OR trial*)” OR “multicent* (study OR studies OR trial*)” OR “follow-up (study OR studies OR trial*)” OR “follow up (study OR studies OR trial*)” OR “prospective (study OR studies OR trial*)” OR “comparative (study OR studies)” OR (drug OR drugs)(3n)comparison*</p> <p>Performed 1 Apr 2002 92 unique records (excludes 5 additional duplicates detected when importing to Reference Manager)</p> <p>BIOSIS – 10 records EMBASE – 34 records MEDLINE - 44 records PASCAL – 4 records ToxFile - 0 records</p> <p>72 unique records for topical (i.e., no clinical trial filter) search (excludes overlap with above set and 15 additional duplicates detected when importing to Reference Manager)</p>
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		<p>BIOSIS – 8 records EMBASE – 35 records MEDLINE - 26 records PASCAL – 3 records ToxFile - 0 records</p>
PubMed	Human	<p>botulinum toxin type a/de botox OR BTX-A OR “BTX A” OR BtxA OR BoNTA OR dysport OR oculinum OR “botulinum toxin type a” OR “botulinum toxin a”</p> <p>AND</p> <p>muscle spasticity/de OR (muscle* OR musculoskeletal OR limb OR limbs) AND (spasm* OR spastic*) OR spasticit*</p> <p>AND</p> <p>arm!/de OR leg!/de OR elbow OR elbows OR forearm OR forearms OR finger OR fingers OR thumb OR thumbs OR shoulder OR shoulders OR hand OR hands OR wrist OR wrists OR arm OR arms OR thenal OR thenals OR thenar OR “upper extremit*” OR “upper limb*” OR leg OR legs OR foot OR feet OR ankle OR ankles OR metatars* OR toe OR toes OR hallux OR heel OR heels OR hip OR hips OR knee OR knees OR thigh OR thighs OR “lower extremit*” OR “lower limb*” OR forefoot OR forefeet OR bicep OR biceps OR quadriceps* OR hamstring* OR gastrosoleus or gastrocnemius OR “extensor hallucis” OR hip(2n)adductor*</p> <p>AND</p> <p>controlled clinical trials!/de OR epidemiologic research design!/de OR comparative study/de OR follow-up studies/de OR prospective studies/de OR dt=meta-analysis OR dt=multicenter study OR dt=randomized controlled trial OR dt=controlled clinical trial</p> <p>random*/ti,ab OR “single (blind* OR dumm* OR mask*)”/ti,ab OR “double (blind* OR dumm* OR mask*)”/ti,ab OR “triple (blind* OR dumm* OR mask*)”/ti,ab OR “treble (blind* OR dumm* OR mask*)”/ti,ab OR placebo*/ti,ab OR “meta</p>

		<p>analy*"/ti,ab OR metaanaly*"/ti,ab OR "quantitative* (review* OR overview*)"/ti,ab OR "systematic* (review* OR overview*)"/ti,ab OR "methodologic* (review* OR overview*)"/ti,ab OR "control* (study OR studies OR trial*)"/ti,ab OR RCT?"/ti,ab OR "control* clinical (study OR studies OR trial*)"/ti,ab OR "multicent* (study OR studies OR trial*)"/ti,ab OR "follow-up (study OR studies OR trial*)"/ti,ab OR "follow up (study OR studies OR trial*)"/ti,ab OR "prospective (study OR studies OR trial*)"/ti,ab OR "comparative (study OR studies)"/ti,ab OR (drug OR drugs)(3n)comparison*"/ti,ab</p> <p>Performed 30 Sept 2002 12 unique records (excludes overlap with results from DIALOG® search and alerts to date)</p>
<p>The Cochrane Collaboration & Update Software Ltd.</p> <p>The Cochrane Library, 2002, Issue 1</p>		<p>Same descriptors and keywords as per DIALOG® MEDLINE® search</p> <p>The Cochrane Database of Systematic Reviews = 2 complete reviews, 2 protocols; The Cochrane Controlled Trials Register = 34 references; The NHS Economic Evaluation Database = 1 record</p>
<p>DIALOG®</p> <p>Alerts: BIOSIS Previews® EMBASE® Alert MEDLINE® PASCAL</p>	<p>Human (BIOSIS, MEDLINE® only)</p>	<p>Same descriptors and keywords as per DIALOG® (all searches run separately)</p>
<p>Websites of health technology assessment and related agencies; clinical trial registries; other databases</p>		<p>e.g. NZHTA; AHRQ; National Research Register; University of York NHS Centre for Reviews and Dissemination – CRD databases; TRIP</p>

Appendix 2: Trial Eligibility Form

Reference ID _____
Author _____
Title _____
Citation _____

Reviewer KG ____ LM ____

1. Study design:
 - a. Randomized controlled trial _____ Yes__ No__ Unsure__
 2. Patient population
 - a. Upper or lower extremity spasticity _____ Yes__ No__ Unsure__
 3. Intervention
 - a. Botulinum Toxin Type A (BTX-A) _____ Yes__ No__ Unsure__
 4. Outcome measures (at least one of the following) _____ Yes__ No__ Unsure__
 - a. Tone intensity as measured by Ashworth scale
 - b. Passive and active range of motion
 - c. Motion analysis and gait analysis
 - d. Patient, caregiver or physician assessment of function and disability
 - e. Pain
 - f. Quality of life
 - g. Adverse events
-

If “yes” to questions 1 to 4, include study.

If “no” to any question, exclude study and give explanation.

____ **Yes (include study)**

____ **No (exclude study)**

Reasons for exclusion:

- ____ Not RCT
____ No control group
____ Neither upper or lower extremity spasticity
____ Study does not include outcome measures of interest
____ Review article
____ Retrospective study
____ Other _____
-
-

Appendix 4: Data Abstraction Form

Part A: Trial and Patient Characteristics

Extractor name: KG LM
 Paper title: _____
 Paper ID: _____
(surname of first author, publication year)
 Reference Manager number: _____

Upper extremity Lower extremity Disease state(s) _____

Other references to which this trial may link: _____

Characteristics of Included Studies		
Design study		
Method of randomization		
Blinding	Patients	
	Investigator	
	Assessor	
Additional notes: (e.g., conflict of interest)		
Intervention		
Setting (country of study population)		
Type of intervention		
Type of control		
Duration of treatment		
Additional notes		
Participants	Treatment Group	Placebo Group
Total eligible for inclusion into trial		
Total number enrolled into trial		
Number of withdrawals or dropouts and reason for withdrawal or dropout		
Number of patients completing the trial		

Baseline Characteristics	Treatment Group	Placebo Group
Age (years)		
Gender (male or female)		
Diagnosis (disease and severity)		
Duration of disease		
Concurrent medications		
Adverse Events	Treatment Group	Placebo Group
Number of patients withdrawn due to adverse events		
Description of types of adverse events (percentage of patients, starting with most common)		
Additional notes		

Part B: Outcome Measures

Extractor name: KG LM

Paper title: _____

Paper ID: _____
(surname of first author, publication year)

Reference Manager number: _____

	Treatment	Control
Description of outcome		
Results (as given in paper): give units of measurement (e.g., mean, SD, median)		
Results (calculated for RevMan entry, e.g., mean, SD, N): give formulae used for calculating data		
Additional notes		

Is further statistical advice needed?

Yes or no

Are authors to be contacted?

Yes or no

Questions for authors:

Additional notes:

Appendix 5: Excluded Articles and Reason for Exclusion

No control

1. Wissel J, Heinen F, Schenkel A, Doll B, Ebersbach G, Müller J, et al. Botulinum toxin A in the management of spastic gait disorders in children and young adults with cerebral palsy: a randomized, double-blind study of "high-dose" versus "low-dose" treatment. *Neuropediatrics* 1999;30(3):120-4.
2. Sampaio C, Ferreira JJ, Pinto AA, Crespo M, Ferro JM, Castro-Caldas A. Botulinum toxin type A for the treatment of arm and hand spasticity in stroke patients. *Clin Rehabil* 1997;11(1):3-7.
3. Siebel A, Zeifang F, Metaxiotis D, Pappas A, Döderlein L. Botulinum toxin A treatment in CP equinus feet - Is there a difference between hemiplegic and diplegic children? [abstract]. *Gait Posture* 1998;7(2):167-8.

Not RCT

1. Yang TF, Chan RC, Chuang TY, Liu TJ, Chiu JW. Treatment of cerebral palsy with botulinum toxin: evaluation with gross motor function measure. *J Formos Med Assoc* 1999;98(12):832-6.
2. Friedrich H, Hesse S, Domasch C, Mauritz KH. Botulinum Toxin a in der Therapie der Armbeugespastik. *Aktuelle Neurol* 1992;19(6):175-8.

Review articles

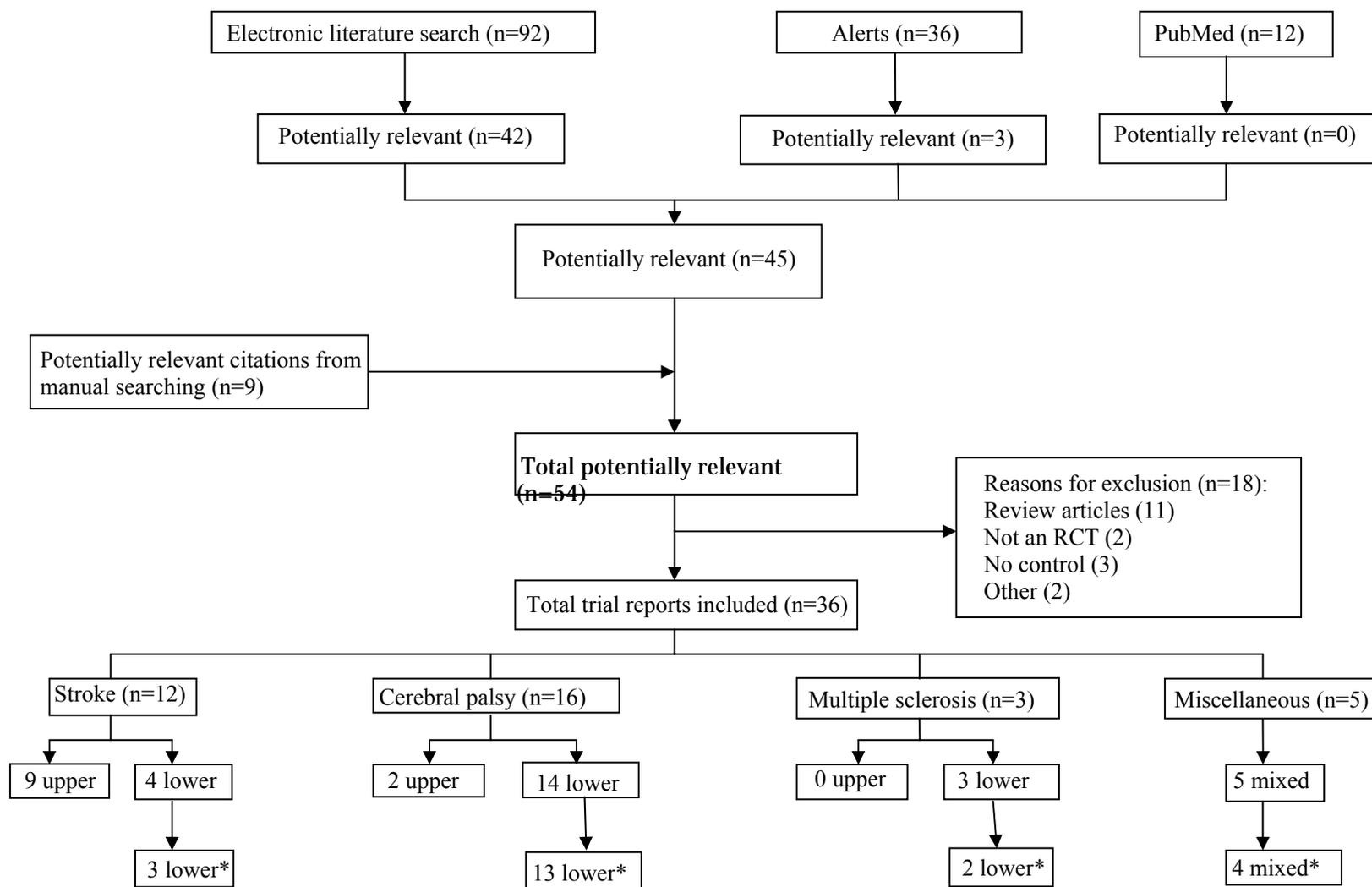
1. Hesse S, Mauritz KH. Management of spasticity. *Curr Opin Neurol* 1997;10(6):498-501.
2. Ade-Hall RA, Moore AP. Botulinum toxin type A in the treatment of lower limb spasticity in cerebral palsy. *Cochrane Database Syst Rev* 2000;(2):CD001408.
3. Gracies JM, Elovic E, McGuire J, Simpson D, BRIN Brin MF. Traditional pharmacological treatments for spasticity part II: general and regional treatments: spasticity: etiology, evaluation, management, and the role of botulinum toxin type A: a training syllabus developed by the Spasticity Study Group. *Muscle Nerve* 1997;Suppl 6:S92-S120.
4. Botulinum toxin type A and dynamic equinus in children with cerebral palsy. Better than repeat casts. *Prescribe Int* 2001;10(51):12-4.
5. Fève A, Decq P, Filipetti P, Kéravel Y. Traitement de la spasticité par injections de toxine botulique. Revue de la littérature. *Neurochirurgie* 1998;44(3):192-6.
6. Berardelli A, Abbruzzese G, Bertolasi L, Cantarella G, Carella F, Currà A, et al. Guidelines for the therapeutic use of botulinum toxin in movement disorders. *Ital J Neurol Sci* 1997;18(5):261-9.
7. Simpson DM. Botulinum toxin in the treatment of spasticity: clinical trials and end-plate localization. *Eur J Neurol* 1997;4 Suppl 2:S31-S32.
8. Houltram J, Noble I, Boyd RN, Corry I, Flett P, Graham HK. Botulinum toxin type A in the management of equinus in children with cerebral palsy: an evidence-based economic evaluation. *Eur J Neurol* 2001;8 Suppl 5:194-202.
9. Boyd RN, Morris ME, Graham HK. Management of upper limb dysfunction in children with cerebral palsy: a systematic review. *Eur J Neurol* 2001;8 Suppl 5:150-66.
10. Fehlings D, Rang M, Glazier J, Steele C. Botulinum toxin type A injections in the spastic upper extremity of children with hemiplegia: child characteristics that predict a positive outcome. *Eur J Neurol* 2001;8 Suppl 5:145-9.

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

Other

1. Mohamed KA, Moore AP, Rosenbloom L. Adverse events following repeated injections with botulinum toxin A in children with spasticity [letter]. *Dev Med Child Neurol* 2001;43(11):791.
2. Bhakta B, Cozens JA, Chamberlain MA. Erratum: the impact of botulinum toxin type A on disability and carer burden due to arm spasticity after stroke: a randomised double blind placebo controlled trial (Journal of Neurology Neurosurgery and Psychiatry (2000); 69: 217-221). *J Neurol Neurosurg Psychiatry* 2001;70(6):821.

Appendix 6: Flow of Articles



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* Duplicate publication or publication on same study.

Appendix 7: Included Articles

Study	Design, Duration	Participants (treatment/control)	Intervention	Eligibility	Outcome Measures	Quality	
						Jadad	Concealment
Trials involving patients with stroke and upper limb spastic							
Bakheit ¹²	R, DB, PC, dose ranging study 16 weeks	63/20 Placebo: 20; 500 U: 22; 1,000 U: 22; 1,500 U: 19	Dysport 500 U, 1,000 U, 1,500 U or placebo	Hemiplegic stroke with severe or moderately severe muscle spasticity (MAS>2 at elbow, wrist fingers), 3 months post-CVA	MAS, ROM, pain, Rivermead motor assessment, Barthel index, functional ability, adverse events	3	Unclear
Brashear ^{17,55}	R, DB, PC 12 weeks	64/58	Botox 200 U to 240 U or placebo	Stroke at least 6 months earlier with focal spasticity of wrist and fingers (Ashworth score=3 or 4 at wrist or ≥2 at fingers)	Functional disability (disability assessment scale), muscle tone (Ashworth scale), global assessment, safety, neutralizing antibodies	3	Unclear
Bakheit ¹³	R, DB, PC 16 weeks	37/32	Dysport 1,000 U or placebo	Hemiplegic stroke and severe or moderately severe muscle spasticity (MAS>2) 3 months post-CVA	Muscle tone (MAS), adverse events, ROM, pain, functional ability, goal attainment, global assessment	5	Adequate
Hesse ¹⁵	R, DB, PC 12 weeks	12/12 Dysport and ES: 6; Dysport: 6; placebo and ES: 6; placebo: 6	Dysport 1,000 U and ES, Dysport 1,000 U, placebo and ES or placebo	Between 6 to 12 months post-stroke, with severe spasticity (MAS=3)	Muscle tone (MAS), ROM, functional ability, pain	3	Unclear
Simpson ¹⁶	R, DB, PC 16 weeks	39 (evaluable patients n=37) 300 U: 9; 150 U: 9; 75 U: 9; placebo: 10	Botox 75 U, 150 U or 300 U or placebo	At least 9 months post-stroke with Ashworth score >2.5	BP, pulse rate, muscle tone (Ashworth scale), caregiver dependency scale, function and pain assessment, motor task/function rating scale, grip strength and global assessment of spasticity scale; other measures include FIM, Rand 36-item health survey and Fugl-Meyer scale	3	Unclear
Bhakta ¹⁴	R, DB, PC 12 weeks	20/20	Dysport 1,000 U or placebo	Chronic hemiparesis due to stroke, at least 6 months earlier, with finger or elbow flexor spasticity (MAS>2) and	Patient disability, caregiver burden, muscle power, grip strength, spasticity (MAS), ROM, pain	5	Adequate

Study	Design, Duration	Participants (treatment/control)	Intervention	Eligibility	Outcome Measures	Quality	
						Jadad	Concealment
				at least moderate difficulty with 2 out of 8 items defining patient disability			
O'Brien ²⁰	R, DB, PC 16 weeks	39 patients total	Botox 75 U, 150 U, 300 U or placebo	Chronic upper limb spasticity after stroke (Ashworth >2)	Tone (Ashworth scale), global assessment of spasticity, adverse events	2	Unclear
Childers ¹⁹	R, DB, PC 24 weeks	65/26	Botox 90 U, 180 U, 360 U or placebo	At least 6 weeks post-stroke with expanded Ashworth score >3 at wrist and >2 at elbow and pulmonary function test >65% of predicted value	Expanded Ashworth scale, pulmonary function test, physician global assessment, adverse effects	2	Unclear
DeBeyl ¹⁸	R, DB, PC 12 weeks	89 patients total	Botox 90 U, 180 U, 360 U or placebo	Upper limb spasticity post stroke	Muscle tone (expanded Ashworth scale), ROM, adverse events	2	Unclear
Trials involving patients with stroke and lower limb spasticity							
Kirazli ²¹ and On ²²	R, DB 12 weeks	20 patients in total	Botox 400 U or 3 mL of 5% phenol	Severe spasticity for >3 months and <12 months (Ashworth >3 at ankle flexor and ankle invertor)	ROM, Ashworth scale, global assessment of spasticity scale	2	Unclear
Johnson ²³	R, PC 12 weeks	12/9	Dysport 600 U and FES and physiotherapy; versus physiotherapy alone	Single stroke of vascular origin with hemiplegia during previous 12 months; inability to achieve heel strike, correctable by FES; between 3 and 6 inclusive on the Hauser ambulation index; increased calf stretch response on examination and premature calf activation during gait identified by EMG activity	Walking speed, physiological cost index of gait	3	Adequate

Study	Design, Duration	Participants (treatment/control)	Intervention	Eligibility	Outcome Measures	Quality	
						Jadad	Concealment
Pittock ²⁴	R, DB, PC 12 weeks	221; 500 U: 55; 1,000 U: 55; 1,500 U: 57; placebo: 54	500 U, 1,000 U, 1,500 U Dysport or placebo	Stroke at least three months earlier; hemiparesis with spastic equinovarus deformity of ankle preventing full active dorsiflexion; ambulatory, but with walking speed of <90% normal over 10 m	Gait (2-minute walking test, step length, stepping rate), PROM, AROM, MAS, pain, adverse events, global assessment of benefit made by patients and investigator	5	Unclear
Trials involving patients with cerebral palsy and upper limb spasticity							
Corry ²⁵	R, DB, PC 12 weeks	7/7	Botox 4 U/kg to 7 U/kg or Dysport 8 U/kg to 9 U/kg or control (no details given) 10 patients received Botox and 4 patients received Dysport	CP with dynamic component to contractures	Thumb extension and abduction, metacarpophalangeal extension, wrist extension, tone at thumb, wrist and elbow, grasp and release ability, coin transfer exercise, subjective opinion of patient or patients on overall change in arm and wrist resonant frequency	3	Unclear
Fehlings ²⁶	R, controlled, single- blinded 24 weeks	15/15	Botox IM 2 U/kg to 6 U/kg BW and community-based occupational therapy (OT) at a minimum of 1 session every two weeks or community-based OT alone	Hemiplegic CP, aged 2.5 to 10 years, moderate spasticity at elbow, wrist or thumb with MAS >2, full passive ROM and ability to initiate voluntary movement of digits	QUEST, PEDI, ROM, grip strength, MAS	2	Unclear
Trials involving patients with cerebral palsy and lower limb spasticity							
Koman ³⁴	R, DB, PC 6 weeks	6/6	Botox given at 1 U/kg body weight for each leg (i.e., 1 U/kg BW for hemiplegic and	CP with equinovarus or equinovarus foot deformities associated with dynamic (non-fixed) joint contracture unresponsive to PT, orthotics	Gait analysis, physical therapy evaluation, Biodex evaluation, PRS and a parent and guardian questionnaire	4	Adequate

Study	Design, Duration	Participants (treatment/control)	Intervention	Eligibility	Outcome Measures	Quality	
						Jadad	Concealment
			2 U/kg BW in diplegic) or saline placebo given at 0 and 2 weeks, where second injection was double initial dose	or other nonoperative modalities including neuropharmacologic agents			
Uhbi ²⁷	R, DB, PC parallel 12 weeks	22/18	Dysport 25 U/kg BW for diplegics and 15 U/kg BW for hemiplegics or placebo for 12 weeks	Children with dynamic equinus and inability to achieve heel strike because of lower limb spasticity mainly affecting calf muscles	VGA, GMFM, passive ankle dorsiflexion and PCI	4	Adequate
Koman ^{29,37,38}	R, DB, PC 12 weeks	145 patients in total	Botox 4 U/kg BW (maximum 200 U at any injection) or placebo at 12 weeks	Ambulatory with CP, aged 2 to 16 years, with spasticity on one or both lower limbs characterized by equinus positioning of foot during stance phase of gait	Dynamic gait pattern during walking, active and passive ankle dorsiflexion, ROM, adverse events, electrophysiologic measurements (EMG)	3	Unclear
Baker ^{36,40}	R, DB, PC 16 weeks	95/31; 10 U/kg BW: 36; 20 U/kg BW: 28; 30 U/kg BW: 31; placebo: 31	Dysport 10, 20 or 30 U/kg BW or placebo	Ambulatory, aged 2 to 9 years, with diplegic CP, dynamic component of >1.5% in at least one leg and potential to benefit from administration of Dysport	Muscle length, PROM, parent and investigator subjective assessment of benefit, gastrocnemius muscle length, adverse events	4	Adequate
Love ³³	Pair-randomized controlled trial 24 weeks	24 patients in total	Botox (dose determined by size of muscle, severity of dynamic contracture and weight of child)	Spastic hemiplegia due to CP, level 1 gross motor function classification system	PROM, dynamic muscle range, dynamic ROM, passive resistance to motion, over-activity or spasticity using MAS, GMFM, parental satisfaction	1	Unclear
Corry ³¹	R, single-blinded, controlled 12 weeks	10/10	Botox 6 U/kg to 8 U/kg and Dysport 15 U/kg (depending on location) or serial casts	Children with CP and a dynamic component of calf equinus (who would have previously been offered serial casts)	Clinical examination, video and Vicon gait analysis, PRS	1	Unclear

Study	Design, Duration	Participants (treatment/control)	Intervention	Eligibility	Outcome Measures	Quality	
						Jadad	Concealment
Flett ³⁰	R, single-blinded controlled 6 months	10/10	Botox 4 U/kg to 8 U/kg BW (maximum 20 U/site) or course of fixed plaster casting for 4 weeks	Ambulatory, aged 2 to 8 years, with CP associated with dynamic muscle tightness and equinovarus or equinovalgus positioning of foot; unresponsive to PT, orthotics or other non-operative modalities; no requirement for surgery	Degree of ankle dorsiflexion, MAS, GMFM, PRS, global scoring scales, gait, parent satisfaction	2	Adequate
Barwood ²⁸	R, DB, PC	8/8	Botox 8 U/kg (2 U/kg per site, 2 sites per limb) or normal saline placebo given pre-operatively	Spastic type CP, aged 2 to 10 years, clinical and radiological evidence of "hips at risk," independently scheduled for isolated adductor release surgery by 1 of 2 orthopedic surgeons	Pain, nausea, vomiting, sedation, vital signs, analgesic requirements, complications, length of admission and remission rate	2	Unclear
Boyd ³⁵	R, single-blinded, PC 12 months	19/20	Maximum dose: Botox 4 U/kg/muscle or Botox 16 U/kg BW and SWASH orthosis and current clinical practice versus current clinical practice alone	Bilateral, spastic CP, aged 1 to 4 years with clinical and radiological evidence of hip displacement; features that might benefit from use of hip abduction brace (SWASH) (i.e., adductor spasticity, scissoring gait or hip displacement)	GMFM, radiologic measures, clinical examination, MAS, questionnaires (compliance, comfort, durability, cosmesis and perceived function in child's usual environment)	3	Adequate
Richman ³⁹	R, PC 12 weeks	20 children in total	Botox 3 U/kg and physical therapy and abduction position wedges versus physical therapy and position wedges	Aged 2 to 18 years, with CP and hip abduction <40%, residence in long-term health care facility	Hip abduction ROM, pain, caretaker burden or care, spasticity	1	Unclear
Sutherland ³²	R, DB, PC	20 children in total	Botox 4 U/kg or saline placebo (all	Ambulatory, with CP and problems with dynamic	Passive ROM, neurological screening tests, muscle strength, gait analysis	4	Adequate

Study	Design, Duration	Participants (treatment/control)	Intervention	Eligibility	Outcome Measures	Quality	
						Jadad	Concealment
	8 weeks		hemiparetic and asymmetric diplegic patients received total dose; patients with bilateral spastic equinus received same dose divided into equal parts: (first dose at week 0, second dose at week 4)	equinus due to increased spasticity in calf muscles, aged 2 to 16 years, no fixed contractures in lower extremities, no prior orthopedic surgery in lower extremities and no previous injections of botulinum toxin	(kinematic measurements, video record, electromyography)		
Reddi-hough ⁴²	R, crossover 6 months	49; group 1: 22; group 2: 27	Botox 8 U/kg to 20 U/kg and physiotherapy versus physiotherapy alone	Children with spastic diplegia or mild to moderate spastic quadriplegia.	GMFM, Vulpe assessment battery, MAS, ROM, parent reported pain, adverse events and perception	1	Unclear
Kanovsky ⁴¹	R, DB, PC 16 weeks	26/26	Dysport 30 U/kg versus placebo	Ambulatory, aged 2 to 7 years, diagnosis of diplegic cerebral palsy without evidence of fixed contracture	VGA of initial foot contact, GMFM, parental and investigator subjective functional assessments	2	Unclear
Trials involving patients with multiple sclerosis and lower limb spasticity							
Snow ⁴⁴	R, crossover, DB, PC 12 weeks	10 patients in total	Botox 400 MU or isotonic saline placebo	Stable chronic MS, chair-bound or bed-bound, spastic contraction of adductor muscles that interfere with sitting, positioning in bed, cleaning or urethral catheterization	Ashworth scale (modified to examine adductors), hygiene and patient care	5	Unclear
Hyman <i>et al.</i> ^{43,45}	R, DB, PC 12 weeks	74 patients in total Dysport 500 U: 21; Dysport 1,000 U: 20; Dysport 1,500 U: 17; Placebo: 15	Dysport 500 U, 1,000 U, 1,500 U or placebo	Adults with definite or probable multiple sclerosis and with disabling spasticity of hip adductor muscles, which have been stable for >6 months	Active and passive hip abduction, MAS, assessment of perineal hygiene, joint range of motion, muscle tone, spasm frequency, upper leg pain, perineal hygiene and clinical global rating of upper	4	Unclear

Study	Design, Duration	Participants (treatment/control)	Intervention	Eligibility	Outcome Measures	Quality	
						Jadad	Concealment
				before entry and which caused moderate pain or difficulty for nurses helping the patient with activities such as washing and dressing	leg spasticity		
Trials involving various disorders and upper and lower limb spasticity							
Grazko ⁴⁶	R, DB, PC, crossover, evaluated 2 weeks post-injection, followed up until return to baseline	12 crossover; diagnoses included stroke (n=3), MS (n=5), perinatal hypoxia (n=1), traumatic brain injury (n=1), traumatic quadriplegia (n=2); spasticity: 4 upper; 8 lower	Botox 25 U to 250 U (mean=138 U) or placebo	MAS \geq 3	MAS, spasm frequency scale	3	Adequate
Burbaud ⁴⁷	R, DB, PC, crossover, evaluated 0, 30, 90 and 120 days post-injection	23 chronic hemiparetic patients; diagnoses included stroke (n=19) and traumatic hemiparesis (n=4); 13 patients received placebo; 10 patients received BTX-A (Dysport or Botox) as first injection	Dysport 1,000 U or placebo distributed among lower limb muscles at 0 and 90 days	Presence for \geq 3 months of moderate to severe spasticity of ankle plantar flexors and foot invertors; lack of response to conventional physical and medical treatment; exclusion criteria included fixed joint posture, pregnancy and neuromuscular diseases	MAS, Fugl-Meyer scale for inferior limb, gait velocity; clinical scales compared one month after each injection	4	Adequate
Smith ⁴⁸	R, DB, PC, several doses used in determining	21 hemiparetic patients; 19/6; 3 stroke and 1 head injury patient originally allocated to placebo, were re-randomized;	Dysport 500 U, 1,000 U or 1,500 U; or equal volume of saline	Spasticity in upper hemiparetic limb due to stroke or traumatic brain injury >1 year previously; flexor deformity at elbow, wrist or fingers in non-functioning or partially functioning arm; those with	PROM and AROM by goniometry and MAS at elbow, wrist and metacarpophalangeal joints, posture, disability (upper body dressing time; Frenchay arm test), global assessment scale	2	Inadequate

Study	Design, Duration	Participants (treatment/control)	Intervention	Eligibility	Outcome Measures	Quality	
						Jadad	Concealment
	optimal dose; 12 weeks	diagnoses included stroke (n=18) and head injury (n=3)		fixed contracture at elbow, wrists or interphalangeal joints were excluded			
Richardson ⁴⁹ and Thompson ⁵⁰	R, DB, PC, parallel group; 12 weeks	52 adults with focal hypertonia; 27/25; 32 upper limb patients (16 BTX-A, 16 placebo); 20 lower limb patients (11 BTX-A, 9 placebo); diagnoses included CVA (n=23), head injury (n=12), spinal cord injury (n=6), tumour (n=5), CP (n=3) and anoxic brain damage (n=3)	Botox (mean dose=183 U)	Moderate to severe spasticity in focal muscle groups with poor response to conventional physical and medical treatment; participation in active rehabilitation and management program; excluded from study if fixed joint posture, progressive neuromuscular disease, previous injection of BTX-A in past 12 months into same limb, injection of BTX-A into separate limb within 6 months, pregnancy on anticoagulants with clotting ratio >2.5	MAS, passive ROM, Rivermead motor assessment scale	4	Adequate

R=randomized, DB=double-blinded, PC=placebo-controlled, MAS=modified Ashworth score, ROM=range of motion, CVA=cardiovascular accident or stroke, FES=functional electrical stimulation, PFT=pulmonary functional test, OP=occupational therapy, QUEST=quality of upper extremity skills test, PEDI=pediatric evaluation of disability inventory, EMG=electromyograph, GMFM=gross motor function measure, PCI=physiological cost index, PRS=physician rating scale, BP=blood pressure, IM=intramuscular, BW=body weight, CP=cerebral palsy, PT=physiotherapy, VGA=video gait analysis, AROM=active range of motion, PROM=passive range of motion.

Appendix 8: Summary of Trial Results

Study	Results								
	Muscle Tone	Passive Range of Motion	Active Range of Motion	Motion Analysis	Physicians' or Caregivers' or Patients' Assessment of Function and Disability	Pain	Quality of Life	AE	Notes
Trials involving patients with stroke and upper limb spasticity									
O'Brien ²⁰	Ashworth scores decreased at weeks 2, 4 and 6 for W and at weeks 2 and 4 for E with 300 U dose (unclear whether difference is significant)	Not reported	Not reported	Not reported	Global assessment by physician or patient: significantly improved at weeks 4 and 6	Not reported	Not reported	Not reported	Not reported
Simpson ¹⁶	Significant improvement in Ashworth score at W and E at weeks 2, 4 and 6 with 300 U dose, also significant improvement at W at week 6 with 75 U dose	Not reported	Not reported	Not reported	Physician rated global assessment: significant improvement at weeks 4 and 6 with 300 U dose; and weeks 2, 4 and 6 with 75 U dose; no significant differences with 150 U; patient-rated global assessment: significant improvement at weeks 4 and 6 with 75 U and 300 U doses	Not reported	Not reported	No significant differences	Not reported
Hesse ¹⁵	No significant differences in MAS at weeks 2, 6 or 12	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Childers ¹⁹	Apparent dose-response relationship using Ashworth score	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

Study	Results								
	Muscle Tone	Passive Range of Motion	Active Range of Motion	Motion Analysis	Physicians' or Caregivers' or Patients' Assessment of Function and Disability	Pain	Quality of Life	AE	Notes
Bakheit ¹²	Significant improvement in MAS at E, W and F at 16 weeks with all doses, except at F (500 U and 1,500 U)	No significant differences at 4 weeks at E, W and F	No significant differences at 4 weeks at E and W	Not reported	Not reported	Not reported	Not reported	Slightly more in placebo group compared to combined BTX-A groups	Not reported
Bhakta ¹⁴	Significant improvement in Ashworth score at F at 2, 6 and 12 weeks; significant improvement at E at week 2	No significant differences with E extension or W dorsiflexion	No significant differences	Not reported	Not reported	No significant differences	Not reported	No significant differences	Not reported
deBeyl ¹⁸	Significant improvement in EAS at W at weeks 1, 4 and 6; and at E at week 4 with 360 U dose; no significant differences with 90 U or 180 U doses	Significant improvements at W and E at all doses	Significant improvements at E at week 6 with 360 U dose; at weeks 1, 4, 6 and 12 with 180 U dose; at weeks 1, 6 and 12 with 90 U dose	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Bakheit ¹³	Significant improvement in MAS at week 16 at W and F	No significant differences at 4 weeks at E and W; significant improvements at 16 weeks at E	No significant differences at E and W at week 4	Not reported	Not reported	Not reported	Not reported	No significant differences	Not reported
Brashear ¹⁷	Significant improvement in Ashworth scale at 6 weeks at W	Not reported	Not reported	Not reported	Significant improvement at weeks 6 and 12	Not reported	Not reported	No significant differences	Not reported

Study	Results								
	Muscle Tone	Passive Range of Motion	Active Range of Motion	Motion Analysis	Physicians' or Caregivers' or Patients' Assessment of Function and Disability	Pain	Quality of Life	AE	Notes
	and F; significant improvement at 12 weeks at W, F and T								
Trials involving patients with stroke and lower limb spasticity									
Kirazli ²¹ and On ²²	Dorsiflexion and eversion significantly improved with BTX-A compared with phenol at week 24	Mean gain in ROM greater in treatment group, significance not reported	Mean gain in ROM greater in treatment group, significance not reported	Not reported	Not reported	Not reported	Not reported	Increased pain reported in patients receiving phenol	Not reported
Johnson ²³	Not reported	Not reported	Not reported	Significant increase in walking speed with BTX-A and physiotherapy compared with physiotherapy alone	Not reported	Not reported	Not reported	Not reported	Not reported
Pittock ²⁴	Significant difference in number of patients demonstrating change in MAS compared with baseline in each treatment group at 4 weeks; no longer significant in 500 U and 1,000	Not reported	Not reported	No statistically significant differences in walking speed, stepping rate and step length between groups; some patients decreased use of walking aids	In all treatment groups, more patients and investigators considered patient's condition improved or much improved compared with those who thought it was same or worse; more said that they were likely to or would definitely use the treatment again	Pain at knee, ankle or foot significantly different from that with placebo at weeks 4, 8 and 12, in 1,000 U and 1,500 U treatment groups: significant differences compared to placebo not	Not reported	Incidence of AE similar for all treatment groups	Not reported

Study	Results								
	Muscle Tone	Passive Range of Motion	Active Range of Motion	Motion Analysis	Physicians' or Caregivers' or Patients' Assessment of Function and Disability	Pain	Quality of Life	AE	Notes
	U at weeks 8 and 12, but significant difference from baseline maintained in 1,500 U group at weeks 8 and 12; not reported whether difference was significant compared to placebo				compared with those who said that they would be unlikely to or would not; no statistically significant differences between groups	reported			
Trials involving patients with cerebral palsy and upper limb spasticity									
Corry ²⁵	Significant improvement at E at week 2 and at W at weeks 2 and 12; no significant improvement at T	Not reported	Extension at E and T significant at week 2; no significant improvement in T abduction and W extension or metacarpophalangeal extension	Not reported	More patients and parents rated their change as better or more, compared with control at weeks 2 and 12	Not reported	Not reported	Not reported	Not reported
Fehlings ²⁶	MAS not significant at E, forearm, W and T at 1, 3 and 6 months	No significant differences in E extension, forearm supination, W extension, palmar T abduction	Not reported	Not reported	Significant improvement in PEDI score at 1, 3 and 6 months compared with placebo; total score for involved side on QUEST showed statistically significant improvement favouring BTX-A treatment group at 1 month	Not reported	Not reported	Not reported	Not reported

Study	Results								
	Muscle Tone	Passive Range of Motion	Active Range of Motion	Motion Analysis	Physicians' or Caregivers' or Patients' Assessment of Function and Disability	Pain	Quality of Life	AE	Notes
Trials involving patients with cerebral palsy and lower limb spasticity									
Koman ³⁴	Not reported	Not reported	Not reported	More patients receiving BTX-A demonstrated improved gait pattern	PRS used to evaluate ambulatory function (maximum=14); average improvement in treatment group greater than that for control group (not reported whether significantly different); patient's or guardian's assessment consisted of five questions about child's progress during study; more patients in treatment group reported improvement	Not reported	Not reported	Both groups experienced soreness at injection site; patients in control group also experienced unsteadiness, fatigue and headache; AE were local and generally lasted 1 to 2 days	Not reported
Richman ³⁹	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Corry ³¹	Tone significantly reduced in BTX-A group at 2 weeks, relapsing by 12 weeks; tone change almost significant at 2 weeks in group with casts but not significant at 12 weeks; 12-week relapse in	No significant differences between two groups in passive ankle dorsiflexion with knee flexed at weeks 2 and 12; maximal dorsiflexion in stance and maximal plantar flexion	Not reported	No significant differences in foot contact score and total score	Not reported	Not reported	Not reported	Not reported	Not reported

Study	Results								
	Muscle Tone	Passive Range of Motion	Active Range of Motion	Motion Analysis	Physicians' or Caregivers' or Patients' Assessment of Function and Disability	Pain	Quality of Life	AE	Notes
		flexion with knee extended at 8 weeks in both groups	placebo; mean loss in placebo group in all three measures						
Barwood ²⁸	Not reported	Not reported	Not reported	Not reported	Not reported	Total pain score calculated by using scores from nursing staff, parents and trial coordinator; total pain score significantly less in treatment group compared with placebo (p<0.003)	Not reported	Not reported	Not reported
Koman ²⁹	Not reported	No significant differences between groups in passive ankle dorsiflexion	Active ankle dorsiflexion significantly greater in BTX-A group at weeks 4 and 12	Composite PRS score, which was used to measure gait pattern, was significantly higher at weeks 2, 4, 6 and 8 compared with control	Not reported	Not reported	Not reported	AE evaluated in 145 patients; all rated mild to moderate and none were severe; more AE in treatment group compared with placebo (17% versus 4%); no withdrawals due to AE	Not reported
Uhbi ²⁷	Not reported	No significant changes between BTX-A and placebo groups	Not reported	VGA used to measure changes in gait; changes in VGA rated as	Not reported	Not reported	Not reported	More AE occurred in treatment group compared	Not reported

Study	Results								
	Muscle Tone	Passive Range of Motion	Active Range of Motion	Motion Analysis	Physicians' or Caregivers' or Patients' Assessment of Function and Disability	Pain	Quality of Life	AE	Notes
		at weeks 2, 6 and 12		better (at least one grade of improvement), same or worse; significant improvement at 6 and 12 weeks; no significant differences between treatment group and placebo in GMFM at weeks 2 and 6; significant difference in GMFM at week 12 in portion of those who showed clinically significant improvement				with control; all AE self limiting	
Boyd ³⁵	Not reported	Not reported	Not reported	GMFM total scores, GMFM goal scores and GMFM 66 score not significantly different between groups	Not reported	Not reported	Not reported	Not reported	Not reported
Love ³³	Intra-pair differences in changes in MAS significantly different at weeks 3 and 6	Not reported	Dynamic muscle range measured by modified Tardieu scale; significantly different at 3 and 6 months	GMFM significantly different at 3 and 6 months	Not reported	Not reported	Not reported	Not reported	Not reported

Study	Results								
	Muscle Tone	Passive Range of Motion	Active Range of Motion	Motion Analysis	Physicians' or Caregivers' or Patients' Assessment of Function and Disability	Pain	Quality of Life	AE	Notes
Baker ⁴⁰	Not reported	Passive ankle dorsiflexion with knee extended significantly greater in combined treatment group compared with placebo at week 4; no significant differences at weeks 8 and 16; significant difference in passive ankle dorsiflexion with knee flexed at week 4, but not at weeks 8 or 16	Not reported	Not reported	No significant differences in GMFM overall score at week 4 or week 16	Not reported	Not reported	Not reported	Not reported
Reddi-hough ⁴²	Most BTX-A and control comparisons of MAS not significant; only MAS at left calf and at left hip adductors at 6 months significant; not all patients included	Most BTX-A and control comparisons of ROM not significant; only right ankle dorsiflexion with knee extended at 3 months and with knee flexed at 6 months significantly different	Not reported	No statistically significant differences in GMFM total score between BTX-A and control phases at 3 or 6 months; VAB results revealed trend for BTX-A group to perform better than control; only fine motor component of VAB demonstrated significant differences	Significantly more parents thought BTX-A injections were of benefit to child at 3 and 6 months	At 3 months, more parents report that child experienced pain compared with report at 6 months	Not reported	Fewer parents reported AE at 3 months compared with 6 months; AE may be associated with BTX-A treatment	Not reported

Study	Results								
	Muscle Tone	Passive Range of Motion	Active Range of Motion	Motion Analysis	Physicians' or Caregivers' or Patients' Assessment of Function and Disability	Pain	Quality of Life	AE	Notes
	examine adductors and spasm frequency								
Trials involving patients with various diseases and upper and lower limb spasticity									
Grazko ⁴⁶	All patients demonstrated clinically significant improvement in tone ≥ 2 grades on MAS	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	No systemic side effects noted; no significant muscle weakness noted; one patient with ecchymosis resolved in a few days	Not reported
Burbaud ⁴⁷	Significant difference ($p < 0.0001$) found at 30 days for Ashworth scores of ankle extension, inversion and active dorsiflexion in all 23 patients receiving BTX-A	Not reported	During active ankle dorsiflexion, improvement of > 1 point found in 18 of 22 patients after receiving BTX-A	Gait velocity improved in 8 of 22 patients after BTX-A injection; when data pooled among 23 patients, gait velocity improved after BTX-A, but this did not reach statistical significance; video score significantly improved after BTX-A ($p = 0.0002$)	3 of 23 patients reported no improvement after treatment with BTX-A; subjective score increased by 2 points in 13 patients; slight significant improvement noted in Fugl-Meyer score after BTX-A in all 23 patients ($p = 0.0028$)	Not reported	Not reported	No general or local side effects; local pain at injection site reported in 3 patients	Not reported

Study	Results								
	Muscle Tone	Passive Range of Motion	Active Range of Motion	Motion Analysis	Physicians' or Caregivers' or Patients' Assessment of Function and Disability	Pain	Quality of Life	AE	Notes
Richardson ⁴⁹	Ashworth scores improved for both groups at week 3, relative to baseline, but subsequent time points insignificant	Aggregated outcome scores for ROM significantly better for group that received BTX-A	Not reported	No difference in gross motor function score noted in aggregate outcome scores	Aggregate outcome scores for 20 cases with lower limb dysfunction significantly better for group that received BTX-A	Not reported	Not reported	No side effects recorded by any of the patients; 4 patients reported pain at time of injection	Groups compared post-baseline for aggregate outcome score
Smith ⁴⁸	At 6 weeks, 500 U Dysport group demonstrated significant decrease in MAS at wrist compared to placebo; when all doses of Dysport are combined and compared to placebo, there was a significant difference at W and F in week 6	1,500 U Dysport group demonstrated significant increase in PROM at E compared with placebo; combined dose at week 6 at W significantly different from placebo; at 12 weeks, no significant differences between any treatment group and placebo, except for small significant increase at E in patients receiving 1,500 Mu Dysport	No significant differences noted	6 of 9 patients walked better after BTX-A based on video assessment of gait quality; four patients gained clinically significant (>20%) increase in gait speed after BTX-A treatment	Not reported	Not reported	Not reported	Dysport well tolerated; one patient reported hip pain; one patient had flu-like symptoms for 2 days post-injection	4 patients re-randomized

E: elbow, W: wrist, F: finger, T: thumb, EAS=expanded Ashworth scale, PEDI=pediatric evaluation of disability inventory, PRS=physician rating scale, AE=adverse event, GSS=global scoring scale, GMFM=gross motor function measure, VGA=video gait analysis, BTX-A=botulinum toxin-A, VAB=Vulpe Assessment Battery, QUEST=quality of upper extremity skills test.

Appendix 9: Commonly Used Scales

Ashworth Scale

The Ashworth scale is an ordinal four-point scale used to measure the degree of spasticity.⁵⁶ 0=no increase in tone; 1=slight increase in tone giving a catch when the limb is moved in flexion or extension; 2=more marked increase in tone, but limb easily flexed; 3=considerable increase in tone, passive movement difficult; and 4=limb rigid in flexion or extension. With the exception of grade 4, this scale describes the resistance perceived while moving a joint through its full range of movement (ROM) without quantifying it in absolute units.

Validity of Ashworth scale: Validity refers to the ability of a scale to measure accurately whatever it is expected to measure. This scale is validated in several studies by health care professionals for its constructs, content and reliability. In terms of construct and content validity, a recent review concluded that despite intervention studies claiming the Ashworth scales are measures of spasticity, evidence suggests that the resistance to passive movement is not an exclusive measure of spasticity.⁵² The authors of two concluded that this scale has good inter-rater reliability for spasticity in different muscles.^{57,58} In one study, authors concluded that the Ashworth scale has limited reliability for measuring spasticity in the lower limbs in patients with spinal cord injury.⁵⁹

Modified Ashworth Scale

The modified Ashworth scale, which is similar to the Ashworth scale, has one additional item.⁶⁰ 0=no increase in tone; 1=slight increase in tone manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension; 1⁺=slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM; 2=more marked increase in muscle tone through most of the ROM, but affected part(s) easily moved; 3=considerable increased in tone, passive movement difficult; and 4=affected part(s) rigid in flexion or extension.

Validity of Modified Ashworth Scale: The issues related to the validity of the modified Ashworth scale are similar to those of the Ashworth scale. One study has shown a good correlation between the modified Ashworth scale scores and the electromyogram parameter derived from simultaneous surface recording from the muscles tested.⁶¹ Seven studies investigated the inter-rater reliability of the modified Ashworth scale,^{59,60,62-66} using different types of statistical analysis. The results vary from low to high inter-rater reliability.

Gross Motor Function Measure (GMFM)

GMFM is an observational instrument used to quantitatively evaluate motor performance. This scale was developed to measure gross motor function in children with cerebral palsy. It has 85 items related to motor functions. Each item is scored on a four-point Likert scale: 0=cannot initiate; 1=initiates independently (<10% of the task); 2=partially completes (10% to <100% of the task) and 3=completes independently. It can be used as an outcome in intervention studies.⁶⁷

Validity of GMFM: The GMFM was tested for its responsiveness and reliability in children with cerebral palsy.⁶⁷ Parents and therapists independently rated the children's function and a sample of paired assessments was videotaped for blind evaluation by a therapist. The correlation between scores for change in motor function and the judgments of change by parents, therapists and a blind evaluator indicated that this instrument is responsive to negative and positive changes. The quality of the motor function, however, is not considered. It is likely that the changes detected reflect part of the change in motor behaviour over time, since many aspects of improved function are qualitative rather than quantitative.

Video Gait Analysis (VGA)

VGA is used to obtain qualitative and quantitative information on the complexity and integrity of normal gait and the deviations of that matter from pathologic gait. In VGA, a video is used to evaluate the structural movement of the body during the gait cycle. One gait cycle represents a single stride (two steps) from one foot's (normally heel but not always) contact with the ground to the next foot's contact with the ground. Different techniques are used for recording and evaluating the motor movements. Depending on the versatility of recording and evaluation, the results are presented in qualitative and quantitative terms.^{68,69} We could not find any information on the validity of this method.

Pediatric Evaluation of Disability Inventory (PEDI)

PEDI is a functional assessment instrument for children with disability. Its items are grouped into three domains: self care, mobility and social function. For each domain, ordinal scoring is performed on three dimensions: functional performance capacity, caregiver assistance and environmental modifications.⁷⁰ Functional performance capacity is scored as 0=is unable to perform in most situations and 1=is capable in most situations or has mastered the skill. Caregiver assistance is scored as 0=total assistance; 1=maximum assistance; 2=moderate assistance; 3=minimum assistance; 4=supervision, prompting, monitoring; 5=independence. Environment modification is graded as N=no modification, C=child oriented, R=rehabilitation equipment needed and E=extensive modification.

Validity of PEDI: PEDI was tested for concurrent validity with the Battelle development inventory screening test (BDIST).⁷⁰ The BDIST is a standardized assessment with developmental and adaptive content. Concurrent validity was supported by moderately high Pearson product-moment correlations between PEDI and BDIST summary scores ($r=0.70-0.80$). In the same study,⁷⁰ construct validity was supported by significant differences between the PEDI scores of the disabled and non-disabled groups and by discriminant analysis identifying the PEDI scores as better group discriminators than the BDIST scores.

Active Range of Motion (AROM) and Passive Range of Motion (PROM)

Joint motion, which can be used as a measure of disability, is measured using a goniometer.⁷¹ Different types of goniometer are available. A standard goniometer contains two arms that rotate around a central axis. The proximal end of the goniometer is held in place while the joint is moved and the distal arm of the goniometer is rotated. When the movement is completed, the degree of joint motion is recorded.

To measure PROM, the examiner moves the limb, but AROM is based on the patient's ability to move his or her limb.

Validity of measurement of AROM and PROM: Inter-tester variability exists when AROM and PROM are measured using a goniometer. In one study, inter-tester variability accounted for approximately half the variability.⁷¹ It was concluded that joint motion may differ by at least 5° with different examiners.

Appendix 10: Ashworth and Modified Ashworth Scales

Ashworth scale (1964)

0=no increase in tone

1=slight increase in tone giving a catch when limb moved in flexion or extension

2=more marked increase in tone but limb easily flexed

3=considerable increase in tone, passive movement difficult

4=limb rigid in flexion or extension.

Modified Ashworth scale (1987)

0=no increase in muscle tone

1=slight increase in muscle tone, manifested by a catch and release or by minimal resistance at end of range of motion when affected part(s) moved in flexion or extension

2=slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout remainder (less than half) of ROM (range of movement)

3=more marked increase in muscle tone through most of ROM, but affected part(s) easily moved

4=considerable increase in muscle tone passive, movement difficult

5=affected part(s) rigid in flexion or extension.

From <http://199.243.225.113/ClinicalAssistant/scales/ashworth.html>.