Efficacy, safety and cost effectiveness of botulinum toxin treatment in patients with cerebral palsy or local dystonia



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NEDERLANDSE LEKENSAMENVATTING

Botulinetoxine blokkeert zenuwen waardoor spasticiteit, dystonieën en overmatig kwijlen wordt verlicht. Dit systematische review laat zien dat botulinetoxine een effectieve en veilige behandeling is voor patiënten met een cervicale dystonie, patiënten met een blepharospasme en voor kinderen met een cerebrale parese die spasticiteit in de bovenste extremiteiten hebben. Bij kinderen met een cerebrale parese die overmatig kwijlen is dit nog niet bewezen, maar de resultaten wijzen veelbelovend richting botulinetoxine. Botulinetoxine type A en B lijken vergelijkbaar effectief, alhoewel type B meer bijwerkingen geeft bij cervicale dystonieën. Bovendien is een review verricht naar kosteneffectiviteit, echter dit leverde geen betrouwbare studies op. Een behandeling met botulinetoxine bij lokale dystonieën zou mogelijk jaarlijks €900-1200 besparen ten opzichte van een reguliere behandeling (niet nader omschreven). Een schatting van de jaarlijkse uitgaven in de zorg voor botulinetoxine: €1.010.000,- voor cervicale dystonie, €213.000,- voor blepharospasmen en €1.092.000,- voor kwijlen bij kinderen met cerebrale parese.

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CHAPTER ONE: SYSTEMATIC REVIEW

Efficacy and safety of botulinum toxin treatment in patients with cerebral palsy or local dystonia – a systematic review

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ABSTRACT

Objectives. Evaluating the efficacy and safety of botulinum toxin in the treatment of drooling and spasticity in the upper limb in children with cerebral palsy and of cervical dystonia and blepharospasm.

Design. Systematic review and meta-analysis

Data sources. Cochrane Central Register of Controlled Trials, Pubmed, Medline, EMBASE and CINAHL

Review methods. Each Cochrane review and subsequently published randomised controlled trial (RCTs) on drooling and spasticity in the upper limb in children with cerebral palsy and on cervical dystonia and blepharospasm has been reviewed by three independent evaluators. Internal validity of each RCT has been evaluated based on a pre-defined Cochrane checklist for quality assessment. Eligible RCTs have been included and data was collected by use of a data extraction form.

Results. Seven Cochrane reviews and fourteen additional valid RCTs were included in this systematic review. Of these RCTs, six trials showed effects of botulinum toxin in cervical dystonia (1082 patients) and six RCTs reported on blepharospasm (229 patients). The other two RCTs had studied drooling children with CP (47 patients). No valid records were found on botulinum toxin treatment of spasticity in the upper limb of children with CP.

Conclusion. Botulinum toxin treatment is beneficial and safe in spasticity of the upper limb in children with CP and in patients with cervical dystonia and blepharospasm. This may be

true for drooling in children with CP, although high quality studies are lacking. BoNT-B is as effective as BoNT-A in cervical dystonia, but is associated with a higher incidence of adverse effects. In the other medical indication, BoNT-B has been insufficiently studied. No differences between brands of BoNT-A have been found in all treatments.

BACKGROUND

Botulinum toxin is a very potent neurotoxin that is produced by the bacterium Clostridium botulinum and is responsible for the disease botulism. When injected locally, botulinum toxin is an effective agent for various treatments in rehabilitation care. Botulinum toxin effectively disables the release of acetylcholine from the pre-synaptic membrane of the neuron as is shown by Burgen et al. in 1949. Botulinum toxin contains a protease that prevents acetylcholine-containing vesicles from fusing with the pre-synaptic membrane. By inhibiting the release of acetylcholine at the synapse, botulinum toxin blocks the nerve impulse and causes paralysis of muscles or any other communicating tissues. The rehabilitation care profits from botulinum toxin by paralysing overactive muscles, excessively producing salivary glands and many other disorders.

Seven serologically distinct types of botulinum toxin (ranging from BoNT-A to -G) have been described, which share the same effect. In current treatment, botulinum toxin type A (BoNT-A) is most commonly used. BoNT-B has also been approved for medical treatment, but differs in potency and side effects. The method of isolation of botulinum toxin also affects its efficacy and potentially its safety. Botox® (Allergan Inc.), Dysport® (Ipsen Ltd), Xeomin® (Merz Pharmaceuticals, LLC) and Prosigne® (Lanzhou University) are brand names of BoNT-A that have been isolated differently. Therefore, these types of BoNT-A cannot be administered without investigating the potential hazards. In general, Botox®, Xeomin® and Prosigne® are injected in equal doses. Dysport®, however, is administered at a dose 2 to 4 times higher depending on the treated disorder. This is possible due to the additional carrier molecule and might have influence on the diffusion of botulinum toxin at the site of injection.

Botulinum toxin is often used in therapy to release the complaints of patients with local dystonia or spasticity (Batla 2012). In a dystonic movement, the agonist and antagonist

muscle contract simultaneously, whereas spasticity is expressed through a hypertonic muscle. In both conditions, the central nervous system is often malfunctioning. Spasticity mostly occurs in disorders that affect the upper motor neuron, which results in a lack of inhibition on the muscle tone. This is clearly expressed in most children with cerebral palsy (CP) in which motor control centres are damaged in the developing stage. Often, this phenotype is accompanied by reduced cognition, communicating skills and in one third of the children also by epilepsy and extensive drooling (Wichers 2009). Dystonia, on the other hand, is less well understood. Its pathology likely resides in the brain tissues that coordinate movement contractions. Especially the basal ganglia and GABA producing Purkinje neurons are subject of study, although a definite cause is not yet clear. Spasmodic torticollis, or cervical dystonia, is the most common type of local dystonia. These patients involuntarily move their neck muscles which results in asymmetric contractures. The local dystonia with the second highest prevalence is blepharospasm, in which the muscles around the eyes are affected. Together, cervical dystonia and blepharospasm make up for roughly 40% of all cases with dystonia in the Dutch population (Speelman 2009).

In the Netherlands, the current state of evidence is summarized in a pharmacotherapeutic report, which indicates that efficacy and safety of botulinum toxin treatment is still unclear (CVZ: CFH-rapport 03/12). Well performed randomised controlled trials (RCTs) that have studied the effect of BoNT-A and BoNT-B in local dystonia and CP children have been reviewed by the Cochrane Collaboration group. Results in these Cochrane reviews are summarised in table 7. To provide an update on these overviews, this systematic review shows the current state of knowledge of botulinum toxin treatment in the most common local dystonia and drooling and upper limb spasticity in children with cerebral palsy.

Objectives

- To appraise the value of botulinum toxin treatment in the care of patients with local dystonia and more specific cervical dystonia and blepharospasm;
- Evaluation of the effectiveness and safety of treatment with botulinum toxin aimed at reducing or eliminating drooling or upper limb spasticity in children with cerebral palsy;

Research question

Efficacy and safety (O) of botulinum toxin (I) compared to any alternative treatment (C) in children with cerebral palsy (for treatment of upper limb spasticity or drooling), or patients with cervical dystonia and blepharospasm (P).

REVIEW METHODS

Search and selection

The following databases have been searched for relevant literature: Cochrane Central Register of Controlled Trials (CENTRAL); Pubmed, Medline and EMBASE via Ovid; and CINAHL via Ebsco (Table 8). The search was performed until the date of 29 November 2011. We based the inclusion of randomised controlled trials (RCTs) on the most recently published relevant Cochrane review and included studies that were published after the study inclusion date of the Cochrane reviewers. Three reviewers (PvE, MvH and BvdB) independently selected the included studies on relevance by judging titles, abstracts and full text reports and differences resolved through discussion. In case of any disagreement a fourth independent and responsible reviewer (JvL) was consulted.

Inclusion and exclusion criteria

Studies were included if all of the following criteria were satisfied:

- Either Cochrane reviews or Randomised Controlled Trial
- Aimed at treatment with botulinum toxin
- Aimed at treatment of drooling or spasticity in the upper extremities in children with CP or aimed at treatment of patients with local dystonia
- Published after the searching date of the latest published Cochrane review of a relevant subject:
    - Studies focused on cervical dystonia: inclusion from 1 June 2003
    - Studies focused on blepharospasm: inclusion from 1 June 2003
    - Studies focused on spasmodic dysphonia: inclusion from 22 July 2009
    - Studies focused on other local dystonia: no limit on publication date
    - Studies focused on drooling in children with CP: inclusion from 1 December 2010*

- Studies focused on spasticity in the upper extremities in patients with CP: inclusion from 1 August 2008

*) In the process of analysing the collected data, a new Cochrane review was published on the effectiveness of botulinum toxin treatment for drooling in children with cerebral palsy (Walshe 2012). For this reason we decided to add their data to this review and to update the inclusion criterion for studies focused on drooling in children with CP.

Validity assessment

The methodological quality of the studies found in literature was evaluated with the officially translated Dutch Cochrane form for evaluating Randomized Controlled Trials (dcc.cochrane.org/sites/dcc.cochrane.org/files/uploads/RCT.pdf), added with questions of the Jadad checklist (Jadad 1996). In table 11 a description is given of the included items in the tool and of the scoring criteria. The quality assessment was performed by three reviewers (PvE, MvH and BvdB). All items were finally scored as being true or accurate (+), false or inadequate (-) or unknown due to inadequate information (?). If any difference in outcome existed a fourth independent reviewer (Jvl) was consulted. Studies that scored below six points based items on the Cochrane checklist (every "+" was rated as one point) were rated as qualitatively poor RCTs and excluded from further analysis.

Data extraction and analysis

Data was extracted by one reviewer (PvE) and checked by a second reviewer (MvH). A standardized form for RCT data extraction developed by the Cochrane collaboration group was used. Additionally, two independent reviewers (PvE and MvH) assessed the risk of bias in each included study. Data analysis of the remaining studies was conducted descriptively. If studies showed sufficient homogeneity in the pre-defined comparisons, a meta-analysis was considered and, when appropriate, conducted in Stata software, version 10.0 (Stata Inc., College Station, Texas). In the meta-analyses, we used the relative change in the primary outcome from baseline to the follow up measurement that recorded the greatest effect. Calculations were performed using a random-effects model. An α value of < 0.05 was considered statistically significant.

RESULTS

Search and selection

Our literature search for RCTs in Pubmed, Medline, Embase and Cinahl resulted in 183 records. The search in the Cochrane databases yielded 7 Cochrane reviews that met our inclusion criteria (Table 7). The literature search is summarised in a flow diagram (Figure 1). After extracting the study inclusion date in each Cochrane review, we were able to set limits on our search for additional RCTs in Pubmed, Medline, Embase en Cinahl as previously mentioned. This limitation resulted in an exclusion of 55 records. Six duplicate articles were retrieved and were also excluded. From the remaining 122 records, each title and subsequently each abstract (n=61) was screened for relevance by the three independent reviewers. In the process of analysing the collected data, a new Cochrane review was published on the effectiveness of botulinum toxin treatment for drooling in children with cerebral palsy (Walshe 2012). As expected, this Cochrane review contained several publications that we had already included. However, two recently published studies (Basciani 2011 and Wu 2011) were not covered by this Cochrane review. For this reason, we decided to include this Cochrane review to our systematic review and to withdraw two RCTs (Lin 2008 and Alrefai 2009). In total, 37 full text reports were assessed for eligibility. Finally, 18 studies were included in the quality assessment (Table 2). Due to poor quality in four RCTs the best evidence synthesis contained 14 studies:

Medical indication	BoNT-A (vs. placebo or dose)	BoNT-B (vs. placebo or dose)	BoNT-A vs. BoNT-B	BoNT-A vs. BoNT-A	Total
Cervical dystonia	2		3	1	6
Blepharospasm	2			4	6
CP drooling	1	1			2

Figure 1. Flow diagram of the literature search

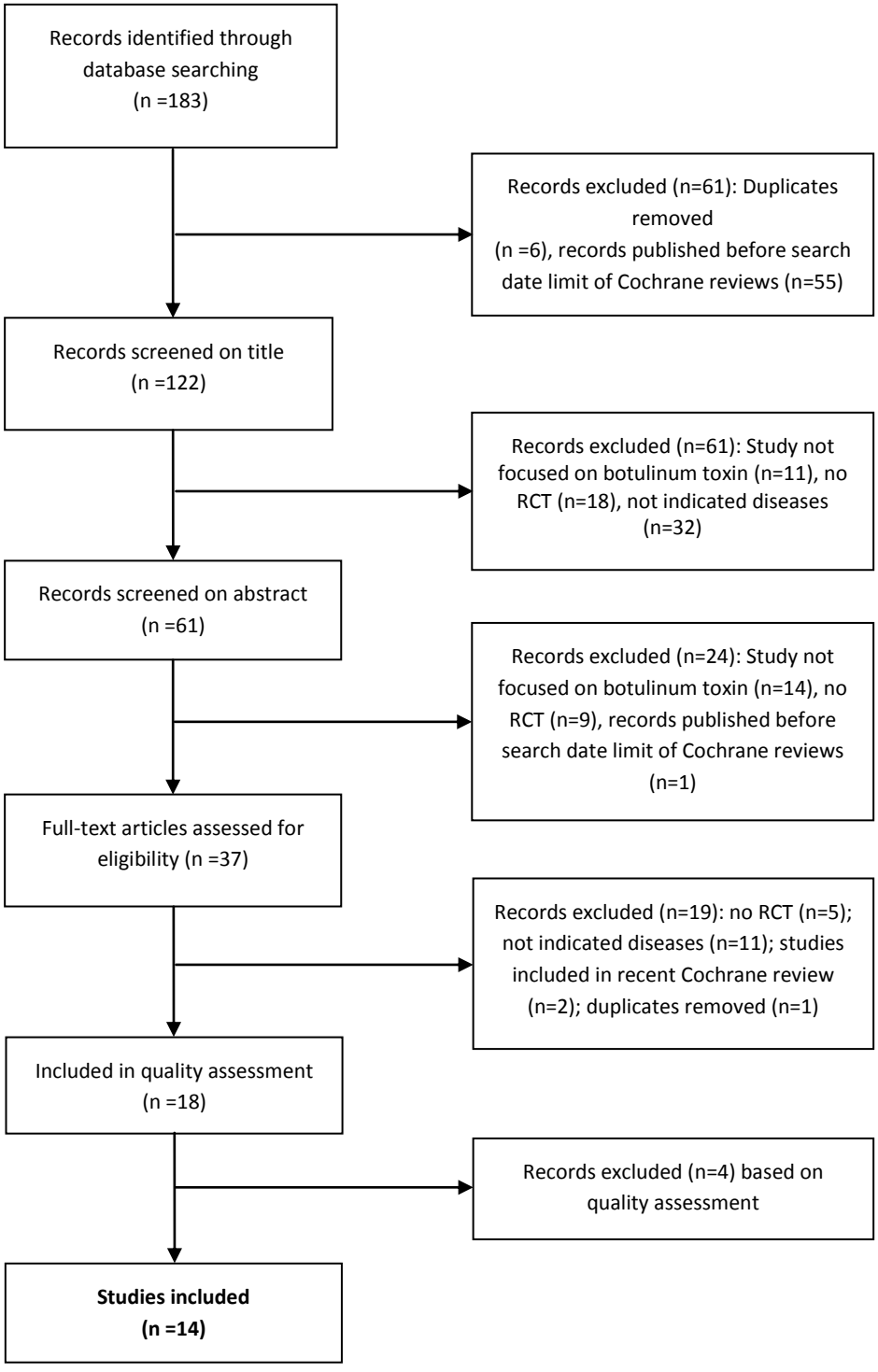


Table 2. Quality assessment

Author	Diagnosis	Intervention well defined	Control well defined	Randomised allocation of patients	Blind inclusion rater	Blind patient	Blind administering investigator	Blind assessor	Comparable study groups	Sufficient number of patients at study completion	Patients analysed according to allocation	Equal treatment in all groups	Subscore (Cochrane validity score of RCTs)	Appropriate randomisation method	Appropriate reportation of withdrawals/dropouts	Groups representative to daily practise	Adequate outcome measures	Clinically relevant effect	Effect of intervention outstands the side-effects	Subscore (Jadad validity score of RCTs)
Basciani 2011	CP drooling	+	?	+	?	-	?	+	+	+	+	+	6	?	+	+	+	+	+	5
Wu 2011	CP drooling	+	+	+	?	+	+	+	+	+	+	?	7	?	+	+	+	+	+	5
Rameckers 2009	CP upper limb spasticity	+	+	+	?	-	-	+	?	+	+	?	4	?	+	?	+	+	-	3
Redman 2008	CP upper limb spasticity	-	-	+	?	-	-	-	+	+	?	?	3	+	-	+	?	?	?	2
Boyle 2009	Blepharospasm	+	+	+	?	-	-	-	?	+	+	-	3	?	-	-	?	+	+	2
Jankovic 2011	Blepharospasm	+	+	+	+	+	+	+	+	+	+	+	9	+	+	+	+	+	+	6
Truong 2008	Blepharospasm	+	+	+	+	+	+	+	+	?	+	+	8	+	+	+	?	+	+	5
Yoon 2009	Blepharospasm	+	+	+	?	+	+	+	+	?	+	+	7	+	+	+	+	+	+	6
Roggenkamper 2006	Blepharospasm	+	+	+	+	+	+	+	+	+	+	+	9	-	+	-	+	+	+	4
Wabbels 2010	Blepharospasm	+	+	+	+	+	+	+	+	+	+	?	8	+	+	+	+	+	+	6
Quagliato 2010	Blepharospasm	+	+	+	+	+	+	+	?	-	+	?	6	-	-	-	+	+	+	3
Pappert 2008	Cervical dystonia	+	+	+	+	+	+	+	+	+	+	+	9	+	+	+	+	+	+	6
Comella 2011	Cervical dystonia	+	+	+	+	+	+	+	+	+	+	-	8	+	+	+	+	+	+	6
Comella 2005	Cervical dystonia	+	+	+	+	+	+	+	?	+	+	-	7	+	+	+	+	+	+	6
Truong 2005	Cervical dystonia	+	+	+	?	+	?	?	+	?	-	+	4	-	-	+	+	+	?	3
Truong 2010	Cervical dystonia	+	-	+	?	+	+	?	+	?	+	+	6	+	+	+	+	+	+	6
Benecke 2005	Cervical dystonia	+	+	+	+	+	+	+	?	+	+	?	7	-	+	+	?	+	+	4
Tintner 2005	Cervical dystonia	+	+	+	?	+	+	+	?	+	+	?	6	-	+	+	+	?	?	3
				Items Cochrane score										Items Jadad score						

All items were scored as being true or accurate (+), false or inadequate (-) or unknown due to inadequate information (?).

Included studies

Fourteen RCTs evaluating the efficacy and safety of botulinum toxin treatment have been included in this review. Of these, twelve studies investigated local dystonia and two trials studied drooling in children with CP. No new valid RCTs were found on spasticity in the upper limb of children with CP.

Here, the main items of each included study will be summarized with the addition of methodological comments (Table 9 provides a systematic overview of the data extraction and table 10 shows the risk of bias in each included study):

Title:	**Botulinum toxin type B for sialorrhoea in children with cerebral palsy: a randomized trial comparing three doses (2011)**
Author:	Basciani et al.
Indication:	**Drooling in CP children**. Study: **Placebo** (*content unknown*) vs. **BoNT-B** (*total of 1500, 3000 or 5000MU Myobloc, Elan Pharmaceutical*)

Basciani and colleagues included 27 CP children with refractory sialorrhea or drooling (mean age 7.8±1.5y; range 5–15y) and they were randomly allocated by a computer-generated program to either a control, 1500MU BoNT-B, 3000MU BoNT-B or 5000MU BoNT-B treatment group (comparable demographic data; dose indicates total dose). Both the parotid and submandibular glands were injected with ultrasound guidance. To objectively measure the extent of drooling before injection of the treatment and again at 4 and 12 weeks, the weight and number of bibs per day were analysed. Only the 3000MU and 5000MU BoNT-B groups showed significantly decreased drooling after 4 and 12 weeks according to the number and weight of bibs (-21.3 bibs and -7.2 grams in the 3000MU group and -22.0 and -9.4 grams in the 5000MU group at 4 weeks; $p<0.01$ for all) and showed great improvement on both the severity and frequency subscale of the Thomas-Stonell rating scale (drooling severity: from 4.6 at baseline to 1.4-1.7 after 4 weeks and 1.3-1.6 after 8 weeks; drooling frequency: from 3.6-3.7 at baseline to 1.3-1.4 after 4 weeks and 1.3 after 8 weeks; no p-values reported). No difference in efficacy was seen between the 3000MU and 5000MU BoNT-B groups ($p>0.25$ for all parameters). However, significantly more adverse events occurred in the groups with the highest dose: Two children in the 5000MU BoNT-B

treatment group developed severe dysphagia and weakness requiring hospitalization and nasogastric tube feeding for two weeks, while one of them also developed aspiration pneumonia. Therefore, the authors conclude the 3000MU BoNT-B treatment is recommended.
Remarks: no blinding of the patient and questionable blinding of the investigators. Unclear method of randomisation. Control treatment is not specified.

Title: **Botulinum Toxin Type A on Oral Health in Treating Sialorrhea in Children With Cerebral Palsy: A Randomized, Double-Blind, Placebo-Controlled Study (2011)**
Author: Wu et al.
Indication: **Drooling in CP children**. Study: **Placebo** (*saline*) vs. **BoNT-A** (*Botox, Allergan*) (*30U for subjects <15 kg, 40U for subjects from 15 to 25 kg and 50U for subject >25 kg*)

A randomised double blind controlled trial compared placebo (saline solution) with BoNT-A (Botox, Allergan) in 20 CP children with a chronic drooling problem (mean age: 8.3 years; comparable demographic data) to study the effect of BoNT-A on the extent of drooling. With ultrasound guidance, each parotid and submandibular gland was injected with 10U/ml BoNT-A or placebo with a dose that depended on the subjects weight (30U for subjects <15 kg, 40U for subjects from 15 to 25 kg and 50U for subject weights >25 kg). Maximum dose for each submandibular gland was 10U. The mean saliva flow rate was measured by calculating the weight increase of gauze after 2-minute chewing. Compared to baseline, the BoNT-A treatment group showed significant decreases in the extent of drooling after both 1 and 3 months (change compared to baseline values: +0.22±0.16 ml/min salivary flow in the placebo group vs. -0.14±0.09 in the BoNT-A group after 1 month and +0.16±0.15 ml/min salivary flow in the placebo group vs. -0.25±0.16 in the BoNT-A-group; p=0.037 and p=0.041, respectively. No adverse events were reported.
Remarks: *the authors did not describe their method of randomisation. Insufficient information to permit judgement on the allocation concealment.*

Title: **Efficacy and Safety of IncobotulinumtoxinA (NT 201, Xeomin) in the Treatment of Blepharospasm—A Randomized Trial (2011)**

Author: Jankovic et al.

Indication: **Blepharospasm**. Study: **Placebo** (*unknown content*) vs. **BoNT-A** (*Xeomin*)(*mean dose: 33.5U per eye)*

In this placebo-controlled trial to study the efficacy and safety of BoNT-A (Xeomin) patients with bilateral blepharospasm and a Jankovic Rating Scale (JRS) severity subscore ≥ 2 (n = 109; mean age: 61.8 years) have been randomised by RANCODE version 3.6 in a 2:1 ratio to either BoNT-A or placebo (demographic characteristics matched for age and JRS and Blepharospasm Disability Index (BSDI) scores). Treatment was based on the last two BoNT-A treatments prior to the study up to a maximum of 50U per eye. As primary outcome parameter the JRS-score was assessed at baseline and 3 and 6 weeks post-injection by both the investigator and patient who were blinded for treatment allocation. In addition, the BSDI was carried out by the patient. Six weeks results showed that patients responded significantly better to BoNT-A treatment compared to placebo in every measurement ($p<0.01$ for all JRS subscales and BSDI). The JRS total score of BoNT-A treated patients decreased 1,59 on average compared to placebo at week 6 (JRS total score at 6 weeks: -24.0% in BoNT-A vs. +3.1% in placebo group). Drug-related adverse events occurred more frequently in the BoNT-A treated patients (45.9%) compared to patients treated with placebo (20.6%), of which eyelid ptosis (17.6% in the BoNT-A group vs. 2.9% in the placebo group) and dry eye (14.9% in BoNT-A vs. 8.8% in placebo) were the most common.
Remarks: *Placebo content is unknown. Results from 3 weeks post-injection are not reported as well as the change in JRS severity subscore at week 6.*

Title: **Efficacy and safety of purified botulinum toxin type A (Dysport) for the treatment of benign essential blepharospasm: A randomized, placebo-controlled, phase II trial (2008)**

Author: Truong et al.

Indication: **Blepharospasm**. Study: **Placebo** (*saline*) vs. **40U/eye** vs. **80U/eye** vs. **120U/eye BoNT-A** (*Dysport, Ipsen*)

Truong and colleagues studied efficacy of BoNT-A (Dysport) in bilateral benign essential blepharospasm by comparing 40, 80 and 120 units/eye to placebo (saline). In this RCT, 120 blinded patients with a score of ≥8 point on the Blepharospasm Disability Scale (BDS) (scale ranges from 0-26; 26 being the most affected state) were randomised to demographic comparable groups by use of computer-generated schedule. The BDS was used as primary outcome result. In addition, the authors used Frequency of Involuntary Movement (FIM) scale and measured severity of oculo-facial spasms using the Severity Rating Scale (SRS). These scores were taken by blinded investigators at baseline and were recorded by telephone interview 2, 4, 8, 12 and 16 weeks after a single injection in the region of the orbicularis oculi muscle (placebo or Dysport at a concentration of 200 units/ml). Compared to placebo, 120 units of BoNT-A (Dysport) per eye provided the best sustained efficacy (50% less normal activity on the BDS until week 12 ($p \leq 0.001$)). However, the incidence of adverse events was also proportional to the dose of BoNT-A. For this reason, both 80 units of BoNT-A (Dysport) per eye seems to be preferable (-42% normal activity on the BDS 4 weeks post-injection and -49% and -36% normal activity on the BDS after respectively 8 and 12 weeks ($p \leq 0.001$ for all)).

Remarks: *Large number of withdrawals (especially in the placebo group (36% of patients remained)) is poorly described, but analysis according to the ITT protocol. Baseline values of all groups and all values of the placebo group are not reported. Results are reported as difference scores only (outcome measure at patient visit minus the baseline score).*

Title:	**Double-Blind, Randomized, Comparative Study of Meditoxin Versus Botox in the Treatment of Essential Blepharospasm (2009)**
Author:	Yoon et al.
Indication:	**Blepharospasm**. Study: **BoNT-A** (*Meditoxin, Medy-Tox*) vs. **BoNT-A** (*Botox, Allergan*) (*2.5-5U per injection site; mean dose: 20.9U per eye)*

Yoon et al. performed a non-inferiority trial to compare two types of BoNT-A (Meditoxin and Botox). A computer generated schedule was used to randomise 60 patients with bilateral essential blepharospasm to one of the BoNT-A treatments (n=31 for Meditoxin (mean age: 61.2±9.1y) and n=29 for Botox (mean age: 62.2±7.0y)). Both the patient and the investigators were blinded when BoNT-A was injected with a dose ranging from 2.5-5U per

injection site (limitation of 60U per person). This dose per injection site was set at 1.25-2.5U for patients that were treated for the first time. Four weeks post-injection, 90.3% of the patients on Meditoxin and 86.2% of patients with Botox treatment showed an improvement of at least one grade in the severity of spasm score (comparison between both BoNT-A: p=0.702). Also the secondary outcome measures (closing force of eyelids and functional visual status at four weeks post-injection) demonstrated no significant differences between both treatment groups. The duration of effect was similar for both BoNT-A treatments (19.5 weeks for Meditoxin and 19.8 weeks for Botox; p=0.835). Both BoNT-A types were also comparable based on the incidence of adverse events (p=0.282).
Remarks: *none.*

Title:	**Efficacy and safety of a new Botulinum Toxin Type A free of complexing proteins in the treatment of blepharospasm (2006)**
Author:	Roggenkämper et al.
Indication:	**Blepharospasm**. Study: **BoNT-A** (*Botox, Allergan*) vs. **BoNT-A** (*Xeomin, Merz Pharmaceuticals*)(*mean dose: 20.1U per eye*)

This double-blind study was set up to compare the effectiveness and safety of two BoNT-A in the treatment of blepharospasm. 304 Patients (mean age: 63±10.3y) were randomised and allocated 1:1 to either Xeomin- or Botox BoNT-A. Dose and dilution on BoNT-A injections, as well as the injection sites, were determined for each patient based on two pre-study Botox BoNT-A injections (≤35 units per eye). At baseline, 3 weeks and at the final visit (16 weeks) the Jankovic Rating Scale (JRS) was assessed in all patients and used as primary outcome measure. Additionally, the Blepharospasm Disability Index (BSDI) was determined and patient evaluation was asked. Results show significant effects of both BoNT-A treatment at both 3 and 16 weeks based on all outcome measures ($p<0.0001$ for all). The JRS score changed -2.83 at 3 weeks and -0.84 at 16 weeks from baseline in the Xeomin treatment group and -2.65 at 3 weeks and -0.66 at 16 weeks from baseline in the Botox group. Mean treatment difference between both BoNT-A treatments was -0.23. The upper limit of the 95% CI (0.22) fell below the non-inferiority delta (0.8). As for the efficacy, also the safety of both BoNT-A treatments were comparable (56 vs. 62 adverse events (Xeomin vs. Botox)). No significant differences in specific events were observed.

Remarks: *Method of randomisation is unclear. Standard deviations of outcome measures are not reported. Authors do not mention the time between pre-study BoNT-A injections and the study injections, which is relevant for potential carry-over effects. Analysis is not performed on the ITT population, although it is methodological correct to discard patients with major protocol deviations.*

Title:	**Double-blind, randomised, parallel group pilot study comparing two botulinum toxin type A products for the treatment of blepharospasm (2011)**
Author:	Wabbels et al.
Indication:	**Blepharospasm**. Study: **BoNT-A** (*Botox, Allergan*) vs. **BoNT-A** (*Xeomin, Merz Pharma*)(*mean dose: 29.0U (Botox) and 27.1U per eye (Xeomin))*

This double-blind, randomised trial compares two BoNT-A products (Botox and Xeomin). Patients with benign essential blepharospasm were randomised to either Botox (n=32 (mean age: 70.7±10.7y)) or Xeomin (n=33 (mean age: 67.1±12.1y)). Subjects were injected with a dose that was equal to that of their most recent pre-study treatment (≥20U/eye). At baseline, 4 and 8 weeks the Blepharospasm Disability Index (BSDI) scores and the Jankovic Rating Scale (JRS) were assessed along with the patient global assessment score (PGA). Results indicate positive effects of both BoNT-A treatments. Results show a tendency toward a stronger improvement with Botox than Xeomin at both 4 and 8 weeks post-injection, but this was statistically insignificant. Change at 4 weeks compared to baseline: mean BSDI scores of Botox were -2.8 and of Xeomin -1.3 (p=0.093) and mean JRS scores of the Botox group were -2.2 and of Xeomin -1.5 (p=0.115). At 8 weeks the effect had faded slightly based on all outcome measures. Regarding the safety of both BoNT-A treatments, no significantly different result was showed between both groups (p=0.752). Periorbital hematoma was reported most frequently (25% of the patients), followed by headache (22%) and eyelid ptosis (11%).
Remarks: *The mean dose BoNT-A per eye differed in the BoNT-A groups (29U/eye in the Botox group vs. 27.1U/eye in the Xeomin group (insignificant)).*

Title: **Prospective, randomized, double-blind study, comparing botulinum toxins type A Botox and Prosigne for blepharospasm and hemifacial spasm treatment (2010)**

Author: Quagliato et al.

Indication: **Blepharospasm**. Study: **BoNT-A** (*Botox, Allergan*) vs. **BoNT-A** (*Prosigne, Lanzhou Laboratory*)(*30U per eye*)

Quagliato et al. reported on the efficacy and the adverse events of two BoNT-A treatments 21 primary blepharospasm patients. In this double-blind study, patients were randomised to either Botox (Allergan) (n=11; mean age: 67.5±6.3y) or Prosigne (Lanzhou Laboratory) (n=10; mean age: 65.9±0.9y). A dose of 30U BoNT-A was injected in each orbicularis oculi and procerus muscles. Xylocaine/lidocaine pomade was applied to anesthetize the injection area. At baseline and 4 and 16 weeks post-injection the Blepharospasm Graduation Scale (BSGS) was scored. Both BoNT-A treatments showed significant improvements at 4 weeks in both subscores of the BSGS (seriousness subscore: -3.8 in Botox group vs. -4.3 in Prosigne group; disability subscore: -11.3 in the Botox group vs. -12.4 in the Prosigne group ($p \leq 0.0001$ for all)). 95% of all patients reported an adverse event. No significant difference was observed between both BoNT-A groups. Both BoNT-A treatments caused a similar number and similar types (90% mild and 10% moderate) of adverse events. Eye burning and lacrimation occurred most frequently (57% and 62%, respectively).

Remarks: *Method of randomisation is not described. Unknown whether all study patients have been treated equally throughout the trial. Low number of study patients. Patient selection is not adequate specified. The baseline characteristics of the study population is poorly described. High number of adverse events implies the BoNT-A injection concentration was too high. The content of the Blepharospasm Graduation Scale is not explained, a reference to its source is missing and was not found on the internet. Drop out has not been reported.*

Title: **Botulinum Toxin Type B vs. Type A in Toxin-Naive Patients with Cervical Dystonia: Randomized, Double-Blind, Noninferiority Trial (2008)**

Author: Pappert et al.

Indication: **Cervical dystonia**. Study: **BoNT-A** (*150U Botox, Allergan*) vs. **BoNT-B** (*10000U Myobloc, Elan Pharmaceutical*)

This double-blind clinical study performed by Pappert and colleagues included 111 patients with cervical dystonia and a baseline Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total score of ≥20. They were randomised at ratio 1:1 to either BoNT-A or BoNT-B (mean age 49.5±12.2 and 48.3±12.9, respectively). The site principal investigator assessed the TWSTRS total score, VAS pain and adverse events at baseline and 4 weeks as outcome parameters. Compared to baseline both BoNT-A and BoNT-B treated patients improved significantly 4 weeks post-injection (BoNT-A: 8.9±8.3 and BoNT-B: 10.9±7.9; p<0.0001). Non-inferior analysis showed that BoNT-A and BoNT-B treatment were comparable in both efficacy and safety, although a mild dry mouth occurred more frequently in patients allocated to BoNT-B (BoNT-A: 5.5% vs. BoNT-B: 32.1%; p<0.0001). Treatment related adverse events were also significantly more frequent in the BoNT-B group (29.1% vs. 51.8%, p=0.02). Remarks: *Results from the ITT protocol analysis is not reported*.

Title: **Efficacy and safety of incobotulinumtoxinA (NT 201, XEOMIN®, botulinum neurotoxin type A, without accessory proteins) in patients with cervical dystonia (2011)**

Author: Comella et al.

Indication: **Cervical dystonia**. Study: **Placebo** (*unknown content*) vs. **120U** vs. **240U BoNT-A** (*Xeomin*)

233 Patients with cervical dystonia of a predominantly rotational form (spasmodic torticollis) and with a baseline TWSTRS total score of ≥20 were randomly allocated (by Rancode version 3.6) to treatment with either placebo or a dose of 120U or 240U BoNT-A (Xeomin). All relevant participants in this study were blinded for treatment allocation. The injecting physician decided upon muscle selection, dosing into each muscle, number of injection sites and use of electromyography. At baseline, 4 weeks and 8 weeks post-injection the

investigators measured outcome by the TWSTRS total score. This study shows a significant improvement in patients treated with either 120U BoNT-A (TWSTRS total scores: mean of -7,5 ($p<0.001$) after 4 weeks and -7,1 ($p<0.001$) after 8 weeks) or 240U BoNT-A (TWSTRS total scores: mean of -9,0 ($p<0.001$) after 4 weeks and -8,6 ($p<0.001$) after 8 weeks) when comparing to placebo treatment. Both BoNT-A treatments scored significantly sustained improvement on every subscale of the TWSTRS score (severity, disability and pain). Additionally, no marked difference was seen in the adverse effects of either BoNT-A treatment.

Remarks: *Placebo content is unknown. Unknown whether study groups have been treated equally due to the individual judgement of the patient's needs by the injecting physician.*

Title:	**Comparison of botulinum toxin serotypes A and B for the treatment of cervical dystonia (2005)**
Author:	Comella et al.
Indication:	**Cervical dystonia**. Study: **BoNT-A** (*Botox, Allergan*) vs. **BoNT-B** (*Myobloc, Elan Pharmaceutical*)(*mean dose: 207U BoNT-A or 8400U BoNT-B*)

Comella and colleagues performed a double-blind RCT to compare BoNT-A with BoNT-B in the treatment of cervical dystonia. Based on previous injection amounts, 139 eligible subjects with cervical dystonia and with a baseline TWSTRS total score of ≥20 were injected with the appropriate study drug with a maximum of 250U BoNT-A and 10000U BoNT-B. Muscle selection, as well as the dose for each muscle and use of EMG, were at the discretion of the injection physician. Based on the TWSTRS total score, the authors concluded that both the BoNT-A and BoNT-B group showed significant improvement at 4 weeks compared to baseline (-9,3 in the BoNT-A group and -10,2 in the BoNT-B group; $p<0.0001$). However, BoNT-A and BoNT-B seem to be equally effective ($p=0.75$). The only difference was reported on the incidence of dysphagia at 4 weeks, which was significantly more after BoNT-B treatment (19% in BoNT-A vs. 48% in BoNT-B patients; $p=0.0005$), and the number of cases with a dry mouth, which also occurred significantly more frequent in BoNT-B patients (41% in BoNT-A vs. 80% in BoNT-B patients; $p<0.0001$).

Remarks: *Significantly shorter period of time of pre-study BoNT-A treatment and start of the clinical trial in BoNT-A group compared to the BoNT-B group ($p=0.02$). Unknown whether*

study groups have been treated equally due to the individual judgement of the patient's needs by the injecting physician.

Title: **Long-term efficacy and safety of botulinum toxin type A (Dysport) in cervical dystonia (2010)**
Author: Truong et al.
Indication: **Cervical dystonia**. Study: **Placebo** (*unknown content*) vs. **BoNT-A** (*500U Dysport, Ipsen*)

This double-blind clinical trial randomised 116 patients with cervical dystonia and a baseline TWSTRS total score of ≥30 to 500 units of BoNT-A (Dysport) or placebo. The study groups were well matched and were followed every 4 weeks for 12 weeks. The efficacy of the treatment was determined by change in the TWSTRS total score and subscale scores. These tests were assessed by investigators that had received training on TWSTRS scoring. The injection physician had the option to use EMG to guide the injection and decided on both the number of muscles that had to be injected and the dose at each site. Results from this study show that treatment with BoNT-A produced significant improvements in the status of the patients at 4 weeks compared to placebo (mean of -15,6 vs. -6,7 on the TWSTRS total score; $p<0.001$). These results sustained for at least 12 weeks (mean of -9,1 vs. -4,9; $p=0.019$). BoNT-A was also tolerated well, except that dysphagia was reported significantly more frequent compared to patients treated with placebo.
Remarks: *Content of placebo is not described. Blinding of assessor is unsure. Two patients are withdrawn without sufficient explanation.*

Title: **A new botulinum toxin type A free of complexing proteins for treatment of cervical dystonia (2005)**
Author: Benecke et al.
Indication: **Cervical dystonia**. Study: **BoNT-A** (*Botox, Allergan*) vs. **BoNT-A** (*Xeomin, Merz Pharmaceuticals*)(*both doses ranges from 70 to 300U*)

In a double blind non-inferiority trial 463 patients (mean age: unknown) with confirmed cervical dystonia and a baseline TWSTRS total score of ≥10 were included and randomly

allocated to either Xeomin BoNT-A (n=231) or Botox BoNT-A (n=232). All patients and investigators were blinded from treatment allocation. Injection doses were based on the patient's two consecutive Botox treatments prior to trial start (ranging from 70 to 300U). At baseline and 4 and 16 weeks post-injection the TWSTRS was scored and the severity subscore was set as primary outcome measure. In addition to the other TWSTRS subscores, the VAS pain and an adapted 9-point Global Response Scale score was used to assess the status of the patient. Results show that patients from both treatment groups improved on the TWSTRS severity score from 18 points at baseline to 11 points by 4 weeks and to 16 points at 16 weeks ($p<0.0001$). Both treatments did not differ from each other (-6.6 points for the Xeomin group and -6.4 points for the Botox group at 4 weeks). The upper limit of the corresponding 95% CI was lower than the predefined difference of $\Delta = 1.3$ points, indicating the non-inferiority of Xeomin to Botox BoNT-A. Based on the reported adverse events both BoNT-A treatments are comparable as well. Dysphagia was the most frequently reported adverse event (9.5%).
Remarks: *Method of randomisation is not described. Baseline values are generally missing and TWSTRS total score values are not reported. Unknown whether all study patients have been treated equally.*

Title:	**Autonomic function after botulinum toxin type A or B: A doubleblind, randomized trial (2005)**
Author:	Tintner et al.
Indication:	**Cervical dystonia**. Study: **BoNT-A** (*Botox, Allergan*) vs. **BoNT-B** (*Myobloc, Elan Pharmaceutical*)(*Mean dose: 227U BoNT-A or 12083U BoNT-B*)

Tintner and colleagues compared BoNT-A and BoNT-B by means of autonomic effect changes (i.e. saliva production) in addition to efficacy on the treatment of cervical dystonia in 20 randomly allocated subjects with cervical dystonia (BoNT-A (n=11) mean age: 55±12y and BoNT-B (n=9) mean age: 64±10y). Dosing was at the discretion of the blinded injection physician. BoNT-B was 50 times as concentrated as BoNT-A due to the difference in effective units. The TWSTRS score was assessed in all patients at baseline and 2 weeks post-injection. An autonomic scoring scale was also included to monitor changes in saliva production (chewing gauze pads (Schirmer's test)). TWSTRS scores were clearly improved two weeks

post-injection in both treatment groups (severity from 17 to 14-15, pain from 10 to 4-6 and disability from 16 to 10-12), but did not differ between both groups. As an adverse event, the saliva production was significantly reduced in only the BoNT-B treatment group (from 3.5 to 2.5 mg saliva/5 min in the BoNT-B group and unchanged at 2.75 mg saliva/5 min in the BoNT-A group; $p<0.05$). Significant increased constipation was also detected in only the BoNT-B group (3/9 patients BoNT-B vs. 0/11 patients BoNT-A; $p=0.037$).

Remarks: Method of randomisation is unknown. The baseline characteristics of the study population is poorly described. Unknown whether all study patients have been treated equally throughout the trial.

Meta-analysis

In this study, we compared botulinum toxin to every alternative in the treatment of drooling in children with cerebral palsy and in the treatment of cervical dystonia and blepharospasm. When more than one study was available on the same diagnosis, data were statistically pooled where appropriate. Due to high heterogeneity in treatments in studies on blepharospasm and drooling in CP children, it was decided to only pool data of studies on cervical dystonia. For this medical indication the following comparisons were studied: BoNT-A vs. placebo (two studies), BoNT-A vs. BoNT-B (three studies) and BoNT-A vs. BoNT-A (one study). Meta analysis is allowed with two studies (Valentine 2010). For this reason, we considered data pooling for the two studies on BoNT-A vs. placebo (Figures 7 and 8) and the three trials on BoNT-A vs. BoNT-B (Figures 9 and 10). These five studies reported equal outcome measures (TWSTRS total score and TWSTRS severity subscore), meaning that calculating the standardised mean differences (Hedges *g*) to cope with the variety in outcome was not required (Higgins 2011 and Chinn 2000).

BoNT-A vs. placebo meta-analysis: Two RCTs were included that both measured the outcome four weeks post-injection. The study population of both studies differed slightly: Comella 2011 et al. included patients with cervical dystonia with a baseline TWSTRS total score of ≥20, whereas Truong 2010 included patients with a baseline TWSTRS total score of ≥30. Also, injection dose is different in both studies. Comella 2011 injected 120U or 240U Botox while Truong 2010 studied the effect of 500U Dysport. For the Comella 2011 study that compared two interventions with a single control group, we merged the two intervention groups to overcome a unit-of-analysis error (Higgins 2011). Even though the inconsistency I^2 test in the meta-analysis showed high heterogeneity for both outcome

measures (81.8% for TWSTRS total score (Figure 3) and 54.8% TWSTRS severity subscore (Figure 4)), we considered the meta-analysis to be appropriate as both studies indicated a significant effect of BoNT-A.

BoNT-A vs. BoNT-B meta-analysis: Two of the three studies (Pappert 2008 and Comella 2005) in this meta-analysis had included patients with cervical dystonia with a baseline TWSTRS total score of ≥20. The third study did not report on the exclusion of cervical dystonia patients with a baseline TWSTRS total score of below 20 (Tintner 2005). Mean dose ranged from 150 to 250U for BoNT-A treatment and from 10000 to 12083U for BoNT-B treatment. The follow up time of the measurements were set on four weeks in two studies (Pappert 2008 and Comella 2005) and two weeks in the third study (Tintner 2005). The inconsistency I^2 test in the meta-analysis on the mean differences of both the TWSTRS total score and TWSTRS severity subscore showed 0,0% heterogeneity (Figure 5 and 6), which indicates good alignment of all study results.

Data analysis of the remaining studies is done descriptively. Assessing publication bias by using a contour-enhanced funnel plot was not considered helpful due to the low number of comparable studies. Therefore, risk of bias is analysed in a descriptive manner (Table 10).

Figure 3. Meta-analysis on 3 studies: BoNT-A vs. placebo in the treatment of cervical dystonia (change in TWSTRS total score (0-75 points)) (2-4 weeks follow up).

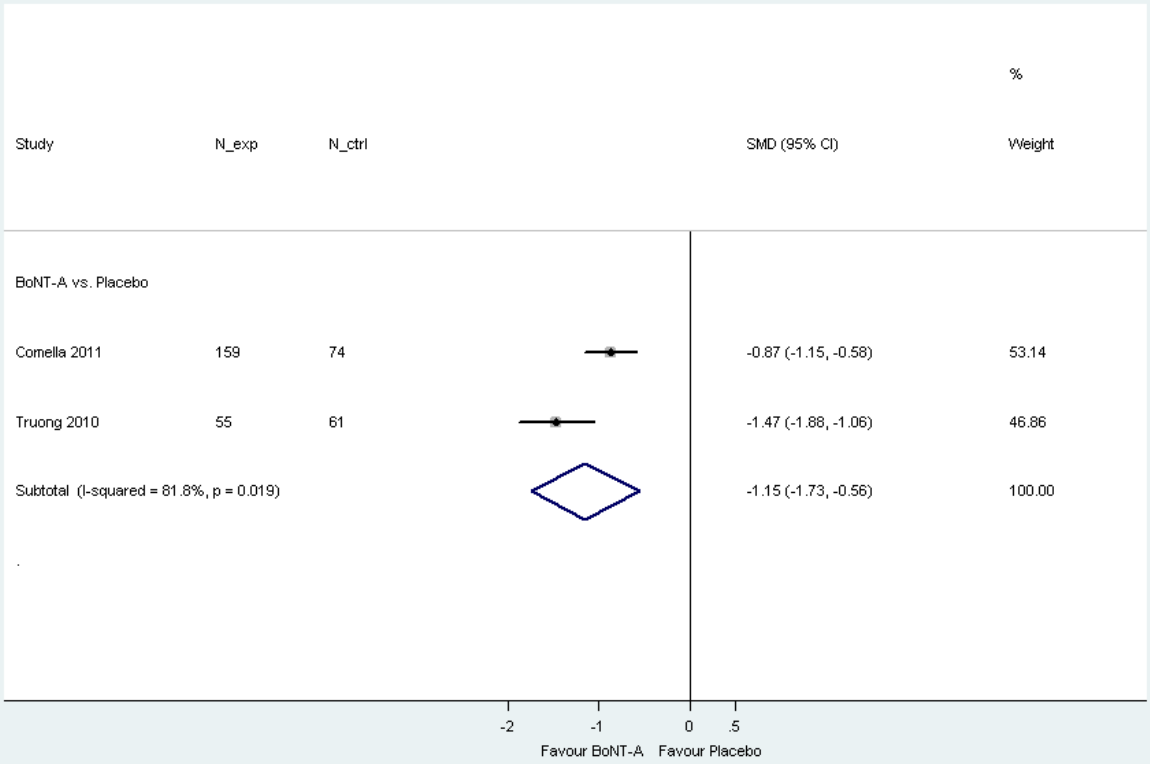


Figure 4. Meta-analysis on 3 studies: BoNT-A vs. placebo in the treatment of cervical dystonia (change in TWSTRS severity subscore (0-35 points)) (2-4 weeks follow up).

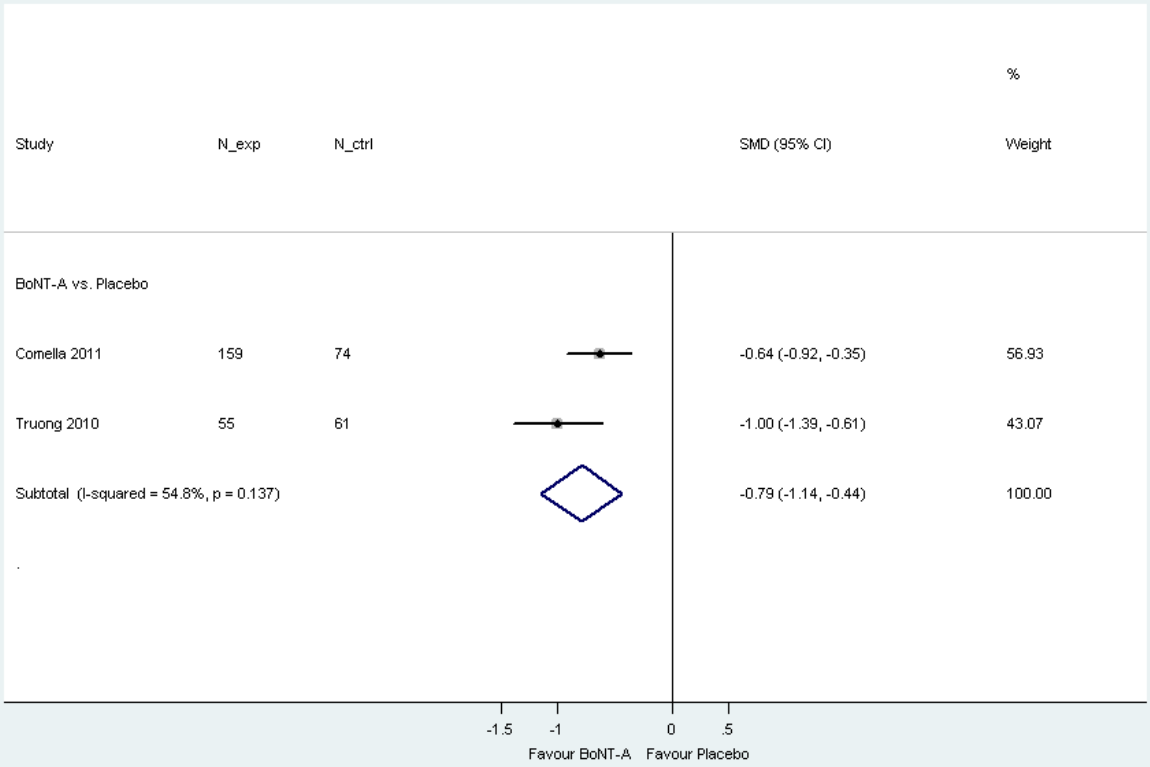


Figure 5. Meta-analysis on 2 studies: BoNT-A vs. BoNT-B in the treatment of cervical dystonia (change in TWSTRS total score (0-75 points)) (4 weeks follow up).

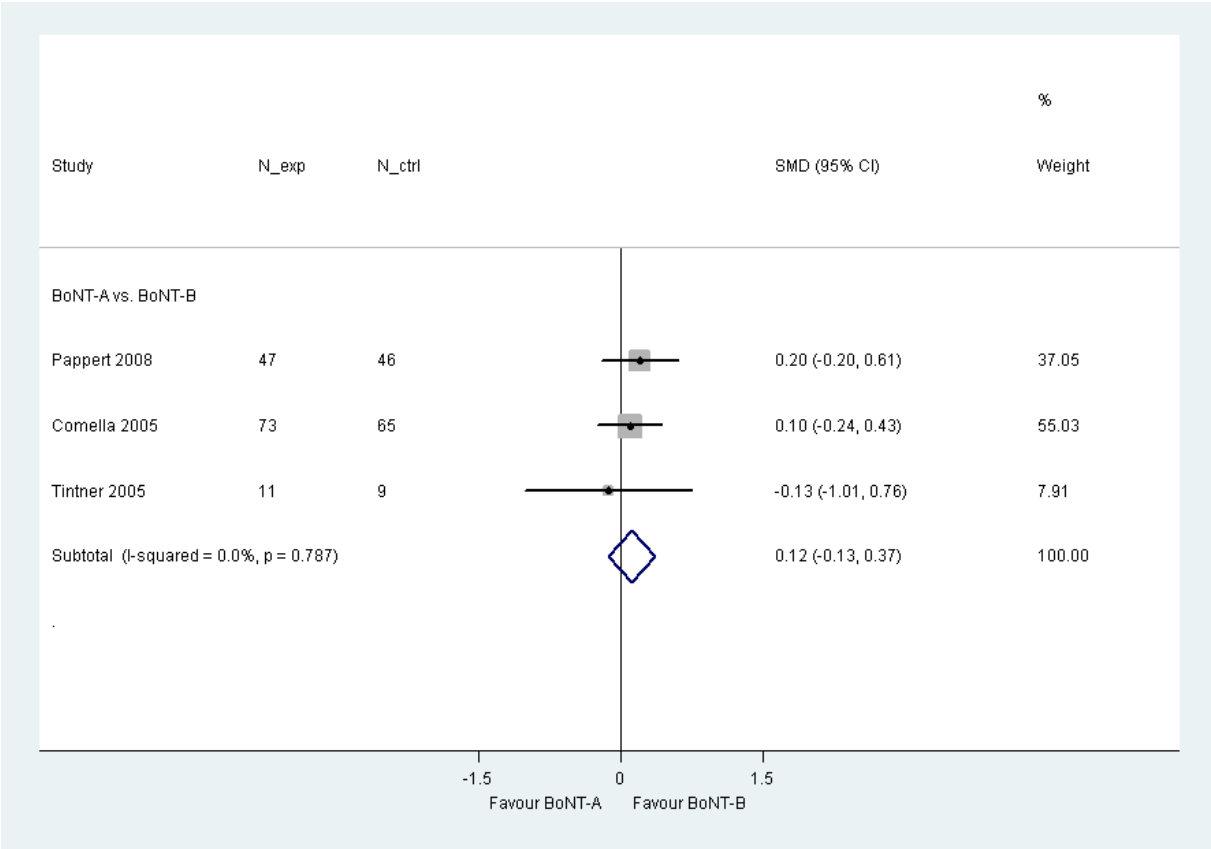
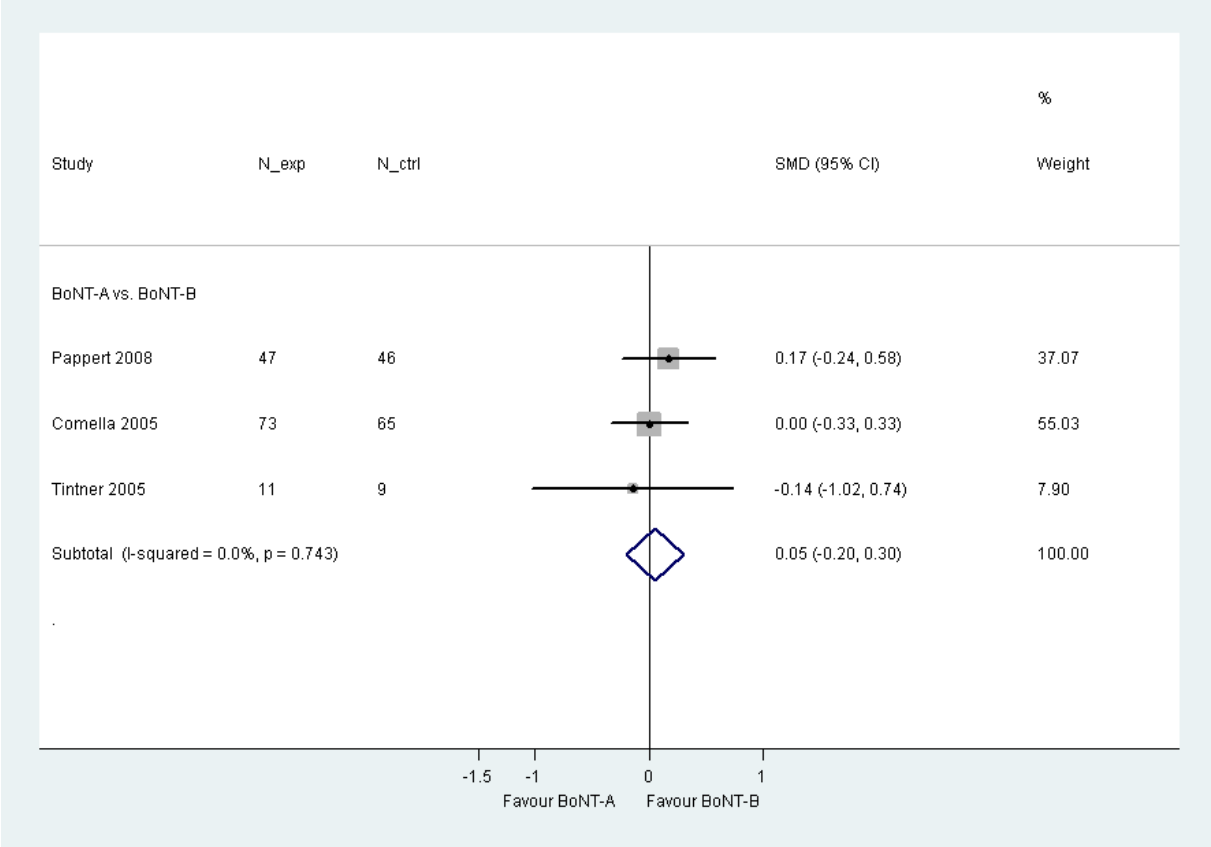


Figure 6. Meta-analysis on 2 studies: BoNT-A vs. BoNT-B in the treatment of cervical dystonia (change in TWSTRS severity subscore (0-35 points)) (4 weeks follow up).



DISCUSSION

The main purpose of this systematic review is to demonstrate the efficacy and safety of botulinum toxin as a treatment for patients with cervical dystonia and blepharospasm, and drooling and upper limb spasticity in children with cerebral palsy

We based our literature search on the evidence found in the Cochrane reviews. Therefore, to evaluate the contribution of botulinum toxin to the treatment of each predefined indication in the next section we combine the previously published evidence with the results found in the current systematic review and with that of relevant clinical trials or observational studies:

Cervical dystonia

Cochrane reviews: Costa and colleagues evaluated BoNT-A and BoNT-B interventions in four systematic reviews (1054 patients). The authors concluded that BoNT-A is a worthwhile treatment for cervical dystonia compared to placebo treatment (Costa 2005a). The reported meta-analysis showed significant improvements in favour of BoNT-A on both objective rating scales (Peto odds ratio [OR] 4.31; 95% confidence interval [CI] 2.68 to 6.94) and subjective rating scales (PetoOR 6.58; 95%CI 4.55 - 9.54). The authors mention a trade-off between effects and adverse events, meaning that both were dose-depended. However, only a few patients withdrew from study due to adverse events. The authors also report that in terms of clinical improvements or adverse events no significant differences between Dysport and Botox were found. It was also demonstrated that BoNT-A is preferred over trihexyphenidyl; an anticholinergic drug (TWSTRS-Disability score: weighted mean difference [95% CI]: 2.50 [0.68 - 4.32] (Costa 2005b). Moreover, BoNT-B injections showed a significant clinical improvement compared to placebo (objective rating scale: Peto OR 4.69; 95% CI 2.06 to 10.69) (Costa 2005c). In all of these studies the patients were injected with a total dose of 10000U BoNT-B. The authors of the Cochrane review that compared BoNT-A to BoNT-B interventions were not able to draw conclusions (Costa 2005d). They identified two ongoing studies with no reported preliminary results.

Current study: We included six RCTs that described the efficacy of either BoNT-A or BoNT-B in the treatment of cervical dystonia (1082 patients). A meta-analysis was performed with

two studies that compared BoNT-A vs. placebo. A second meta-analysis was performed with three studies which showed the clinical effects of BoNT-A vs. BoNT-B. Both meta-analyses were analyzed with the same outcome measures: the TWSTRS total score and the TWSTRS severity subscore. We found a moderate methodological quality of the included studies and therefore, suitable for a meta-analysis. The results showed significant improvements in favour of BoNT-A injections compared to placebo based on the TWSTRS total score (standardised mean difference (SMD): 1.15; 95% CI 1.73 to 0.56) and the TWSTRS severity subscore (SMD: 0.79; 95% CI 1.14 to 0.44). The reported adverse events show a dose-response correlation, although BoNT-A was generally tolerated well. Dysphagia was reported most frequently in the BoNT-A groups (9 – 16% of the patients).
As for the meta-analysis of RCTs comparing BoNT-A with BoNT-B, we conclude that the efficacy of BoNT-A at four weeks post-injection is not significantly different from BoNT-B. This conclusion is based on both the TWSTRS total score (SMD: 0.12; 95% CI -0.13 to 0.37) and the TWSTRS severity subscore (SMD: 0.05; 95% CI -0.20 to 0.30). We found that all studies are consistent with the incidence of adverse events: BoNT-B injections result in a significantly higher frequency of mild dry mouth (varying outcome measures; $p<0.05$) (Pappert 2008, Comella 2005 and Tintner 2005). Additionally, higher frequency of dysphagia four weeks after BoNT-B injection (19% vs. 48%; p=0.0005) (Comella 2005) and significantly increased constipation after two weeks in the BoNT-B group compared to BoNT-A treatment (0% vs. 33%; p=0.037) has been reported (Tintner 2005).

Evidence of relevant clinical trials or observational studies: No relevant studies found.

Overall conclusion: Both BoNT-A and BoNT-B are effective and efficient interventions to treat patients with cervical dystonia. A single injection cycle of either type of botulinum toxin significantly improves clinical outcome. As for safety, BoNT-A is preferred over BoNT-B. It is shown that BoNT-B injections lead to a higher risk of a dry mouth, dysphagia and constipation (Pappert 2008, Comella 2005 and Tintner 2005). We are not aware of any evidence demonstrating the beneficial use of ultrasound or electromyographic guidance. The total dose injected per participant varied significantly between studies, ranging from 50 to 280U for Botox and from 250 to 1000U for Dysport (Costa 2005a). Reported meta-analyses that considered arbitrarily defined sub-categories by dose of BoNT-A showed that adverse events were dose related. Injections of >200U Botox or >960U Dysport resulted in

significantly more adverse events while the clinical effect on the cervical dystonia remained comparable to that of doses of 50-200U Botox or 250-500U Dysport (Costa 2005a). No significant differences have been reported between brands of BoNT-A. We could not find evidence for the most suitable injection sites or the number of injection per muscle and therefore, no further conclusions can be drawn.

Blepharospasm

Cochrane reviews: No studies have been included for analysis due to poor quality of the clinical trials (Costa 2005e). The authors recognise that clinical trials and observational studies showed that BoNT-A is highly effective and safe in the treatment of blepharospasm. Therefore, it may be unethical to perform new placebo-controlled trials. No statements have been made on the efficacy of BoNT-B or the recommended dose or method of injection of BoNT-A.

Current study: We have included two high quality RCTs (229 patients) that compare BoNT-A to placebo treatment. Due to a wide range in injection dose, outcome measures and different brands of products with BoNT-A (Xeomin and Dysport), a description of both studies is given. Both studies showed a significant clinical improvement in blepharospasm in favour of BoNT-A 6 weeks post-injection (relative difference score of -24.0% in BoNT-A vs. +3.1% in placebo group; Jankovic 2011) and 4-12 weeks post-injection (relative difference score of -31% in 40U/eye BoNT-A group vs. -42% in the 80U/eye BoNT-A group vs. -50% in the 120U/eye BoNT-A group Truong 2008). Various adverse events are reported. Eyelid ptosis occurred most often in the BoNT-A group and appeared to be dose-depended (reported in 13%, 39% and 58% of patients in the 40U, 80U and 120U BoNT-A (Dysport) group, respectively). Blurred vision and lagophthalmos were reported more frequently at higher doses as well (Truong 2008). The remaining four non-inferiority RCTs that have been included in this systematic review compared the efficacy of different BoNT-A brands (Botox vs. Xeomin, Botox vs. Meditoxin and Botox vs. Prosigne). No significant differences between the brands of BoNT-A have been found (Yoon 2009, Roggen-kamper 2006, Wabbels 2010 and Quagliato 2010).

Evidence of relevant clinical trials or observational studies: No relevant studies found.

Overall conclusion: Based on the evidence of the two placebo-controlled RCTs and with the support of several open studies, we conclude that BoNT-A is an efficient and safe intervention for patients with blepharospasm. The safety of BoNT-A injections is dose-depended, although we found little evidence related to the preferred dose. Due to the low quality of the studies evaluating BoNT-B, no conclusions can be drawn on the efficacy and safety of BoNT-B. No differences in BoNT-A products have been reported. The beneficial use of ultrasound or electromyography guidance has not been demonstrated. Additionally, no further conclusions can be drawn on the most suitable injection sites.

Drooling in children with cerebral palsy

Cochrane reviews: Six RCTs or clinical controlled studies (173 patients) have been included in the Cochrane review by Walshe et al. (Walshe 2012). The diversity in the study population within and across studies was high. Due to a high heterogeneity, a poor methodological quality of the reviewed studies, and a high risk of selection bias, the authors were not able to draw any conclusions.

Current study: Two RCTs evaluating the treatment of drooling in children with CP (47 patients) were eligible for inclusion. One study compared BoNT-A to placebo (Wu 2011) whereas the other compared BoNT-B and placebo (Basciani 2011). For this reason, a meta-analysis could not be performed. In both studies the methodological quality was moderate. Even though both studies demonstrate a significant large effect of botulinum toxin compared to placebo treatment, we found a high risk of bias. In the study of Basciani et al. the patients seemed not to be blinded, wheras the independent examiner was. The study of Wu et al. showed a high risk of selection bias due to poor randomisation and allocation of study patients. Moreover, in both studies a considerably low number of patients was included and no sample size calculation was performed at the start of the study. This could indicate that the reported effects are overestimated.

Evidence of relevant clinical trials or observational studies: A controlled clinical trial by Jongerius et al. demonstrated the mean submandibular flow in CP children treated with BoNT-A or scopolamine (Jongerius 2004). Even though the reported response rates were

lower in the group treated with BoNT-A (69% compared to 95% in the scopolamine group), the effect was large (maximal decrease of 42% compared to 25% during scopolamine).

Overall conclusion: Although the study results indicate botulinum toxin as an intervention for drooling in children with CP, no strong evidence was found. Even though almost all RCTs report a significant effect of botulinum toxin injections in the salivary glands, none of these studies showed a high methodological quality and were free of bias. One study indicates that an ultrasound guidance is likely to improve the results of the botulinum toxin injections in the salivary glands (Jongerius 2003). As for dosage, Wu et al. suggests to set the maximal total dose of BoNT-B on 3000MU. It is assumed that in drooling a higher dose will result in comparable results, but it substantially increases the frequency of adverse events (Basciani 2011). To our knowledge, no further conclusions can be drawn either on the ideal dosage of BoNT-A, or the most suitable injection sites, or the choice between BoNT-A and BoNT-B, or any differences between products.

Upper limb spasticity in children with cerebral palsy

Cochrane reviews: Hoare and colleagues included ten trials (688 patients) and concluded that high level evidence supports the use of BoNT-A as an adjunct to managing the spasticity in the upper limb in children with CP (Hoare 2010) A combination of BoNT-A and occupational therapy has proven to be more effective than either one alone. The authors mention that BoNT-A was tolerated well in the treatment of upper limb spasticity in children with cerebral palsy. Injection doses (Botox) ranging from 50U/1.0ml saline to 200U/1ml saline with a dose from 0.5U to 16U/kg body weight up to a total of 220 to 410U is considered as safe in this population with minimal adverse events. Electrical stimulation or ultrasound guidance to localise the correct muscles is recommended (Chin 2005).

Current study: No studies have been included for analysis due to poor quality of the clinical trials.

Evidence of relevant clinical trials or observational studies: No relevant studies found.

Overall conclusion: Based on conclusions from the Cochrane review (Hoare 2010), BoNT-A is considered as a safe addition to therapeutic care for spasticity in the upper limb in children with CP. No qualitatively valid studies have addressed the contribution of BoNT-B treatment. Use of electrical stimulation or ultrasound guidance is recommended during BoNT-A injections.

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Table 7. Overview of results in Cochrane reviews on local dystonia and drooling and upper limb spasticity in CP children

Author	Study inclusion date	Subject	Comparison	Number of studies	Number of patients	Results
Costa	1 June 2003	Cervical dystonia	BoNT-A vs. placebo	13	N = 680	Peto OR 4.31 (95% confidence interval of 2.68 to 6.94)
	1 June 2003		BoNT-B vs. placebo	3	N = 308	Peto OR 4.69 (95% confidence interval of 2.06 to 10.69)
	1 June 2003		BoNT-A vs. BoNT-B	0	Not applicable	Not applicable
	1 June 2003		BoNT-A vs. anti-cholinergics	1	N = 66	BoNT-A vs. trihexyphenidyl: Three point improvement in TWSTRS-Disability scale (primary outcome): Peto OR 3.14 (95% confidence interval of 1.10 to 8.97)
Costa	1 June 2003	Blepharo-spasm	BoNT-A vs. placebo	0	Not applicable	Not applicable
Walshe	1 December 2010	Drooling in children with cerebral palsy	BoNT-A vs. placebo	4	N = 107	Insufficient evidence to evaluate the effectiveness and safety; great heterogeneity among studies and high risk of bias in all studies
Hoare	1 August 2008	Spasticity in the upper limb in children with cerebral palsy	BoNT-A or BoNT-A combined with occupational therapy vs. any alternative	10	N = 688	BoNT-A vs. placebo or no treatment: no effect (moderate evidence). Addition of BoNT-A to occupational therapy is more effective than only occupational therapy in reducing impairment and improving activity levels

Table 8. Results of the literature search (search date 29 November 2011)

	Search	Source	# hits
1)	Botox or Botulinum toxin* *All fields*	Pubmed (OVID)	12049
		Medline (OVID)	11675
		Embase (OVID)	19160
		CINAHL (Ebsco)	2196
		Cochrane (NHSEED)	27
2)	1. muscle spasticity or spasm or hypertonicity 2. "upper limb" 3. 1 and 2 4. drooling or sialorrhea or dysphagia 5. 3 or 4 6. cerebral palsy 7. 5 and 6 8. dystonia or cervical dystonia or blepharospasm or spasmodic dysphonia or hemifacial spasm 9. 7 or 8 *All fields*	Pubmed (OVID)	18592
		Medline (OVID)	12567
		Embase (OVID)	20593
		CINAHL (Ebsco)	1218
		Cochrane (NHSEED)	-
3)	1 (Intervention) AND 2 (Populations)	Pubmed (OVID)	2131
		Medline (OVID)	1872
		Embase (OVID)	3847
		CINAHL (Ebsco)	281
		Cochrane (NHSEED)	10
4)	Limits Activated: Randomized Controlled Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Controlled Clinical Trial	Pubmed (OVID)	127
		Medline (OVID)	115
		Embase (OVID)	141
		CINAHL (Ebsco)	2
		Cochrane (NHSEED)	N/A
		TOTAL (5 databases) (excluding duplicates)	**183**

Table 9. Summary of data extraction

Author	Medical indication	Products in study	Dose	Study population	Outcome measures	Results	Relative change	Adverse events
Basciani 2011	**Drooling in CP children**	**Placebo** (*unknown*) vs. **BoNT-B** (*Myobloc, Elan Pharmaceutical*)	Total of 1500, 3000 or 5000MU	27 CP children with refractory sialorrhea or drooling (mean age 7.8±1.5y): 6 in the 1500MU BoNT-B group and 7 in each other group (100% completed the study and were analysed according to ITT protocol)	Number and net weight of bibs used per day for 3 days and evaluation of drooling by Thomas-Stonell rating scale	The 1500MU BoNT-B treatment showed no significant change in both number (p=0.351) and netto weight of bibs (p=0.952) at any time points. Significant results in favour of 3000MU and 5000MU BoNT-B treatment according to number and netto weight of bibs at 4 and 12 weeks (-21.3 bibs and -7.2 grams in the 3000MU group and -22.0 and -9.4 grams in the 5000MU group at 4 weeks; p<0.01 for all). However, no significant difference between both doses according all outcome measures.	Number of bibs at 4 weeks: -4.6% bibs in the placebo group vs. -79.8% bibs in the 3000MU group vs. -80.6% bibs in the 5000MU group	Two children in the 5000MU BoNT-B treatment group developed severe dysphagia and weakness requiring hospitalization and nasogastric tube feeding for two weeks, while one of them also developed aspiration pneumonia. No or significantly less problems observed in the other groups.
Wu 2011	**Drooling in CP children**	**Placebo** (*saline*) vs. **BoNT-A** (*Botox, Allergan*)	30 U for subjects <15 kg, 40 U for subjects from 15 to 25 kg and 50 U for subject	20 CP children with a chronic drooling problem (mean age 8.3y): 10 children in both the placebo and BoNT-A group (100% completed the study and were analysed according to ITT protocol)	Mean saliva flow rate was measured by calculating the weight increase of gauze after 2-minute chewing	No changes in the placebo group. Significant reduction in drooling after both 1 and 3 months of BoNT-A treatment compared to placebo (change compared to baseline values: +0.22(±0.16) ml/min salivary flow in the placebo group vs. -0.14(±0.09) in the BoNT-A group after 1 month and +0.16(±0.15) ml/min salivary	Salivary flow rate change at 1 month: +24.4% in the placebo group vs. -14.0% in the BoNT-A-group	All children tolerated the treatment well and no adverse events were reported

Author	Medical indication	Products in study	Dose	Study population	Outcome measures	Results	Relative change	Adverse events
			>25 kg			flow in the placebo group vs. -0.25(±0.16) in the BoNT-A-group; p=0.037 and p=0.041, respectively).		
Jankovic 2011	**Blepharospasm**	**Placebo** (*unknown*) vs. **BoNT-A** (*Xeomin, Merz Pharma*)	Mean dose: 33.5U per eye	109 patients with bilateral blepharospasm and a Jankovic Rating Scale (JRS) severity subscore ≥ 2 (mean age 61.8y): 75 allocated to BoNT-A and 34 received placebo treatment (94% completed the study; 100% is analysed according to ITT protocol)	Jankovic Rating Scale (JRS) and Blepharospasm Disability Index (BSDI) scores	Significant improvements in favour of BoNT-A treatment based on all JRS scores and the BSDI at week 6 (p<0.01 for all). The JRS total score of BoNT-A treated patients decreased 1,59 on average (1,98 SD) compared to placebo at week 6.	JRS total score at 6 weeks: -24.0% in BoNT-A vs. +3.1% in placebo group	Drug-related adverse events were reported more frequently in the BoNT-A group (45.9% vs. 20.6%) of which eyelid ptosis and dry eyes and mouth were most common. Four severe adverse events were reported in the BoNT-A group (dry eye, dysphagia, epiglottis and muscular weakness) compared to none in the placebo group.
Truong 2008	**Blepharospasm**	**Placebo** (*saline*) vs. **40U**/eye vs. **80U**/eye vs. **120U**/eye **BoNT-A** (*Dysport, Ipsen*)	40, 80 or 120U per eye	120 patients with bilateral benign essential blepharospasm (age range: 35-91y): 4 treatment groups (1:1:1:1 ratio) (71% of all patients	Percentage of normal activity on the Blepharospasm Disability Scale (BDS) at 4 weeks, frequency of Involuntary Movement (FIM)	120 units of BoNT-A (Dysport) per eye provided the best sustained efficacy (50% less normal activity on the BDS until week 12 compared to placebo (p≤0.001)). Until 12 weeks the efficacy of 40U, 80U and 120U remained significantly improved based on	Percentage of normal activity on the BDS at 4 weeks compared to placebo: -31% in 40U/eye	Incidence of adverse events were proportional to the dose of BoNT-A. Eyelid ptosis 13%, 39% and 58% of patient in 40U, 80U and 120U BoNT-A group, respectively), blurred vision (23%, 19%

Author	Medical indication	Products in study	Dose	Study population	Outcome measures	Results	Relative change	Adverse events
				finished the study (36% of all placebo-treated patients remained in study); 100% is analysed according to ITT protocol)	scale and severity of oculo-facial spasms using the Severity Rating Scale (SRS)	the BDS (30-55% less normal activity), FIM (median difference ranging from -2.0 to -3.0) and SRS (median difference ranging from -1.0 to -2.0) (p≤0.001 for all).	BoNT-A group vs. -42% in the 80U/eye BoNT-A group vs. -50% in the 120U/eye BoNT-A group	and 42%) and lagophthalmos (10%, 6% and 23%) were reported most often.
Yoon 2009	**Blepharospasm**	**BoNT-A** (*Meditoxin, Medy-Tox*) vs. **BoNT-A** (*Botox, Allergan*)	Mean dose: 20.9U per eye	60 patients with bilateral essential blepharospasm: 31 allocated to Meditoxin (mean age: 61.2±9.1y) and 29 received Botox (mean age: 62.2±7.0y) (87% completed the study; 100% is analysed according to ITT protocol)	Percentage of patients that improved after 4 weeks on the severity of spasm score	90.3% of the patients on Meditoxin and 86.2% of patients with Botox treatment showed an improvement of at least one grade in the severity of spasm score 4 weeks post-injection (comparison between both BoNT-A: p=0.702)	Not applicable	No serious adverse events were reported. Ptosis occurred most frequently (8.3% of all patients). Both BoNT-A types were comparable based on the incidence of adverse events (p=0.282).
Roggen-kamper 2006	**Blepharospasm**	**BoNT-A** (*Botox, Allergan*) vs. **BoNT-A** (*Xeomin, Merz Pharma*)	Mean dose: 20.1U per eye	300 patients with blepharospasm: 148 allocated to Xeomin (mean age: 63±10.3y) and 152 received Botox (84% completed the	The Jankovic Rating Scale (JRS), the Blepharospasm Disability Index (BSDI) and patient evaluation	Significant effects of both BoNT-A treatment at both 3 and 16 weeks based on all outcome measures (p<0.0001 for all). The JRS score changed -2.83 at 3 weeks and -0.84 at 16 weeks from baseline in the Xeomin treatment group and	JRS total score at 3 weeks: -52.8% in Xeomin BoNT-A vs. -48.1% in Botox BoNT-A	Both BoNT-A treatments were comparable (56 vs. 62 adverse events (Xeomin vs. Botox)). No significant differences in specific events were observed.

Author	Medical indication	Products in study	Dose	Study population	Outcome measures	Results	Relative change	Adverse events
				study and is analysed (remaining 16% had major protocol deviations))		-2.65 at 3 weeks and -0.66 at 16 weeks from baseline in the Botox group. Mean treatment difference between both BoNT-A treatments was -0.23. The upper limit of the 95% CI (0.22) fell below the non-inferiority delta (0.8).		
Wabbels 2010	**Blepharospasm**	**BoNT-A** (*Botox, Allergan*) vs. **BoNT-A** (*Xeomin, Merz Pharma*)	Mean dose: 29.0U (Botox) and 27.1U per eye (Xeomin)	65 patients with benign essential blepharospasm: 32 allocated to Botox (mean age: 70.7±10.7y) and 33 received Xeomin (mean age: 67.1±12.1y) (97% completed the study and 98% is analysed according to ITT protocol (one patient withdrew consent)	Blepharospasm Disability Index (BSDI) scores, the Jankovic Rating Scale (JRS) and the patient global assessment score (PGA)	Results show a tendency toward a stronger improvement with Botox than Xeomin at both 4 and 8 weeks post-injection, but this was statistically insignificant. Change at 4 weeks compared to baseline: mean BSDI scores of Botox were -2.8 and of Xeomin -1.3 (p=0.093) and mean JRS scores of the Botox group were -2.2 and of Xeomin -1.5 (p=0.115). At 8 weeks the effect had faded slightly based on all outcome measures.	JRS total score at 4 weeks: -30.6% in Xeomin BoNT-A vs. -41.7% in Botox BoNT-A	No significant difference in adverse events between both groups (p=0.752). Periorbital hematoma was reported most frequently (25% of the patients), followed by headache (22%) and eyelid ptosis (11%).
Quagliato 2010	**Blepharospasm**	**BoNT-A** (*Botox, Allergan*) vs. **BoNT-A** (*Prosigne,*	30U per eye	21 primary blepharospasm patients: 11 allocated to Botox (mean age: 67.5±6.3y) and 10	Blepharospasm Graduation Scale (BSGS)	Both BoNT-A treatments showed significant improvements at 4 weeks in both subscores of the BSGS (seriousness subscore: -3.8 in Botox group vs. -4.3 in Prosigne	BSGS at 4 weeks: -55.1% in the Botox BoNT-A group vs. -60.6% in	Both BoNT-A treatments caused a similar number and similar types (90% mild and 10% moderate) of adverse events. Eye

Author	Medical indication	Products in study	Dose	Study population	Outcome measures	Results	Relative change	Adverse events
		Lanzhou)		received Prosigne (mean age: 65.9±0.9y) (100% completed the study and is analysed according to ITT protocol)		group; disability subscore: -11.3 in the Botox group vs. -12.4 in the Prosigne group (p≤0.0001 for all)). 95% of all patients reported an adverse event. No significant difference was observed between both BoNT-A groups.	the Prosigne BoNT-A group	burning and lacrimation occurred most frequently (57% and 62%, respectively)
Pappert 2008	**Cervical dystonia**	**BoNT-A** (*Botox, Allergan*) vs. **BoNT-B** (*Myobloc, Elan Pharmaceutical*)	150U (Botox) or 10000U (Myobloc)	111 patients with cervical dystonia and a baseline TWSTRS total score of ≥20: 55 allocated to BoNT-A (mean age 49.5±12.2y) and 56 received BoNT-B (48.3±12.9y) (84% is analysed according to PPP protocol)	TWSTRS	Compared to baseline both BoNT-A and BoNT-B treated patients improved significantly 4 weeks post-injection (BoNT-A: 8.9±8.3 and BoNT-B: 10.9±7.9; p<0.0001). Mean treatment difference between BoNT-A and BoNT-B was -2.2 points (90% CI [-4.9, 0.6]). The upper limit of the 90% CI (0.6) fell below the non-inferiority delta (4). Median time of duration of effect was 13.1 weeks for BoNT-A and 13.7 weeks for BoNT-B from injection.	TWSTRS total score at 4 weeks: -19.1% in BoNT-A vs. -24.3% in BoNT-B	Significantly more treatment related adverse events in the BoNT-B group compared to BoNT-A (29.1% vs. 51.8%, p=0.02). Likely, this is related to the more frequently reported mild dry mouth in the BoNT-B treatment group (5,5% vs. 32,1%, p=0.0005). No significant difference in moderate, severe or serious was observed.
Comella 2011	**Cervical dystonia**	**Placebo** (*unknown*) vs. **120U** vs. **240U BoNT-A** (*Xeomin*)	120U or 240U	233 patients with spasmodic torticollis and a baseline TWSTRS total score of ≥20 (mean age 52.8y): 74 were	TWSTRS	Compared to placebo, both doses of BoNT-A showed significant improvement. TWSTRS total scores after 4 weeks 120U BoNT-A: mean of -7,5 (p<0.001); and after 8 weeks: -7,1 (p<0.001).	TWSTRS total score at 4 weeks: -5.3% in the placebo group vs. -23.2% in the	No marked difference was seen in the adverse effects of either BoNT-A treatment. Dysphagia has been reported most frequently as a related

Author	Medical indication	Products in study	Dose	Study population	Outcome measures	Results	Relative change	Adverse events
				allocated to placebo, 78 received 120U BoNT-A and 81 received 240U BoNT-A (94% completed the study; 100% is analysed according to ITT protocol)		After 4 weeks of 240U BoNT-A treatment, the mean TWSTRS total scores changed -9,0 (p<0.001) after 4 weeks and -8,6 (p<0.001) after 8 weeks. Both BoNT-A treatments scored significantly sustained improvement on every subscale of the TWSTRS score (severity, disability and pain).	120U BoNT-A group vs. -25.9% in the 240U BoNT-A group	adverse event (10,3% in the 120U group, 16,0% in the 240U group and 2,7% in the placebo group).
Comella 2005	**Cervical dystonia**	**BoNT-A** (*Botox, Allergan*) vs. **BoNT-B** (*Myobloc, Elan Pharmaceutical*)	Mean dose: 207U BoNT-A or 8400U BoNT-B	139 patients with cervical dystonia and a baseline TWSTRS total score of ≥20 (mean age 56.7±11.6y) : 74 were allocated to BoNT-A and 65 received BoNT-B (n=65) (99% completed the study; 99% is analysed according to ITT protocol)	TWSTRS	Both the BoNT-A and BoNT-B group showed significant improvement at 4 weeks compared to baseline (p<0.0001). However, BoNT-A and BoNT-B seem to be equally effective (-9,3 vs. -10,2 (p=0.75) on the TWSTRS total score) at 4 weeks.	TWSTRS total score at 4 weeks: -22.7% in BoNT-A vs. -23.8% in BoNT-B	Dysphagia was significantly more reported after 4 weeks in the BoNT-B treatment group (19% in BoNT-A vs. 48% in BoNT-B patients; p=0.0005). The same goes for the number of cases with a dry mouth (41% in BoNT-A vs. 80% in BoNT-B patients; p<0.0001)
Truong 2010	**Cervical dystonia**	**Placebo** (*unknown*) vs. **BoNT-A** (*Dysport,*	500U	116 patients with cervical dystonia and a baseline TWSTRS total score of ≥30: 61	TWSTRS	Treatment with BoNT-A resulted in significant improvements in the status of the patients at 4 weeks compared to placebo (mean of -	TWSTRS total score at 4 weeks: -35.6% in the BoNT-A	BoNT-A was tolerated well. Dysphagia is the only adverse event that has been reported

Author	Medical indication	Products in study	Dose	Study population	Outcome measures	Results	Relative change	Adverse events
		Ipsen)		were allocated to placebo (mean age 53.9±12.5y) and 55 received BoNT-A (51.9±13.4y) (72% completed the study; 100% is analysed according to ITT protocol)		15,6 vs. -6,7 on the TWSTRS total score; p<0.001). These results sustained for at least 12 weeks (mean of -9,1 vs. -4,9; p=0.019).	group vs. -14.6% in the placebo group	significantly more frequent in patients treated with BoNT-A (9%) in comparison with placebo treated patients (0%).
Benecke 2005	**Cervical dystonia**	**BoNT-A** (*Botox, Allergan*) vs. **BoNT-A** (*Xeomin, Merz Pharma*)	Dose ranges from 70 to 300U	463 patients with cervical dystonia and a baseline TWSTRS total score of ≥10 (mean age: unknown): 231 were allocated to Xeomin and 232 received Botox (100% is analysed ITT, 90.7% TPP)	Primary: TWSTRS severity subscore; Secondary: remaining TWSTRS scores, VAS pain and Global Response Scale score	Both treatment groups improved on the TWSTRS severity score from 18 points at baseline to 11 points by 4 weeks and to 16 points at 16 weeks (p<0.0001). Treatments were non-inferior to each other (-6.6 points for the Xeomin group and -6.4 points for the BOTOX group at 4 weeks)(upper limit of the 95% CI was lower than the predefined difference (1.3 points)).	TWSTRS severity score at 4 weeks: -39% in both the BoNT-A groups (Xeomin and Botox)	Based on the reported adverse events both BoNT-A treatments are comparable as well. Dysphagia was the most frequently reported adverse event (9.5%).
Tintner 2005	**Cervical dystonia**	**BoNT-A** (*Botox, Allergan*) vs. **BoNT-B** (*Myobloc, Elan*	Mean dose: 227U BoNT-A or 12083U	20 patients with cervical dystonia: 11 were allocated to BoNT-A (mean age: 55±12y) and 9 received BoNT-B	TWSTRS score and a saliva production scale (chewing gauze pads (Schirmer's test))	TWSTRS scores were improved two weeks post-injection in both treatment groups (severity from 17 to 14-15, pain from 10 to 4-6 and disability from 16 to 10-12), but did not differ between both	TWSTRS total score at 2 weeks: -30.2% in BoNT-A vs. -27.9% in BoNT-B	Saliva production was significantly reduced in only the BoNT-B group (from 3.5 to 2.5 mg saliva/5 min in the BoNT-B group vs. unchanged

Author	Medical indication	Products in study	Dose	Study population	Outcome measures	Results	Relative change	Adverse events
		Pharmaceutical)	BoNT-B	(mean age: 64±10y) (100% completed the study and is analysed according to ITT protocol)		groups.		level at 2.75 mg saliva/5 min in the BoNT-A group; p<0.05). Significant increased constipation detected in only the BoNT-B group (3/9 patients BoNT-B vs. 0/11 patients BoNT-A; p=0.037).

Table 10. Risk of bias

To guarantee a proper consideration of each type of bias, we assessed the risk of bias in each eligible study by using the classification scheme for bias from the Cochrane Collaboration handbook (http://www.cochrane.org/handbook/table-84a-common-classification-scheme-bias). We classified all biases into selection bias, performance bias, detection bias, attrition bias and reporting bias:

- Selection bias: systematic differences between baseline characteristics of the compared groups;
- Performance bias: systematic differences between groups in the intervention that is provided or in exposure to any other factor other than the intervention;
- Detection bias: systematic differences between groups in determining the outcome values;
- Attrition bias: systematic differences between groups in withdrawal or lost-to-follow-up of patients;
- Reporting bias: systematic differences in reported findings.

Author	Disease of study	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias
Basciani 2011	**Drooling in CP children**	Randomisation performed by unclear computer software	No blinding of both patients and investigator delivering treatment			Control treatment is not specified
Wu 2011	**Drooling in CP children**	Method of randomisation is not described; Insufficient information to permit judgement on the allocation concealment				
Jankovic 2011	**Blepharospasm**				Method of imputation of dropped out patients in the full analysis set data is unknown	10 patient scores are lacking (8 from BoNT-A and 2 from the placebo group) in the full analysis set data from the JRS diary analysis at 6 weeks;

Author	Disease of study	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias
						Control treatment is not specified; Results from 3 weeks post-injection are not reported as well as the change in JRS severity subscore at week 6
Truong 2008	**Blepharospasm**				Large number of withdrawals is poorly explained, but analysis according to the ITT protocol	Baseline values of all groups and all values of the placebo group are not reported; Results are reported as difference scores only
Yoon 2009	**Blepharospasm**					
Roggenkämper 2006	**Blepharospasm**	Method of randomisation is unclear		Authors do not mention the time between pre-study BoNT-A injections and the study injections, which is relevant for potential carry-over effects		Standard deviations of outcome measures are not reported; patient characteristics are inadequately described
Wabbels 2010	**Blepharospasm**		Unknown whether all study patients have been treated equally throughout the study (mean dose of injection was different (but not significantly)			

Author	Disease of study	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias
Quagliato 2010	**Blepharospasm**	Method of randomisation is not described; Patient selection is not adequate specified	Unknown whether all study patients have been treated equally throughout the trial; High number of adverse events implies the BoNT-A injection concentration was too high	Low number of study patients; The content of the Blepharospasm Graduation Scale is not explained, a reference to its source is missing and was not found on the internet.	The baseline characteristics of the study population is poorly described; Drop out has not been reported	
Pappert 2008	**Cervical dystonia**					Authors state results in ITT population are similar. However, data is not reported.
Comella 2011	**Cervical dystonia**		Unknown whether study groups have been treated equally due to the individual judgement of the patient's needs by the injecting physician			
Comella 2005	**Cervical dystonia**		Unknown whether study groups have been treated equally due to the individual judgement of the patient's needs by the injecting physician	Significantly shorter period of time of pre-study BoNT-A treatment and start of the clinical trial in BoNT-A group compared to the BoNT-B group (p=0.02)	16 patients were excluded from data analysis due to no change in the primary outcome at week 4	
Truong 2010	**Cervical dystonia**		Blinding of assessor unsure		Two patients are withdrawn without	Content of placebo is unclear

Author	Disease of study	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias
					sufficient explanation	
Benecke 2005	**Cervical dystonia**	Method of randomisation is unclear	Unknown whether all study patients have been treated equally			Baseline values are generally missing and TWSTRS total score values are not reported
Tintner 2005	**Cervical dystonia**	Method of randomisation is unclear		Unknown whether all study patients have been treated equally throughout the trial	The baseline characteristics of the study population is poorly described.	

Table 11. Items included in the quality assessment

Dutch form for Quality assessment of a randomised controlled trial (RCT) by the Cochrane Collaboration (Offringa 2008):

Item 1: Was the allocation of patients to the intervention randomised?

Item 2: Was the physician who included patients to the study blinded to the treatment allocation?

Item 3: Were patients blinded to the treatment allocation?

Item 4: Were the treating physicians blinded to the treatment allocation?

Item 5: Were the assessors blinded to the treatment allocation?

Item 6: Were all groups in study comparable to each other at the start of the trial?

Item 7: Is a complete data set present of an adequate number of study patients?

Item 8: Were all included study patients analysed according to their treatment allocation?

Item 9: Were all groups treated equally, apart from the intervention?

Jadad Checklist

	Aspect	Description		Yes	No	Unsure
	Randomisation	Was the study described as randomised?				
		Was the method of randomisation described and appropriate?				
	Blinding	Was the study described as double blind?				
		Was the method of blinding described and appropriate?				
	Lost patients	Was there a description of withdrawals and dropouts?				

Clinical Relevance

	Aspect	Description		Yes	No	Unsure
	Randomisation	Are the patients described in detail so that you can decide whether they are comparable to those that you see in your practice?				
		Are the interventions and treatment settings described well enough so that you can provide the same for your patients?				
	Blinding	Were all clinically relevant outcomes measured and reported?				
		Is the size of the effect clinically important?				
	Lost patients	Are the likely treatment benefits worth the potential harms?				

List of abbreviations

Abbreviation		Range of measurement outcome
BDS	Blepharospasm Disability Scale	
BoNT-A	Botulinum toxin type A	
BoNT-B	Botulinum toxin type B	
BSDI	Blepharospasm Disability Index	0-4 (0 = no experienced disabilities) 0.7 points is considered clinically meaningful in non-inferiority trials (Jankovic 2009)
BSGS	Blepharospasm Graduation Scale	
BvdB	Bart van den Bemt [author]	
CI	Confidence interval	
CP	Cerebral palsy	
FIM	Frequency of Involuntary Movement scale	
I squared	Measure in meta-analysis to indicate the heterogeneity between studies	With 0% meaning low heterogeneity and 100% meaning highly heterogenic
ITT protocol	Intention to treat protocol	
JRS	Jankovic Rating Scale	JRS (sum score): 0-8 (0 = best) JRS (severity subscore): 0-4 JRS (frequentcy subscore): 0-4 2 points on the total JRS score is considered clinically relavant (Jankovic 2009)
MM	Margriet Moret [author]	
MvH	Miranda van Hooff [author]	
OR	Odds ratio	
PGA	Patient global assessment score	
PPP protocol	Per-protocol population protocol	
PvE	Peter van Essen [author]	
RCT	Randomised controlled trial	
SMD	Standardized Mean Difference	
SRS	Severity Rating Scale	
TWSTRS	Toronto Western Spasmodic Torticollis Rating Scale	TWSTRS (total score): 0-75 (0 = no experienced disabilities) TWSTRS (severity subscore): 0-35 (0 = no experienced disabilities)
U	Units	

CHAPTER TWO: COST-EFFECTIVENESS

Cost-effectiveness of treatment with botulinum toxin in patients with local dystonia or cerebral palsy. A systematic review

INTRODUCTION

Besides a review on the clinical effectiveness and safety of botulinum toxin, we systematically searched for evidence on the cost-effectiveness of botulinum toxin in the same indications. Evidence on the cost effectiveness of botulinum toxin provides information about its relative costs and effects as compared to alternative interventions for each indication. Ideally, botulinum toxin is compared to current clinical practice or the best alternative intervention available.

Research questions

What is the cost-effectiveness (O) of botulinum toxin (I) in patients with cerebral palsy suffering from upper limb spasticity or drooling, or patients with cervical dystonia or blepharospasm (P)?

METHODS

We searched for relevant literature in Medline and Embase databases via OVID, and the NHS Economic Evaluations Database via the Cochrane Library. We searched for relevant articles published until 29th November 2011. We based our search on the search strategy developed for the systematic review on the effectiveness of botulinum (chapter one). We used the same search terms for the intervention (botulinum toxin) and the populations (local dystonia and cerebral palsy). Finally, we applied a filter for identifying economic evaluations. A detailed description of our search is presented in table 12. Two reviewers independently selected potentially relevant studies after reading titles and abstracts. Next, one reviewer selected relevant studies based on full text reports. Choices made were discussed with the second reviewer. Inclusion criteria were:

- a full economic evaluation:
  1) measuring both costs and effects (unless a cost-minimization analyses was performed, assuming equal effectiveness), and
  2) a comparison between botulinum toxin with an alternative intervention, placebo, or no treatment.
- intervention: treatment with botulinum toxin
- population:
  - patients with local dystonia (cervical dystonia or blepharospasm), or
  - patients with cerebral palsy with upper extremity spasticity or drooling

RESULTS

Search and selection

Our search in the three databases yielded 60 hits. Eleven duplicate records were removed. Two researchers independently screened the titles and abstracts of the remaining 49 records for relevance. The full text reports of ten potentially relevant articles were obtained for further assessment. Seven studies were excluded. Two studies reported on the costs of botulinum treatment in several populations, but no comparison was made with an alternative treatment, no treatment or a placebo (Schnider 1999, Burbaud 2011). From two studies, only conference abstracts were available. Three studies were no economic evaluations. Finally, three economic evaluations were included in this review.

Included studies

Three economic evaluations reported the results of botulinum toxin in patients with local dystonias. The study characteristics and results are summarized in table 13 and 14 respectively.

Gudex (1997) reported on an exploratory study to assess the feasibility of a cost-utility analysis. Costs and utilities were measured in a group of dystonia patients who visited one of two participating clinics in the UK. Most of these patients were treated with botulinum toxin. Additionally, a control group of not-currently botulinum treated dystonia patients was sought through the Dystonia Society Register. Main objective was to develop a methodology for measuring patient benefit using quality of life. Quality of life was measured using the EuroQol 5D. Participants had to complete at least five consecutive EuroQol questionnaires over a minimum of six months. Costs were calculated with data from patient questionnaires and medical records. Included costs were: botulinum toxin, clinic related costs, and travel costs. The mean total costs per year were €1,161 for botulinum treated patients and €173 for non-botulinum treated patients. For a 1-year period, the difference in quality of life was 0.015. This resulted in an incremental ratio of €65,824 per QALY for patients with local dystonia. Sensitivity analyses were performed, such as another tariff for weighting quality of life, age, employment status, including only patients already established on botulinum. No other information on uncertainty was presented.

Drawbacks of this study: The non-botulinum group included both patients who had been treated with botulinum in the past and patients who had never been treated with botulinum toxin. No information was given on which treatments were given in the non-botulinum group. Finally, it is unclear how cost data were collected (for example prospectively).

Chadda et al (2000) reported on a cost-utility analysis based on Markov modelling. Analyses were performed separately for patients with spasmodic torticollis and patients with blepharospasm. In both patient groups, treatment with botulinum toxin was compared to a placebo. Sixteen cycles of 12 weeks were modelled corresponding to a time horizon of 3.5 years. Quality of life data

were based on the EuroQol 5D questionnaire. Costs included only direct health care costs (botulinum treatment, hospital costs, outpatient visits). In patients with spasmodic torticollis, the differences in costs were €3,046 and the differences in quality of life 0.40. The corresponding incremental cost-effectiveness ratio is €7,615 per QALY. In patients with blepharospasm, the differences in costs were €976 and the differences in quality of life 0.18. The incremental cost-effectiveness ratio is €4,422 per QALY. Main costs difference between treatment groups were the costs of botulinum injections themselves. Furthermore, botulinum was associated with lower costs for outpatient visits. One-way sensitivity analyses had been performed (baseline utility, doses, incidence of adverse events, frequency of administration). The authors concluded that results were highly sensitive to baseline utility and the differences between baseline and best utility. The ICER remained below €23,800 (UK: GBP 20,000) under all plausible dose ranges.

A limitation of this study is that botulinum toxin is compared to treatment with a placebo, whereas usual care (do nothing) should have been preferred to establish cost-effectiveness. A potential placebo effect cannot be excluded. Furthermore, there was limited information on input data concerning transition probabilities. The authors' conclusion that main costs differences were related to the costs of the injections follows from the model's structure, in which the costs for hospitalization and adverse events were estimated to be €0 in the baseline calculations.

Brefel-Courbon et al. (2011) analyzed the costs and quality of life in a cohort of patients with spasmodic torticollis. The costs during treatment with botulinum were compared with the situation of these patients before they started treatment with botulinum toxin based on retrospective analyses. Patients' quality of life (Nottingham Health Profile, score 0-100, higher score indicates a poorer level of health) was measured before patients started with botulinum treatment and after 8 months of treatment. Quality of life measures indicated a significant improvement in pain scores (baseline 26.8, after 8 months of treatment 14.1). No statistically significant differences were found on the other domains of quality of life. No QALYs could be calculated. Difference in total costs per month was on €99. This corresponds with an annual cost difference of €1,180. The authors concluded that the increase in costs could be explained by the costs of botulinum itself. The other costs were comparable in the two periods. Only little savings were found in costs for hospital inpatients care (€25).

Remarks: the study was partly retrospective. Costs were measured differently for the period during botulinum treatment and the period preceding botulinum treatment. Quality of life was measured before and a few months after starting botulinum treatment. Thus, the results may be sensitive to bias. No information was given on the treatment the patients had received during the period preceding botulinum treatment. Finally, no information on the uncertainty in the results was presented.

DISCUSSION

Three studies were identified on botulinum treatment in patients with local dystonia. No economic evaluations were found on the use of botulinum toxin in patients with cerebral palsy and upper extremity spasticity or drooling.

The level of evidence of the three included economic evaluations was weak to moderate. Two studies were based on partly retrospectively collected data in a cohort of patients treated with botulinum toxin. The third study was a modelling study in which botulinum toxin was compared to a placebo. In general, the use of placebo as comparator is limited in economic evaluations. Finally, hardly any information about uncertainty was presented.

In two studies, botulinum treatment was compared to the *usual care* patients received before they started botulinum treatment (Brefeld Courbon 2011, Gudex 1997). Differences in annual costs ranged between € 990-1,200. However, no information was given on what usual care was provided.

It seems that the difference in total costs of care could be explained mainly by the differences in the application of botulinum. In these studies, treatment with botulinum toxin did not result in major savings elsewhere in the provision of health care.

The differences in quality of life were small (Gudex 1997). Brefeld –Courbon (2000) showed that patients experienced an improvement in pain, but not in other domains of quality of life.

CONCLUSION

Only a few, on weak to moderate evidence based, reports about the cost effectiveness of botulinum toxin were found. The results of these studies suggest that botulinum toxin has a small effect on patients quality of life and does not seem to result in savings elsewhere in the health care system, for example hospitalization. However, the choice of study comparators can be questioned (placebo) or were unclear (undefined standard care).

References included studies (n=3)

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Table 12. Results of literature searchers (search date 29 November 2011)

	Search	**Source**	**# hits**
1)	Botox or Botulinum toxin* *All fields*	Medline (OVID)	12239
		Embase (OVID)	18821
		Cochrane (NHSEED only)	23
2)	1. muscle spasticity or spasm or hypertonicity 2. "upper limb" 3. 1 and 2 4. drooling or sialorrhea or dysphagia 5. 3 or 4 6. cerebral palsy 7. 5 and 6 8. dystonia or cervical dystonia or blepharospasm or spasmodic dysphonia or hemifacial spasm 9. 7 or 8 *All fields*	Medline	13110
		Embase	20139
		Cochrane (NHSEED only)	6
3)	1. exp Cost-Benefit Analysis/ 2. (cost-effectiveness or cost-benefit or cost - minimization or cost-utility or health technology assessment or pharmacoeconomic* or economic evaluation).mp 3. (cost and cost analysis).mp 4. 1 or 2 or 3	Medline (OVID)	134747
		Embase (OVID)	210459
		Cochrane (NHSEED only)	-
4)	1 (Intervention) AND 2 (Populations) AND 3 (EEs)	Medline (OVID)	11
		Embase (OVID)	46
		Cochrane (NHSEED)	3
		TOTAL (3 databases)	**60**

Figure 13. Flow Diagram Economic Evaluations Botulinum Toxin

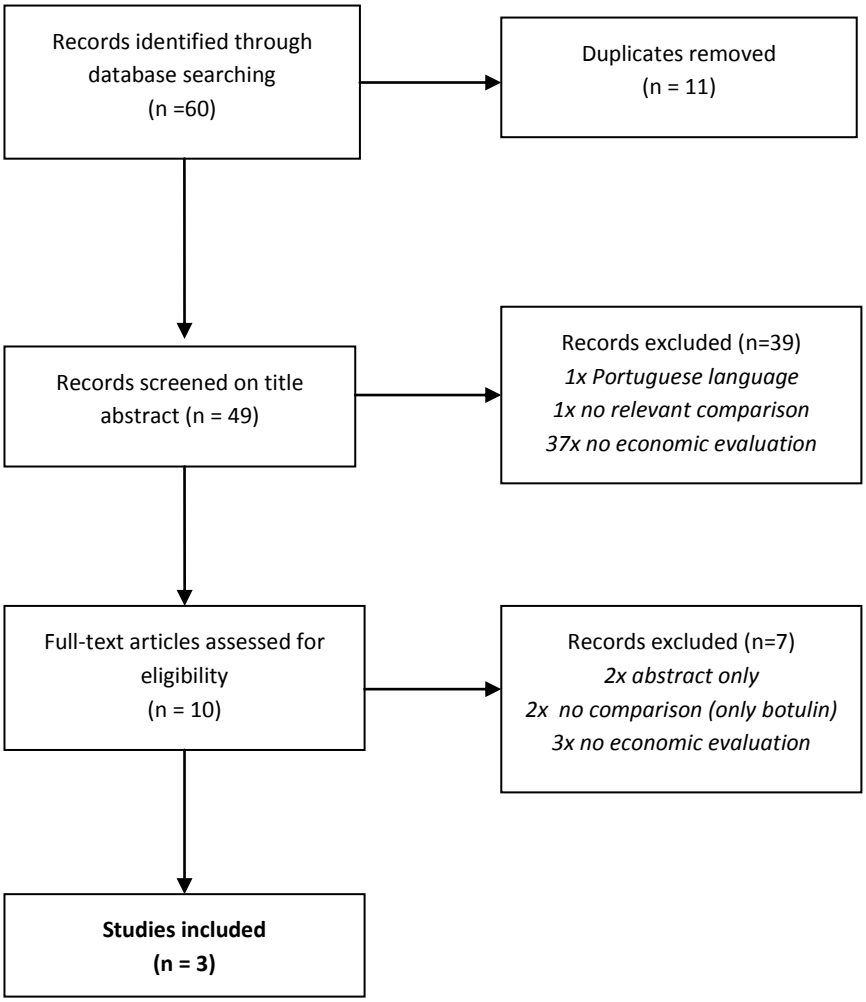


Table 14. Evidence table; economic evaluations botulinum toxin: study characteristics

Reference / country	Design/ Type EE	Population	Interventions	Measurement	Cost categories	Effectiveness	Sensitivity analysis	Discounting	Remarks
Gudex 1997/ England	• *CUA* • *Feasibility study*	• *196 dystonia patients* • *registered at 2 clinics (almost all on BTX) + patients who responded to invitation (control)* • 37/196 patients non-focal dystonia • No further information on type of dystonia	Botulinum users (n=102) versus not-botulinum users (n=28)	1st questionnaire: interview; Follow-up measurements: by post Questionnaire and medical records Price BTX: £ 175 / 500 U	*Questionnaires and medical records* • *Direct costs: Botulinum, clinic related costs, ambulance use, other drugs)patients costs), travelling costs* • *Other drugs related to dystonia / comorbid conditions not included*	*EuroQol*	+/- Different methods for calculating QoI (VAS vs. ITT) Age / employment status Selection populations		Differences between users and non-users? Non-botulinum users: 39% treated with BTX in past ? costs BTX: not measured, but calculation based on assumptions?
Brefel-Courbon 2000/ France	• Cost-effectiveness analysis; • Cohort; comparison with retrospective data; • 2x 8 months	• all patients with Spasmodic torticollis (cervical dystonia) • visited university hospital for 1st time between 1996-1997 • no botulinum	botulinum toxin (BT), Dysport Patients instructed to return when effects of previous injection began to wear off	Pre: patient's information and general practitioners' information During BT: patient questionnaires and medical records	• Health care costs • Inpatient, outpatient costs, physiotherapy, drugs • drug acquisition FF 1,736 for 500U • Reimbursement prices	• Postural head deviation • Patient's global assessment of improvement • QoL, Nottingham Health Profile (scores 0 to 100. A higher	-	-	Costs measures pre-botulinum and during botulinum treatment differently measured QoI at t=8 months: can effects of

Reference / country	Design/ Type EE	Population	Interventions	Measurement	Cost categories	Effectiveness	Sensitivity analysis	Discounting	Remarks
		previously used • n=21				score indicates a poorer level of health;			injections be measured? (cyclic course)
Chadda 2009 / UK	• Cost-utility analysis • Markov modelling • 16 cycles of 12 weeks = 3.5 yrs	1. Blepharospasm (BP) 2. Spasmodic torticollis (Cervical dystonia, CD) Based on published data - cohort 616 patients with CD - trial of 304 patients with BP	botulinum toxin (Xeomin) vs placebo	Input utilities / costs presented No data on transition probabilities	Direct health care costs= treatment, outpatient visits, administration costs, hospital costs	QALYs (based in EuroQol)	+	+ Costs and effects 3.5 %/yr	Study on Xeomin, but data about Dysport and Botox used in analyses resource utilization mainly via expert opinion Only costs for outpatient visits?

Table 15. Evidence table; economic evaluations botulinum toxin: results

Reference	Results costs	Results effects		ICER	Uncertainty	Remarks / conclusions authors
Gudex 1997	Total cost/year (£, 1994) BT: £975 = € 1161 Non-BT: £ 145 =€ 173 ΔC = £ 830 = € 988	QALYs (Time 1 yr) ΔQALY =0.015		All patients: €65,866 / QALY Focal dystonia only: €65,824 / QALY	-	
Brefel-Courbon 2000	Mean number injections 2.9; mean dose 450 U (range 160-1120) Costs per month (±SEM): Mean costs BT alone FF 771 ±131 Mean total costs pre: FF 479 ±143 Mean total costs BT: FF 1,126±147 *ΔC FF 647 = €99 (SEM* 22)* Mean annual costs (FF, 1997) Pre: FF 5,744 /yr BT: FF 13.485/yr ΔC = FF 7,741/yr ± 2,472 *= € 1180/yr* ±377	QoL, mean scores *scores 0 to 100;* *higher score is* *poorer health* T= 0 *Sleep 30.3* *Physical 12.7* *Social 21.8* *Pain 26.8* *Emotional 28.4* *Energy 29.5* ** pain: p=0.02*	T=8 months *Sleep 34.3* *Physical 11.3* *Social 16.2* *Pain 14.1** *Emotional 21.6* *Energy 27.2*	-	-	Differences in costs explained by costs BT itself Medical visits after 1 month (=protocol) included in cost analysis
Chadda 2009	Mean total costs (£) CD: Xeomin: £4347 Placebo: £1788 *ΔC £2.559 = €3046* BP: Xeomin: £2457 Placebo: £1788 *ΔC* £669 = *€796*	QALYs (3.5 yrs) CD: Xeomin: 2.54 Placebo: 2.14 *ΔQALY = 0.40* BP: Xeomin: 2.29 Placebo: 2.11 *ΔQALY = 0.18*		CD:€6715/QALY BP:€4422/QALY	Univariate sensitivity analyses Results highly sensitive to baseline utility, *Δ* baseline – best utility ICERs < €23.800 under all plausible dose ranges	Cost implications of Xeomin were mainly costs preparation Xeomin injections themselves

*) Exchange rates: 1 € = 13,7603 Austrian Schilling / 1 € = 6,55957 French Francs/ 1 € = 0,84011 British Pounds (dd 14-12-2011)

QALY = quality adjusted life years; ΔQALY = difference in QALY between groups; ΔC = differences in costs between groups; ICER = incremental cost-effectiveness ratio = ΔC / ΔQALYs

CHAPTER THREE: BUDGET IMPACT ANALYSIS

Costs of botulinum toxin in patients with local dystonia and children with cerebral palsy suffering from drooling. A budget impact analysis

INTRODUCTION

Previous chapters reported on the clinical effectiveness of botulinum toxin in several indications. The review on the effectiveness showed a beneficial effect of botulinum toxin in patients with cervical dystonia, blepharospasm, and in patients with cerebral palsy who suffered from drooling.

Here, we report on the estimated annual costs of botulinum toxin in these three indications. The purpose of this budget impact analysis (BIA) is to estimate the financial consequences of adoption of a new health-care intervention within a specific health-care setting (Mauskopf 2007).

Although botulinum toxin is already indicated for conditional extra funding (policy rule for high cost medicines) in patients with local dystonia treated in rehabilitation centres, we included these indications in our analyses.

Research Question

What are the expected annual costs of treatment with botulinum toxin in patients with cervical dystonia or blepharospasm, or treatment of drooling in children with cerebral palsy?

METHODS

For calculating the annual costs of treatment with botulinum toxin, information is needed about the number of patients annually treated with botulinum toxin and the mean costs per patient.

Literature was searched for information about the prevalence of the diseases. Furthermore, the systematic review on the cost effectiveness of botulinum toxin (Chapter two) revealed studies that were useful for this budget impact analysis (Brefeld Courbon 2000, included in the review, and Burbaud 2011 excluded from the review).

When available, data from the Netherlands are preferred. If no Dutch data were available, experts were asked to judge whether international data were applicable to the Dutch situation.

Finally, expected annual costs for botulinum treatment for the Dutch population were calculated. Costs were calculated by combining the information about prevalence, percentage of users and costs per patient. In our analyses, we used 1) the costs of botulinum toxin alone and 2) if available, the incremental medical costs for botulinum treatment as

compared to an alternative intervention. Costs were calculated in 2011 Euro's and rounded up to the nearest 1000. Older cost data are adjusted to 2011 values by using indices for consumer prices (OECD statistics).

Sensitivity analyses were performed in which the impact of uncertainty in prevalence of diseases and the mean costs per patient on estimated annual costs for the Dutch situation was assessed.

Results are reported for each indication separately.

RESULTS

Table 16 presents the data used in the baseline analyses, sensitivity analyses, and its sources.

Table 16. Data used in costs analyses

Parameter	Value	Range*	Description /remark	Source
Population size				
All citizens	16.655.000			CBS data 2011
All children (until 20 yrs of age)	3.900.000			CBS data 2011
Prevalence disease				
Cervical dystonia	57/million	51-63	data EU (population > 20yrs); estimated prevalence and 95% confidence interval	ESDE Collaborative Group (2000)
Blepharospasm	36/million	31-41	data EU (population > 20yrs); estimated prevalence and 95% confidence interval	ESDE Collaborative Group (2000)
Cerebral palsy	2.4/1000		Prevalence among live births	Wichers 2001
Drooling in children with cerebral palsy	30%	10-38%	Review of literature in the introduction	Jongerius 2004
Annual costs per patient (BTX alone)				
Cervical dystonia	€1064	1017-1111	France, adults; average costs and 95% confidence interval	Burbaud 2011

Blepharospasm	€355	330-380	France, adults; average costs and 95% confidence interval	Burbaud 2011
Drooling	€389	323-453	France, annual costs botulinum toxin for adults with autonomic disorders; average costs and 95% confidence interval	Burbaud 2011
Incremental medical costs (versus standard care)				
Cervical Dystonia	€ 1573			Brefel-Courbon 2000

*)Ranges used in sensitivity analyses

Cervical dystonia

In 1999, results from an European survey on the prevalence of focal dystonia were published. Prevalence data were collected in ten adult neurology units in eight European countries. No Dutch units were included. The prevalence for cervical dystonia was 57 (confidence interval 51-63) per million. Considering all Dutch citizens, the estimated number of patients with cervical dystonia is approximately 950.

No studies reported on the costs of botulinum treatment in the Netherlands. Burbaud (2011) reported the daily costs for botulinum treatment in a cohort of botulinum users in France. Detailed information on these studies is presented in table 20. In the study by Burbaud, for patients with cervical dystonia, the annual costs of BTX alone were on average €1064. The total medical costs (including medical and nurses time, injection equipment, nursing, EMG guidance) were €1225. Assuming 100% botulinum use, the annual costs of botulinum toxin alone in the Netherlands are approximately €1.010.000,-. The results of the sensitivity analyses are reported in table 17.

Brefeld Courbon (2000; see references in chapter on cost-effectiveness) reported the incremental medical costs of botulinum toxin versus standard care (not defined). In 1997, the incremental costs per patient were €1180. After indexing to 2011, the annual incremental costs are €1573 per patient. Extrapolating these data to the whole Dutch population, the annual incremental costs are approximately €1.493.000.

Table 17. Sensitivity analyses: impact of changes in disease prevalence and cost per patient on estimated annual costs of botulinum toxin for cervical dystonia in the Netherlands

	Estimated annual costs botulinum treatment for cervical dystonia		
	Lowest estimate	Baseline estimate	Highest estimate
Prevalence cervical dystonia	€ 904.000	€ 1.010.000	€ 1.116.000
Costs botulinum toxin per patient per year	€ 965.000	€ 1.010.000	€ 1.055.000

Blepharospasm

For patients with blepharospasm, botulinum toxin is considered a first choice treatment (Hallett 2008). The European survey on focal dystonia (1999) reported a prevalence of blepharospasm of 36 (confidence interval 31-41) per million. Considering all Dutch citizens, the estimated number of patients with cervical dystonia is approximately 600.

In the study by Burbaud (2011), the annual costs of BTX alone were on average €355 for patients with blepharospasm. The total medical costs (including medical and nurses time, injection equipment, nursing, EMG guidance) were €486. Assuming 100% botulinum use, the annual costs of botulinum alone are approximately €213.000,-. The results of the sensitivity analyses are reported in table 18 For patients with blepharospasm, no valid information on the incremental costs of botulinum toxin versus alternative interventions was found.

Table 18. Sensitivity analyses: impact of changes in disease prevalence and cost per patient on estimated annual costs of botulinum toxin for blepharospasm in the Netherlands

	Estimated annual costs botulinum treatment for cervical dystonia		
	Lowest estimate	Baseline estimate	Highest estimate
Prevalence blepharospasm	€ 183.000	€ 213.000	€ 242.000
Costs botulinum toxin per patient per year	€ 198.000	€ 213.000	€ 228.000

Drooling in Cerebral Palsy

The prevalence of cerebral palsy is 2.4 per 1000 live births (Wichers 2001). Of these patients, approximately 30% suffers from drooling (Jongerius 2004). Considering a number of

3.900.000 children in the Netherlands (CBS data, people until 20 years of age), the number of children with cerebral palsy and suffering from drooling is approximately 2800.

In the study by Burbaud, for adult patients with autonomic disorders (including hyperhidrosis, salivary glands, Frey's syndromes), the annual costs for botulinum alone were €389. The total medical costs were €475. Currently, the use of botulinum toxin children with cerebral palsy and suffering from drooling is limited to a few centers in the Netherlands. Assuming a 100% botulinum use, and annual costs cost per patient of €389, the expected costs of botulinum alone in the Netherlands are approximately €1.092.000,- per year. The results of the sensitivity analyses are reported in table 19. For children with cerebral palsy suffering from drooling, no information on the incremental costs of botulinum toxin versus alternative interventions was found.

Table 19. Sensitivity analyses: impact of changes in disease prevalence and cost per patient on estimated annual costs of botulinum toxin for drooling in cerebral palsy in the Netherlands

	Estimated annual costs botulinum treatment for cervical dystonia		
	Lowest estimate	Baseline estimate	Highest estimate
Prevalence of drooling among children with cerebral palsy	€ 364.000	€ 1.092.000	€ 1.383.000
Costs botulinum toxin per patient per year	€ 908.000	€ 1.092.000	€ 1.273.000

DISCUSSION

Our calculations represented a static situation based on prevalence data. Eventual growth (increasing incidence) or shrinkage of the population (early death or curation) was not included.

Prevalence estimates for cervical torticollis and blepharospasm were based on a European survey (ESDE 2000). These estimates were lower as the data reported in Speelman (2009), reprinted at the internet. Using European prevalence data, the estimated number of patients with cervical dystonia in the Netherlands was 950 (Speelman 3000) and the number of patients with blepharospasm 600 (Speelman 1500). We decided to use the data from the European survey, because the original reports behind the data of Speelman could not be traced.

No data were available on the percentage of botulinum users for each indication. Not on current botulinum use neither for a potential future situation in which botulinum toxin will be reimbursed (policy rule for high cost medicines). Therefore, maximum estimates were reported assuming 100% use in indicated populations.

Ideally, potential savings related to botulinum treatment should also be incorporated in the analyses. Annual costs should be calculated by extrapolating the incremental costs of botulinum treatment as compared to current practice. However, information about the incremental costs of botulinum treatment in these populations was limited. The review on economic evaluations (separately reported) revealed two economic evaluations on botulinum in patients with blepharospasm. In one study, the population consisted of dystonia patients, without any subdivision. In the other economic evaluation, treatment with botulinum was compared to a placebo. No economic evaluations on botulinum for patients with cerebral palsy and drooling were found. For patients with cervical dystonia, data on the incremental costs were available (Brefeld Courbon 2000). These data suggested that savings resulting from treatment with botulinum toxin were minimal. The incremental costs were comparable to the additional costs of botulinum toxin.

Costs data from French studies were used. Data from France might not always be applicable to the Dutch situation. For judging the transferability of costs data, the similarity of health care system characteristics and populations characteristics should be assessed (Welte 2004). Main criteria for the health care system are absolute and relative prices, practice variation and technology availability. We assumed that the French data on the costs of botulinum toxin alone are reasonably applicable to the Dutch situation. Additionally, information about the price of botulinum toxin, frequency of treatment, and doses used were reported. Estimates considering all medical costs should be handled more cautiously. For children with cerebral palsy, estimated medical costs might not be transferable to the Dutch situation, because children are mostly admitted to a rehabilitation centre for a long period in France. Burbaud did not include children, but only adults. We used these data concerning the costs in adults for our population of children. Possibly, the costs are overestimated due to higher doses in adults.

We identified two other studies that reported on the annual costs of treatment with botulinum toxin. Dodle (1997) reported on medical costs in patients with dystonia and hemifacial spasm in Germany and the USA. Schnider (1999) reported on costs of botulinum toxin in patients with spasmodic torticollis, blepharospasm, or hemifacial spasm in Austria. However, data were older (Schnider: 1989-1997, Dodel: 1994-1997), retrospectively collected (Schnider), and less transparent with regard to the amount of BTX used and frequency of use. The estimated annual medical costs reported by Dodel were higher compared to the French data (blepharospasm €706 per year per patient; cervical dystonia €3144 per year per patient, adjusted to 2011 price level), but it was difficult to assess whether the same cost components were included. In the study by Schnider et al., the costs for botulinum toxin were comparable to the French data (blepharospasm €277 per year per patient; cervical dystonia €1026 per year per patient, adjusted to 2011 price level).

In sum, assuming 100% use in the defined populations, the estimated annual costs for botulinum toxin are approximately €1.010.000,- for cervical dystonia, €213.000,- for blepharospasm and €1.092.000,- for drooling in children with cerebral palsy.

Table 20. Study characteristics

Item	**Burbaud 2011**
Country	France
Design	Prospective, observational
Context	patients on botulinum in 2 departments (physical medicine and rehabilitation) from university clinic
Population	3108 injections in 870 patients, > 18 yrs, with dystonia, spasticity, nerve compression, or dysautonomic symptoms (including injections in salivary glands)
Follow up period	2 years, Jan 2007 – Jan 2009
Type of costs	Botulinum + additional costs treatment
Sources data	Case record form
Price	Price botulinum (France 2010): €154 for 100 UI Botox €215 for 500 UI Dysport
Dose / type botulinum	Botox or Dysport (free choice) Mean doses in this population: -Blepharospasm: 81 UI (Botox) or 238 UI (Dysport) -Cervical Dystonia: 635 UI (Dysport) -Autonomic disorders: 190UI (Botox) or 360(UI Dysport)
Frequency	Repeated injection when patient felt the effect was clearly wearing off Duration effect (average): -Blepharospasm: 15.4 weeks -Cervical Dystonia: 14.3 weeks -Autonomic disorders: 27.6 weeks Frequency injections (number of injections per year) -Blepharospasm: 3.4 -Cervical Dystonia: 3.6 -Autonomic disorders: 1.9

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Bijlage: Werkpakket 3 ‘Gebruik Botulinetoxine’

ACHTERGROND

‘On-Label‘ indicatiegebieden

Lijst dure geneesmiddelen:

Beleidsregel BR/CU-2017 (versie: 06 september 2011) (website Nederlandse Zorgauthoriteit (NZa)):

- Botulinetoxine (locale dystonieën): Met ingang van 1 januari 2006 is gebruik beperkt tot revalidatie-instellingen en revalidatiebehandeling in de in de reikwijdte van deze beleidsregel genoemde zorgaanbieders.

Farmacotherapeutisch Kompas (http://www.fk.cvz.nl/)**:**

- Blefarospasme;
- Hemifacialisspasme;
- Cervicale dystonie (spasmodische torticollis) bij patiënten van 12 jaar en ouder;
- Persistente primaire bilaterale hyperhidrose van de okselklieren die het dagelijks leven verstoort bij patiënten van 18 jaar en ouder.
- Focale spasticiteit geassocieerd met een spitsvoet, misvorming door spasticiteit bij ambulante kinderen (2 j. en ouder) met spastische verlamming.
- Focale spasticiteit van pols en hand na een CVA.
- Spasticiteit van de arm na een CVA.
- Azzalure en Bocouture: Bij volwassenen jonger dan 65 jaar voor de tijdelijke verbetering van het uiterlijk door matig ernstige tot ernstige verticale rimpels tussen de wenkbrauwen (glabellalijnen) bij het fronsen, als de patiënt hierdoor ernstig psychisch lijdt.

METHODE

Doelstelling Werkpakket 3:

Het beantwoorden van gebruikgerelateerde vragen met betrekking tot:

- indicatiegebieden anders dan de bovengenoemde 'On-Label indicatiegebieden (zogenaamde 'witte vlekken');
- opname in beroepsgroep gerelateerde richtlijnen of behandelprotocollen of consensusdocument;
- inschatting van het aantal behandelde patiënten en de hieraan gerelateerde kosten.

Middelen

1. Raadpleging netwerk revalidatiegeneeskunde.

- Uit een eerste globale inventarisatie in de regio bleek dat meerdere verschillende medisch specialismen botulinetoxine als behandeling inzetten. Gezien het feit dat DBC-onderhoud ondermeer het aantal verstrekkingen per diagnose per medisch specialisme registreert zijn aldaar de gegevens opgevraagd en verwerkt.
- Omdat de verhouding verstrekking en behandeling verschilt kunnen de gerelateerde kosten niet worden berekend.

2. Raadpleging richtlijnen voor beroepsgroepen.
3. Raadpleging netwerk farmacie (of farmaceutische industrie).

- Apothekers zijn benaderd met de vraag naar hun verstrekkingen botulinetoxine. Respons bleek erg laag en bovendien weinig informatief aangezien apothekers vaak niet konden specificeren voor welk medische indicatie botulinetoxine gebruikt werd.
- Leveranciers van botulinetoxine zijn gevraagd om hun verkoopcijfers te bespreken en hierop heeft Ipsen Farmaceutica B.V. als enige positief gereageerd. Na overleg werd hun inschatting van de Nederlandse markt voor botulinetoxine gedeeld.
- Helaas kon de Stichting Farmaceutische Kengetallen (SFK) geen overzicht verstrekken.

RESULTATEN m.b.t. doelstelling & middelen

1. OVERZICHT VAN BOTULINUM TOXINE VERSTREKKINGEN (DBC-ONDERHOUD)

Overzicht van verstrekkingen van botulinum toxine in het jaar 2009 en 2010 bij de medische specialisten (Tabel 1 t/m 3).

Per medische specialisme dat gebruik maakt van botulinetoxine zijn de voornaamste diagnoses die in aanmerking komen voor behandeling met botulinetoxine opgenomen in tabel 1. Het overzicht is gebaseerd op de DIS data (DBC informatiesysteem) van alle ziekenhuizen, samengesteld uit DIS aanleveringen van DBC gegevens (afgesloten DBC's). Aangezien er (nog) geen landelijke conventie bestaat ten aanzien van de eenheden die worden aangeleverd aan DIS zijn per DBC het aantal verstrekkingen bepaald. Een verstrekking staat voor één behandelingsepisode van één patiënt.

Uit tabel 2 valt op te maken hoeveel verstrekkingen er jaarlijks zijn gedaan per medisch specialisme. Zo is duidelijk dat de afdeling Neurologie het grootste botulinetoxine verbruik heeft (met name door de behandeling van dystonieën), gevolgd door Dermatologie en Revalidatie.

Tabel 1. Aantal verstrekkingen van botulinum toxine in 2009 en 2010 per diagnose bij verschillende medisch specialismen (zoals bekend bij DBC Onderhoud)

Medisch specialisme	Diagnose code	Diagnose omschrijving	Aantal verstrekkingen 2009	2010
Chirurgie	116	Fissuur en fistel ano-rectaal	500	563
Chirurgie	117	Hemorroïden	50	74
Chirurgie	329	Overige niet maligne gastro-intestinale aandoeningen		14
Dermatologie	27	Diagnose nno	3521	6284
Dermatologie	9	Fleb overig en lymfologie	27	44
Dermatologie	14	Maligne dermatosen		14
Gastro-enterologie (maag-darm-lever-arts)	631	Proctologie*	29	38
Gastro-enterologie (maag-darm-lever-arts)	305	Overige oesofagale motiliteitstoornissen	30	29
Gastro-enterologie (maag-darm-lever-arts)	304	Achalasie	17	25
Gastro-enterologie (maag-darm-lever-arts)	632	Bekkenbodemproblematiek		11

Inwendige geneeskunde	936	Proctologische aandoening	16	29
Keel-, neus- en oorheelkunde	53	Dysfonie	205	267
Keel-, neus- en oorheelkunde	18	Afwijkingen van nervus facialis	132	164
Keel-, neus- en oorheelkunde	31	Allergie / hyperreactiviteit		18
Keel-, neus- en oorheelkunde	71	Sialoadenosen, sialoadenitis		16
Keel-, neus- en oorheelkunde	92	Acute luchtwegobstructie	29	15
Keel-, neus- en oorheelkunde	36	Sinusitis		14
Keel-, neus- en oorheelkunde	55	Globus / slikklachten		13
Neurologie	511	Dystonieën	14348	16221
Neurologie	551	Aandoeningen autonome zenuwstelsel	685	983
Neurologie	1121	Resttoestand (verworven hersenletsel)	195	231
Neurologie	799	Overige hoofdpijn		38
Neurologie	701	Migraine + migraine-varianten	10	30
Neurologie	9902	Pijn, niet elders geclassificeerd		25
Neurologie	501	M. Parkinson	13	13
Neurologie	801	N. medianus (incl. carpale tunnelsyndroom)		12
Oogheelkunde	259	Overige pathologie oogleden	187	533
Oogheelkunde	859	Overige neuro-ophthalmologie	51	209
Oogheelkunde	204	Concomitant scheelzien		22
Oogheelkunde	257	Ec- en entropion	12	21
Oogheelkunde	255	Dermatochalazis		12
Oogheelkunde	205	Incomitant scheelzien		12
Plastische chirurgie	3	Kortdurige conservatieve (mede)behandeling, litteken	104	188
Plastische chirurgie	4	Langdurige conservatieve (mede)behandeling, litteken	16	11
Plastische chirurgie	330	Inspuiting(en)tendinitis, volledig	10	
Revalidatie	313	CVA	1358	1855
Revalidatie	311	Cerebrale functiestoornissen inclusief	430	644

		congenitaal		
Revalidatie	411	Neurologie cerebrospinaal	224	242
Revalidatie	415	Overige neurologische aandoeningen	236	226
Revalidatie	414	Neuromusculaire aandoeningen	82	148
Revalidatie	511	Dwarslaesie C1-C8, T1-T6	98	124
Revalidatie	314	Contusio cerebri	89	90
Revalidatie	115	Overige aandoening O.E.	44	71
Revalidatie	512	Dwarslaesie T7-T12 en lager	31	56
Revalidatie	317	Overige hersenaand.	40	40
Revalidatie	114	Overige aandoening B.E.	13	38
Revalidatie	316	Tumor cerebri	35	33
Revalidatie	413	Perifeer zenuwletsel/zenuwaandoeningen	23	27
Revalidatie	116	Aandoening wervelkolom, romp	22	23
Revalidatie	119	Overige aandoeningen bewegingsapparaat	15	19
Revalidatie	715	Overige pijn	21	17
Revalidatie	312	DCD		17
Revalidatie	113	Overige aangeboren aandoeningen bewegingsapparaat		17
Revalidatie	513	Spina bifida		16
Revalidatie	711	Chronische pijnsyndroom WPN 1		15
Revalidatie	315	Infectieuze hersenaandoeningen	16	
Revalidatie	712	Chronisch pijnsyndroom WPN 2	12	
Revalidatie	412	Plexusletsel	10	
Urologie	35	Urge-incontinentie/oab	296	503
Urologie	37	Neurogene blaas	77	101
Urologie	82	Interstitiele cystitis	19	26
Urologie	83	Overige blaaspathologie		21
Urologie	82	Interstitiele cystitis	12	17
Urologie	41	BPH/BH obstructie		16
Urologie	32	Blaasinfectie		11
Urologie	34	Stress-incontinentie/prolaps	12	

Toelichting: diagnoses met <10 verstrekkingen per jaar zijn niet in de tabel opgenomen.

Tabel 2. Aantal botulinum toxine verstrekkingen per jaar (Tabel 1) afgezet tegen elk medische specialisme

	Aantal verstrekkingen	
Medisch specialisme	**2009**	**2010**
Dermatologie	3548	6342
Chirurgie	550	651
Urologie	416	695
Revalidatie	2799	3718
Plastische chirurgie	130	199
Gastro-enterologie (maag-darm-lever-arts)	76	103
Oogheelkunde	250	809
Neurologie	15251	17553
Keel-, neus- en oorheelkunde	366	507
Inwendige geneeskunde	16	29
Totaal	**23402**	**30606**

Tabel 3. Afkortingenlijst gekoppeld aan tabel 1.

Afkorting	Vertaling
CVA	Cerebro vasculair accident
Nno	Niet nader omschreven
Oab	Overactieve blaas
O.E. / B.E.	Onderste extremiteiten / Bovenste extremiteiten
DCD	Developmental coördination disorder
BPH/BH	Benigne prostaathyperplasie
WPN	Werkgroep Pijn Nederland
COPD	Chronic Obstructive Pulmonary Disease

2. RAADPLEGING RICHTLIJNEN VAN BEROEPSGROEPEN

Overzicht van verstrekkingen van botulinum toxine in het jaar 2009 en 2010 bij de medische specialisten gerelateerd aan Richtlijnen van Medisch Specialisten (Tabel 4).

Tabel 4. Overzicht van Richtlijnen van de Kwaliteitskoepel Medisch Specialisten waarin botulinum toxine als behandelvorm wordt aanbevolen, gerelateerd aan de diagnose omschrijvingen genoemd in Tabel 1 (zoals aangereikt door DBC-onderhoud).

(http://www.kwaliteitskoepel.nl/)

Medisch specialisme	Diagnose omschrijving (Tabel 1)	Aanbeveling in Richtlijn Medisch Specialisten
Chirurgie	Fissuur en fistel ano-rectaal	-
Chirurgie	Hemorroïden	-
Chirurgie	Overige niet maligne gastro-intestinale aandoeningen	-
Dermatologie	Diagnose nno	Acneiforme dermatosen
Dermatologie	Fleb overig en lymfologie	-
Dermatologie	Maligne dermatosen	-
Gastro-enterologie (maag-darm-lever-arts)	Proctologie*	-
Gastro-enterologie (maag-darm-lever-arts)	Overige oesofagale motiliteitstoornissen	-
Gastro-enterologie (maag-darm-lever-arts)	Achalasie	-
Gastro-enterologie (maag-darm-lever-arts)	Bekkenbodemproblematiek	-
Gastro-enterologie (maag-darm-lever-arts)	-	Inflammatoire darmziekten (IBD) volwassenen *(opm. niet genoemd in Tabel 1)*
Inwendige geneeskunde	Proctologische aandoening	-
Keel-, neus- en oorheelkunde	Dysfonie	-
Keel-, neus- en oorheelkunde	Afwijkingen van nervus facialis	-
Keel-, neus- en oorheelkunde	Allergie / hyperreactiviteit	-
Keel-, neus- en oorheelkunde	Sialoadenosen, sialoadenitis	-
Keel-, neus- en oorheelkunde	Acute luchtwegobstructie	-
Keel-, neus- en oorheelkunde	Sinusitis	-
Keel-, neus- en oorheelkunde	Globus / slikklachten	-

Neurologie	Dystonieën	-
Neurologie	Aandoeningen autonome zenuwstelsel	-
Neurologie	Resttoestand (verworven hersenletsel)	-
Neurologie	Overige hoofdpijn	Hoofdpijn
Neurologie	Migraine + migraine-varianten	-
Neurologie	Pijn, niet elders geclassificeerd	Whiplash
Neurologie	M. Parkinson	-
Neurologie	N. medianus (incl. carpale tunnelsyndroom)	-
Neurologie	-	Diagnostiek en behandeling van patienten met een glioom *(opm. niet genoemd in Tabel 1)*
Oogheelkunde	Overige pathologie oogleden	-
Oogheelkunde	Overige neuro-ophthalmologie	-
Oogheelkunde	Concomitant scheelzien	-
Oogheelkunde	Ec- en entropion	-
Oogheelkunde	Dermatochalazis	-
Oogheelkunde	Incomitant scheelzien	-
Plastische chirurgie	Kortdurige conservatieve (mede)behandeling, litteken	-
Plastische chirurgie	Langdurige conservatieve (mede)behandeling, litteken	-
Plastische chirurgie	Inspuiting(en)tendinitis, volledig	-
Revalidatie	CVA	-
Revalidatie	Cerebrale functiestoornissen inclusief congenitaal	Kinderen met spastische cerebrale parese
Revalidatie	Neurologie cerebrospinaal	-
Revalidatie	Overige neurologische aandoeningen	-
Revalidatie	Neuromusculaire aandoeningen	-
Revalidatie	Dwarslaesie C1-C8, T1-T6	-
Revalidatie	Contusio cerebri	-
Revalidatie	Overige aandoening O.E.	-
Revalidatie	Dwarslaesie T7-T12 en lager	-
Revalidatie	Overige hersenaand.	-
Revalidatie	Overige aandoening B.E.	-
Revalidatie	Tumor cerebri	-
Revalidatie	Perifeer zenuwletsel/zenuwaandoeningen	-
Revalidatie	Aandoening wervelkolom, romp	-
Revalidatie	Overige aandoeningen bewegingsapparaat	-
Revalidatie	Overige pijn	-

Revalidatie	DCD	-
Revalidatie	Overige aangeboren aandoeningen bewegingsapparaat	-
Revalidatie	Spina bifida	-
Revalidatie	Chronische pijnsyndroom WPN 1	-
Revalidatie	Infectieuze hersenaandoeningen	-
Revalidatie	Chronisch pijnsyndroom WPN 2	-
Revalidatie	Plexusletsel	-
Urologie	Urge-incontinentie/oab	-
Urologie	Neurogene blaas	-
Urologie	Interstitiele cystitis	-
Urologie	Overige blaaspathologie	-
Urologie	Interstitiele cystitis	-
Urologie	BPH/BH obstructie	-
Urologie	Blaasinfectie	-
Urologie	Stress-incontinentie/prolaps	-

Tabel 5. Overzicht van grote indicatiegebieden voor botulinetoxine gebruik gerelateerde aan de richtlijnen en de 'on label' indicatiegebieden zoals genoemd in het farmacotherapeutisch kompas.

Medisch specialisme	Diagnose	Aantal verstrekkingen 2009	Aantal verstrekkingen 2010	Aanbeveling in Richtlijn Medisch Specialisten	Farmacotherapeutisch Kompas
Neurologie	Dystonieën	14348	16221	-	Blefarospasme; Hemifacialisspasme; Cervicale dystonie
Dermatologie	Diagnose nno	3521	6284	Acneiforme dermatosen	Hyperhidrose; rimpels tussen de wenkbrauwen (glabellalijnen)
Revalidatie	CVA	1358	1855	-	Focale spasticiteit van pols en hand na een CVA; Spasticiteit van de arm na een CVA.
Neurologie	Aandoeningen autonome zenuwstelsel	685	983	-	-
Revalidatie	Cerebrale functiestoornissen inclusief congenitaal	430	644	Kinderen met spastische cerebrale parese	Focale spasticiteit geassocieerd met een spitsvoet
Chirurgie	Fissuur en fistel ano-rectaal	500	563	-	-
Oogheelkunde	Overige pathologie oogleden	187	533	-	-
Urologie	Urge-incontinentie/oab	296	503	-	-
Neurologie	Overige hoofdpijn		38	Hoofdpijn	-
Neurologie	Pijn, niet elders geclassificeerd		25	Whiplash	-
Gastro-enterologie (maag-darm-lever-arts)				Inflammatoire darmziekten (IBD) volwassenen	-
Neurologie				Diagnostiek en behandeling van patienten met een glioom	-

De ‘on label’ indicatiegebieden blijken uit grote doelgroepen te bestaan. Er zijn echter geen richtlijnen voor het gebruik van botulinetoxine door de medische specialisten beschikbaar (Tabel 5). Uit de beleidsregel BR/CU-2017 van de NZa blijkt dat botulinetoxine alleen vergoed wordt voor revalidatieartsen als zij lokale dystonieën behandelen. Deze diagnose blijkt echter voornamelijk behandeld te worden door neurologen. Voor behandeling van hoofdpijn, whiplash, IBD en gliomen zijn richtlijnen voor medisch specialisten beschikbaar. Echter, botulinetoxine wordt niet verstrekt aan patiënten die een van deze voorgenoemde diagnoses hebben. Botulinetoxine wordt in grote mate verstrekt bij een viertal diagnoses (Tabel 5), maar hiervoor is geen richtlijn of beschrijving in het farmacotherapeutisch kompas beschikbaar.

3. RAADPLEGING NETWERK FARMACIE (/FARMACEUTISCHE INDUSTRIE)

Overzicht van de schatting van de marktwaarde van botulinum toxine in het jaar 2011 volgens Ipsen Farmaceutica B.V. (Tabel 6). De berekening van de totale marktwaarde voor botulinetoxine is gebaseerd op de bruto verkoopcijfers (zonder kortingsregelingen) van Ipsen Farmaceutica B.V. en een inschatting van hun marktaandeel op basis van gesprekken met hun klanten.
Uit gesprek met Ipsen Farmaceutica B.V. bleek dat hun netto marktaandeel rond de 5 á 6 miljoen ligt. Hun inschatting is dat Allergan B.V. 2 tot 3 keer groter is. Deze twee bedrijven zijn praktisch de enige leveranciers van botulinetoxine in Nederland.

Tabel 6. Inschatting van de totale marktwaarde van botulinetoxine in 2011.

Medisch specialisme		
Revalidatie	Aantal flacons	10.530
	Marktwaarde	€ 2.471.926
Neurologie	Aantal flacons	13.347
	Marktwaarde	€ 3.422.644
Overige medische specialismen	Aantal flacons	18.900
	Marktwaarde	€ 4.459.470
Totale markt	Aantal flacons	42.777
	Marktwaarde	€ 10.354.040

CONCLUSIE

1. In Nederland blijkt binnen de verschillende medisch specialismen in de periode 2009-2010 Neurologie de grootste verstrekker van botulinetoxine gevolgd door respectievelijk Dermatologie en Revalidatiegeneeskunde.

2. Het gerealiseerd gebruik bij verschillende diagnosegebieden verschilt met de in formele beroepsgroepspecifieke richtlijnen genoemde diagnosegebieden.

3. De geschatte totale marktwaarde van botulinetoxine in 2011 is ongeveer €10.000.000,-.