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Clin Rehabil 2009; 23; 394 originally published online Apr 23, 2009;
DOI: 10.1177/0269215508099860

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Safety of botulinum toxin type A among children with spasticity secondary to cerebral palsy: a systematic review of randomized clinical trials

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Received 29th April 2008; returned for revisions 26th July 2008; revised manuscript accepted 7th October 2008.

Objective: To assess the safety of botulinum toxin type A for children with cerebral palsy using data from randomized clinical trials.

Data sources: A search was conducted of MEDLINE database for the period January 1990 to February 2008. A complementary search was carried out of references from previous reviews. From 122 articles, 20 randomized clinical trials were selected for the review.

Review methods: Two authors independently assessed eligibility of the studies and methodological quality of those according to CONSORT guidelines. For each adverse effect, relative risk was calculated, and when more than one study reported adverse effects, a meta-analysis was carried out. Sensitivity analyses with different continuity corrections factors were performed when zero cases were reported in a study arm.

Results: There were 882 participants in the 20 studies included in the meta-analysis. Six studies reported zero adverse effects. Thirty-five different adverse events were reported. Botulinum toxin type A use was related to respiratory tract infection, bronchitis, pharyngitis, asthma, muscle weakness, urinary incontinence, falls, seizures, fever and unspecified pain. Two deaths were reported in the study with higher person-time follow-up (relative risk (RR) 4.69, 95% confidence interval (CI) 0.23–95).

Conclusions: Botulinum toxin type A has a good safety profile during the first months of use. However the occurrence of adverse events is more frequent among children with cerebral palsy than individuals with other conditions. Severe adverse events are potentially related with the use of botulinum toxin type A, but data are sparse and additional study is required to clarify the causal relation.

Introduction

Cerebral palsy is a syndrome characterized by motor and postural limitations, with a broad severity range, caused by lesions to the central nervous system during the development period.

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10.1177/0269215508099860

Within the pharmaceutical options for treatment, botulinum toxin type A has an important role in spasticity management.¹ Although it is one of the most poisonous substances known, producing muscular relaxation in the region where it is applied, among patients with cerebral palsy botulinum toxin type A has been shown to reduce pain and to improve muscular function. It acts by blocking the Ca^{2+} -dependent release of the neurotransmitter acetylcholine from presynaptic nerve terminals at neuromuscular junctions.² There are three commercial presentations of botulinum toxin type A available at present: Botox, Dysport, and Xeomin. These presentations have different manufacturing process, as well as different excipients and required doses.^{3,4}

Several reviews have assessed the therapeutic effect of botulinum toxin type A for different indications, including spasticity secondary to cerebral palsy,⁵⁻⁹ yet data on safety are very limited. In February 2008 the US Food and Drug Administration (FDA) expressed concern about potential severe adverse effects (respiratory compromise and death) of Botox, based on received reports of children treated for cerebral palsy-associated limb spasticity. These concerns are contrary to the evidence summarized in previous reviews, where toxin safety profile was reported as good. Thus, it is possible that the margin of benefit and harm is narrower than previously reported. In these reviews the authors merged the results of a large number of different therapeutic indications that use lower doses (such as cosmetic uses). This procedure could conceal some adverse events.

Some authors suggest that the development of neutralizing antibodies explains the occurrence of adverse effects related to botulinum toxin type A.¹⁰ These antibodies appear after the toxin is administered and can diminish its effectiveness. Thus, in order to obtain the desired therapeutic effect in subsequent sessions, it is necessary to increase the dose. Since a dose-response relationship has been observed in the frequency and severity of adverse events,⁹ it is possible that children with cerebral palsy have a higher probability of occurrence since they require high doses of toxin relative to their body mass. This paper presents the results of a systematic review of randomized clinical trials that assess botulinum toxin type A safety in children with cerebral palsy.

Only randomized clinical trials were considered to explore the possible causal relationship between toxin and adverse effects¹¹; an analysis not possible with other epidemiological designs.

Methods

Literature search and eligibility criteria

Botulinum toxin type A has been assessed since the 1990s in the treatment of spasticity secondary to cerebral palsy. To identify articles relevant to our key question about toxin safety, we searched the MEDLINE database. To capture articles relevant to the scope of our topic, our search period was January 1990 to 10 February 2008 (Table 1). We used the MeSH terms 'botulinum toxin', 'cerebral palsy', and 'clinical trial' limiting by 'all children: <18 years'. The MEDLINE search was followed by a manual search of reference lists in relevant review articles to complete the search. The articles identified were assessed to verify compliance with the following inclusion criteria: (1) a study of patients under 18 years of age; (2) a randomized clinical controlled trial epidemiological design; (3) intramuscular injection with botulinum toxin type A (Botox, Dysport and/or Xeomin) treatment of spasticity secondary to cerebral palsy; (4) administration of placebo and/or rehabilitation in the comparison group to ensure a better counterfactual design; and (5) publication language of English, French, Spanish or German. Studies with botulinum toxin type B were excluded because of the more frequent autonomic adverse effects with this toxin, despite the fact that its biological activity is less than toxin type A.^{3,4} With these very different characteristics botulinum toxin type B will require another review. Two authors (CAH and JMR) independently assessed the titles and abstracts of potential papers. Disagreement between the authors was readily resolved through discussion.

Collection of data

The following data were abstracted from each of the identified studies: type of cerebral palsy, signs, commercial presentation of the toxin and dose administered, comparator, duration of follow-up,

Table 1 Randomized clinical trials that met the inclusion criteria ($n=20$)

Authors, year	CONSORT score ^{a,b}	Follow-up time	Anatomic region	Sample	Age (months) ^c	Toxin	Doses (U/kg)	Comparator
Koman <i>et al.</i> , 2004 ¹	13	6 weeks	LL	12	48–132	Botox	1–2	Placebo
Corry <i>et al.</i> , 1997 ²³	17	12 weeks	LL	20	58.8 (24–108)	Botox	6–8	Placebo
Sutherland <i>et al.</i> , 1999 ⁴³	13	8 weeks	LL	20	73.2 (28.9–150)	Dysport	15	Placebo
Ubhi <i>et al.</i> , 2000 ³²	18	3 months	LL	40	66 (33.6–196)	Dysport	15–25	Placebo
Koman <i>et al.</i> , 2000 ³³	19	12 weeks	LL	114	24–192	Botox	4	Placebo
Boyd <i>et al.</i> , 2001 ³⁴	15	12 months	LL	35	38 (31–48)	Botox	16	Rehabilitation
Love <i>et al.</i> , 2001 ⁴⁴	12	6 months	LL	24	76.8 (36–156)	Botox	2.8–7.3	Placebo
Detrembleur <i>et al.</i> , 2002 ⁴⁵	16	6 months	LL	12	60 (56–72)	Botox	7–17.5	Electrical stimulation
Baker <i>et al.</i> , 2002 ³⁵	19	16 weeks	LL	122	61 (24–108)	Dysport	10, 20, 30	Placebo
Reddihough <i>et al.</i> , 2002 ³⁶	17	6 months	LL	49	49 (22–80)	Botox	8–20	Rehabilitation
Barwood <i>et al.</i> , 2000 ⁴⁶	15	Undefined	LL	16	57	Botox	8	Placebo
Kay <i>et al.</i> , 2004 ⁴⁷	15	12 months	LL	23	85.2 (52–166)	Botox	8	Casting
Ackman <i>et al.</i> , 2005 ³⁷	18	12 months	LL	34	70.6 (40–105)	Botox	4	Placebo and casting
Speth <i>et al.</i> , 2005 ⁴⁸	15	9 months	UL	20	48–192	Botox	2–3	Intensive rehabilitation
Mall <i>et al.</i> , 2006 ³⁸	14	3 months	LL	60	73 (SD 37)	Dysport	30	Placebo
Russo <i>et al.</i> , 2007 ³⁹	19	6 months	UL	43	104.4 (84–124.8)	Botox	8	Rehabilitation
Wallen <i>et al.</i> , 2007 ⁴⁰	19	6 months	UL	72	68 (SD 37)	Botox	0.5–2	Rehabilitation
Bjornson <i>et al.</i> , 2007 ⁴¹	15	6 months	LL	33	66 (36–144)	Botox	12	Placebo
Lowe <i>et al.</i> , 2007 ¹⁷	19	30 months	UL	42	48 (SD 19)	Botox	7.6 (5.5–8)	Placebo
Graham <i>et al.</i> , 2008 ⁴²	18	3 years	LL	91	36–38	Botox	4	Rehabilitation

^aAssessed by two independent epidemiologists.^bBased on the CONSORT guidelines extended to adverse events.¹²^cMean (minimum–maximum).

UL, upper limb; LL, lower limb; SD, standard deviation.

patient sex and age, as well as specific data on adverse events: incidence, intensity and possible relationship with the medication. The report on the incidence of adverse events prepared by the studies' authors in relative terms (e.g. percentages or relative risks) was omitted, and these were estimated anew with the descriptive data present in the article following a per-protocol analysis. The review and extraction of this information was performed independently by two authors (CAH and JMR), then compared. Disagreements between the two authors were revised jointly with the third author (AJI) to obtain a single criterion.

Validity assessment and analysis of data

The quality of the studies was assessed using the CONSORT guidelines with the extension for adverse events.¹² In cases when only one study reported an adverse event, relative risks (RR) were calculated with the corresponding 95% confidence intervals (95% CI) using the data extracted. When in one cell there were zero cases, 0.5 was added to all four cells of a 2×2 table.¹³ When more than one study described an adverse event, the association estimators obtained in each of the studies was summarized via meta-analysis. The use of fixed or random methods was determined based on the results of the DerSimonian and Laird test to assess heterogeneity.¹⁴ Since adverse effects were rare (mainly in the group unexposed to botulinum toxin type A) – thus affecting confidence intervals and heterogeneity tests – a sensitivity analysis¹⁵ using two different continuity corrections factors (0.5 and 0.1) were calculated. All analyses were performed with the Stata 9 statistical program (Stata Corporation, College Station, TX, USA).

Results

Figure 1 summarizes the literature search. During the initial search 121 papers were found, and one additional article was identified during the review of references. Of these papers, we found 35 randomized clinical trials potentially appropriate for our analysis. We eliminated 15 studies: one randomized clinical trial studied an indication other

than cerebral palsy¹⁶; in four studies the comparators were not placebo or rehabilitation^{17–20}; three randomized clinical trials were preliminary studies of other randomized clinical trials^{21–23}; two were written in other languages^{24,25}; and five randomized clinical trials lacked safety data.^{26–30} For this reason we limited the review to 20 randomized clinical trials,^{31–48} but six of these explicitly report zero adverse events.^{43–48} A very good agreement between the evaluators was observed (kappa: 0.92).

While we only reviewed the MEDLINE database, a comparison with previous meta-analyses^{5–9} that searched articles in other databases (i.e. EMBASE, CINAHL, ClinPSYC, Database of Abstracts of Reviews of Effectiveness DARE, the Physiotherapy Evidence Data base PEDro and Cochrane) allowed us to confirm that this search was sufficient to identify the randomized clinical trials. Only the most recent studies were not included in previous systematic reviews. The assessed studies were published between 1994 and January 2008, and most of them were of patients diagnosed with cerebral palsy treated with botulinum toxin type A in the lower limbs ($n=16$, 80%). Botox is the most studied commercial presentation of the toxin, used in 17 studies (85%); Dysport was the subject of four studies (20%). In one study Botox and Dysport were jointly used. No randomized clinical trial with Xeomin was found. Individuals participating in the studies were between 22 months and 16 years old. There were 882 participants in the 20 studies reviewed, and 542 adverse events related with toxin use were reported.

Quality of the methodological report and evidence level

According to the criteria of the CONSORT guidelines, the reports of the clinical trials fulfilled 16.3 of the items in average (range: 12–19). These scores were assumed reasonable and therefore merited the inclusion of the studies in this systematic review.

Adverse events

Clear definitions of adverse events were not included in the articles, which makes it difficult

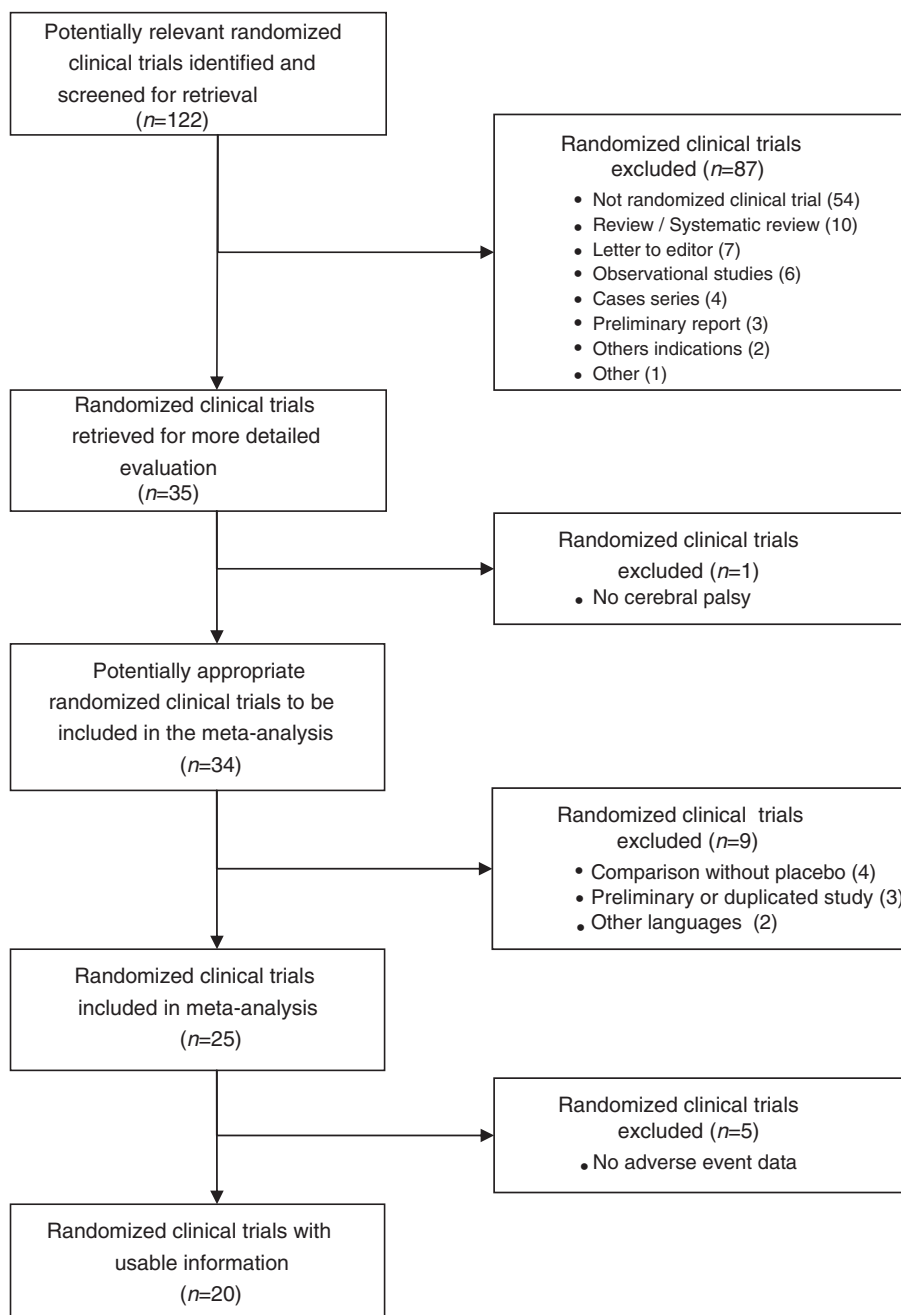


Figure 1 Review flowchart.

to evaluate if the findings are comparable across studies. The studies reported 33 different types of adverse events. In 13 of the 14 studies, it was possible to obtain specific incidence data of each adverse effect. The study of Lowe *et al.*¹⁷ only reported that there were 31 adverse events among 15 individuals, which were considered to be unrelated to treatment, without differentiating between those who received botulinum toxin type A and placebo. Unfortunately, it was not possible to obtain specific data for all the events reported. For this reason we only included cases when these were explicit in the text. The most frequent events were those that were present in more than one study.

Figure 2 summarizes the statistically significant results. Our analyses indicate that respiratory tract infection, bronchitis, pharyngitis, asthma, muscle weakness, urinary incontinence, falls, seizures, fever and unspecified pain are related to botulinum toxin type A. Other adverse effects such as fatigue, headache, local infection, diarrhoea, gastroenteritis, urticarial rash or eczema, generalized weakness and cough were not associated with the toxin.

According to sensitivity analyses with two continuity correction factors, all adverse effects are underestimated because zero cases were reported in the exposed group of some of the randomized clinical trials. It was more difficult to define the relationship of local infection, diarrhoea, and urticarial rash or eczema with botulinum toxin type A. In these cases results are non-significant using the two continuity correction factors. However, the crude data report that adverse effects occurred in the exposed group. Finally, the adverse effects reported in only one study are summarized in Table 2. No clear evidence of safety issues are shown in any of cases, a result of the small samples in the randomized clinical trials. The case of death will require special attention since only two cases were reported in the exposed arm of one study, although the authors mention that these were not related to botulinum toxin type A use.⁴²

Conclusion

In general, the results of this analysis suggest that botulinum toxin type A has a relatively good

safety profile during the first months of use. Extrapolations to long-term use are not possible with the available data. Excluding the observed deaths, the severity of adverse events associated with the toxin was low. Our analysis suggests that botulinum toxin type A is related to pharyngitis, unspecific pain, falls, respiratory tract infection, bronchitis, vomit, seizures, urinary incontinence, asthma and viral upper respiratory tract infection. To be able to observe this range of adverse effects, it was necessary to have three or more studies reporting the adverse effect, since only three isolated randomized clinical trials allowed identification of adverse effects with conventional statistical methods.

This finding is consistent with previous systematic reviews. However in our review it was possible to detect a greater number of adverse events related to botulinum toxin type A. This could only be achieved by performing an explicit analysis of studies with individuals diagnosed with cerebral palsy who receive high doses of toxin. Moreover, patients included in these studies are generally children. The inclusion of studies with indications for conditions that are more common among adults does not permit adequate assessment of the safety profile. For instance, in Naumann and Jankovic's meta-analysis⁶ only 25% of the studies included children with cerebral palsy. The other therapeutic indications were dystonia and movement disorders (25%, total dose range: 50–300), gastrointestinal and urologic disorders (19.44%, total dose range: 20–100), hyperhidrosis (8.33%, total dose range: 6–50), pain or headache (13.89%, total dose range: 25–200), and cosmetic (8.34%, total dose range: 6–20).⁶ Note that some indications are only present among adults, who have a higher body weight–dose ratio than children.

The occurrence of two deaths in the randomized clinical trial conducted by Graham *et al.*⁴² suggests that under specific conditions severe adverse effects could occur. According to the authors, autopsy findings suggested that these deaths resulted from asphyxiation related to epilepsy. Nevertheless, deaths related to the toxin use have been previously reported in the scientific literature. For instance, a review of serious adverse effects reported to the FDA (December 1989 to May 2003) includes 28 deaths related to therapeutic

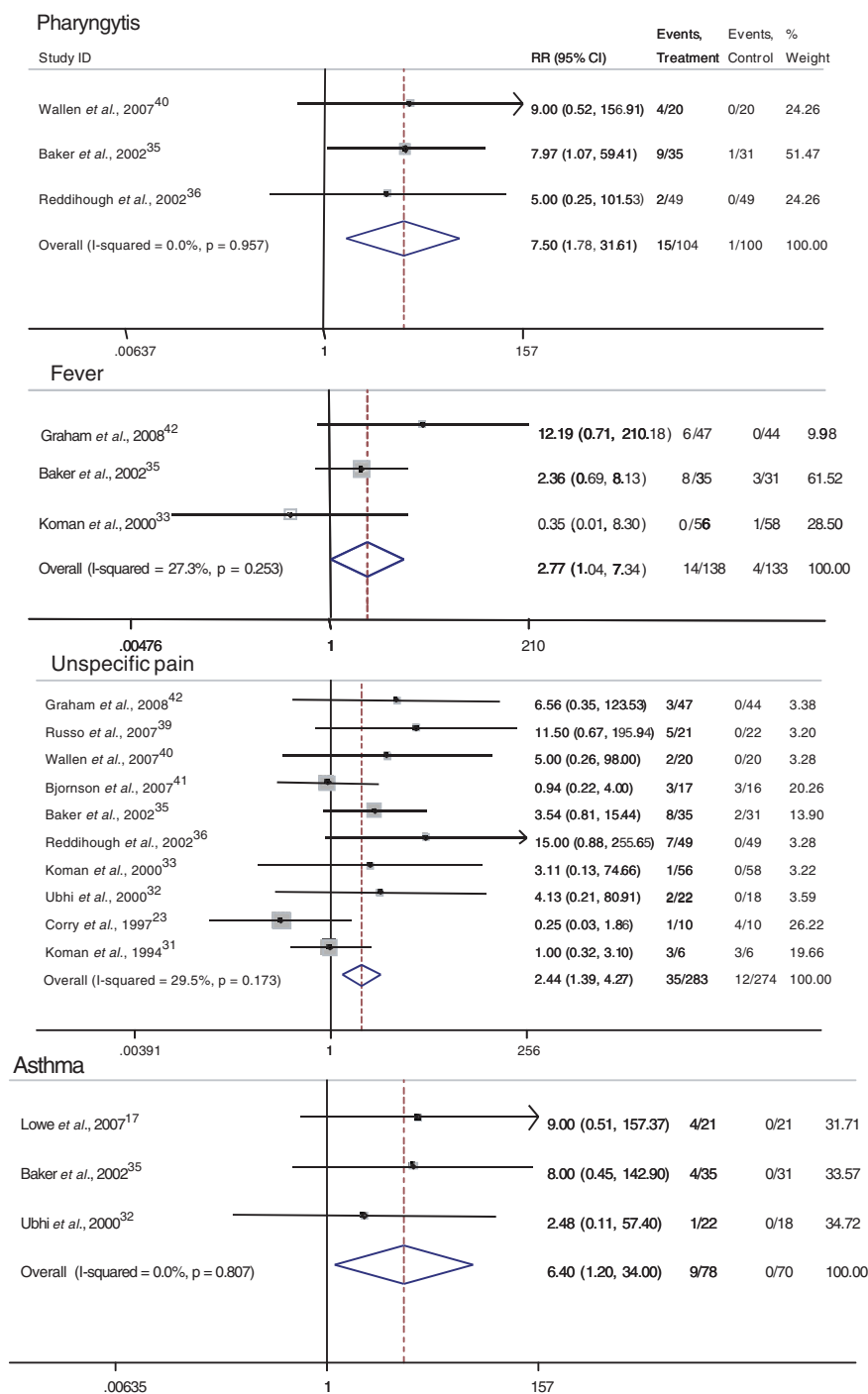


Figure 2 Adverse effects described in two or more randomized clinical trials.

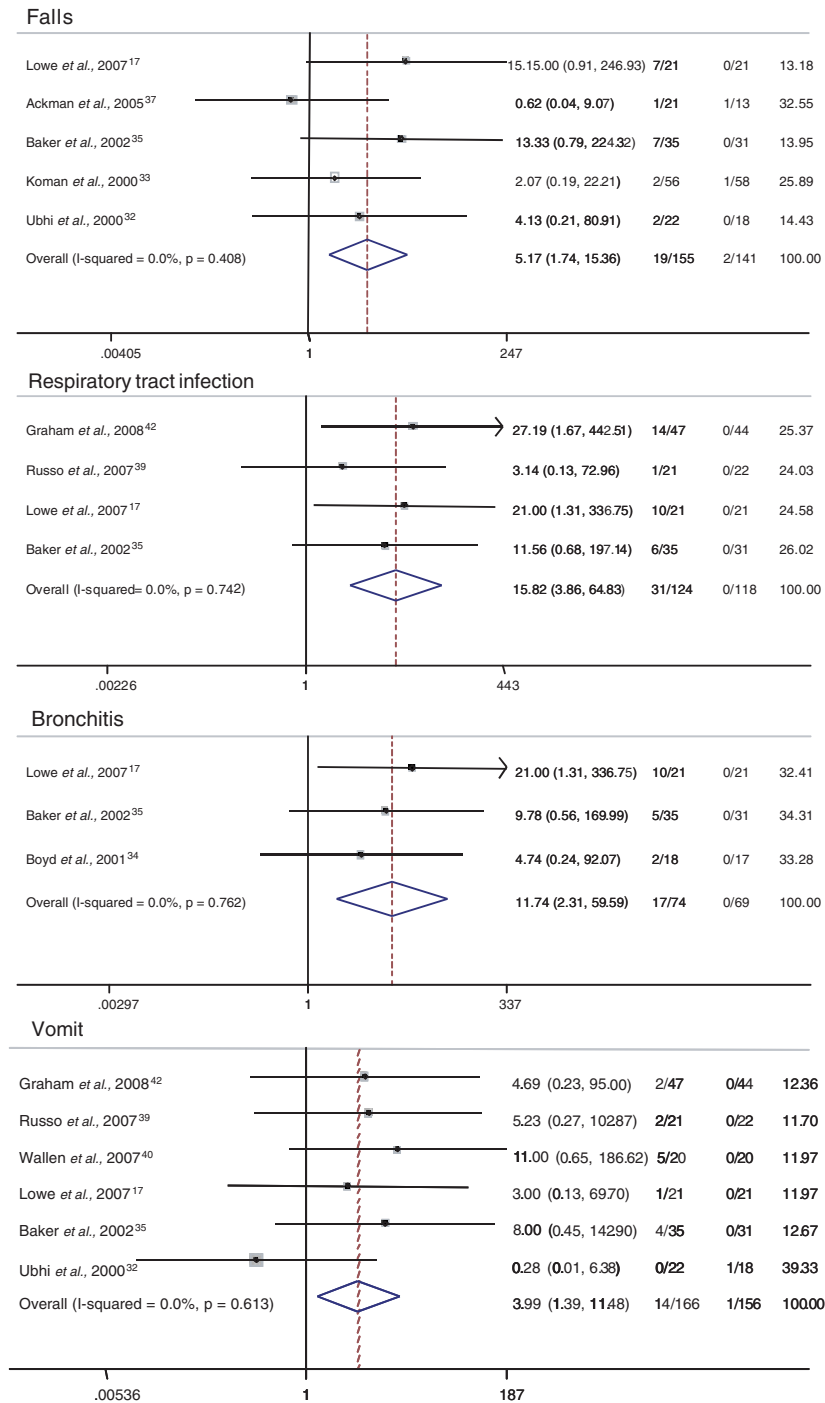


Figure 2 Continued.

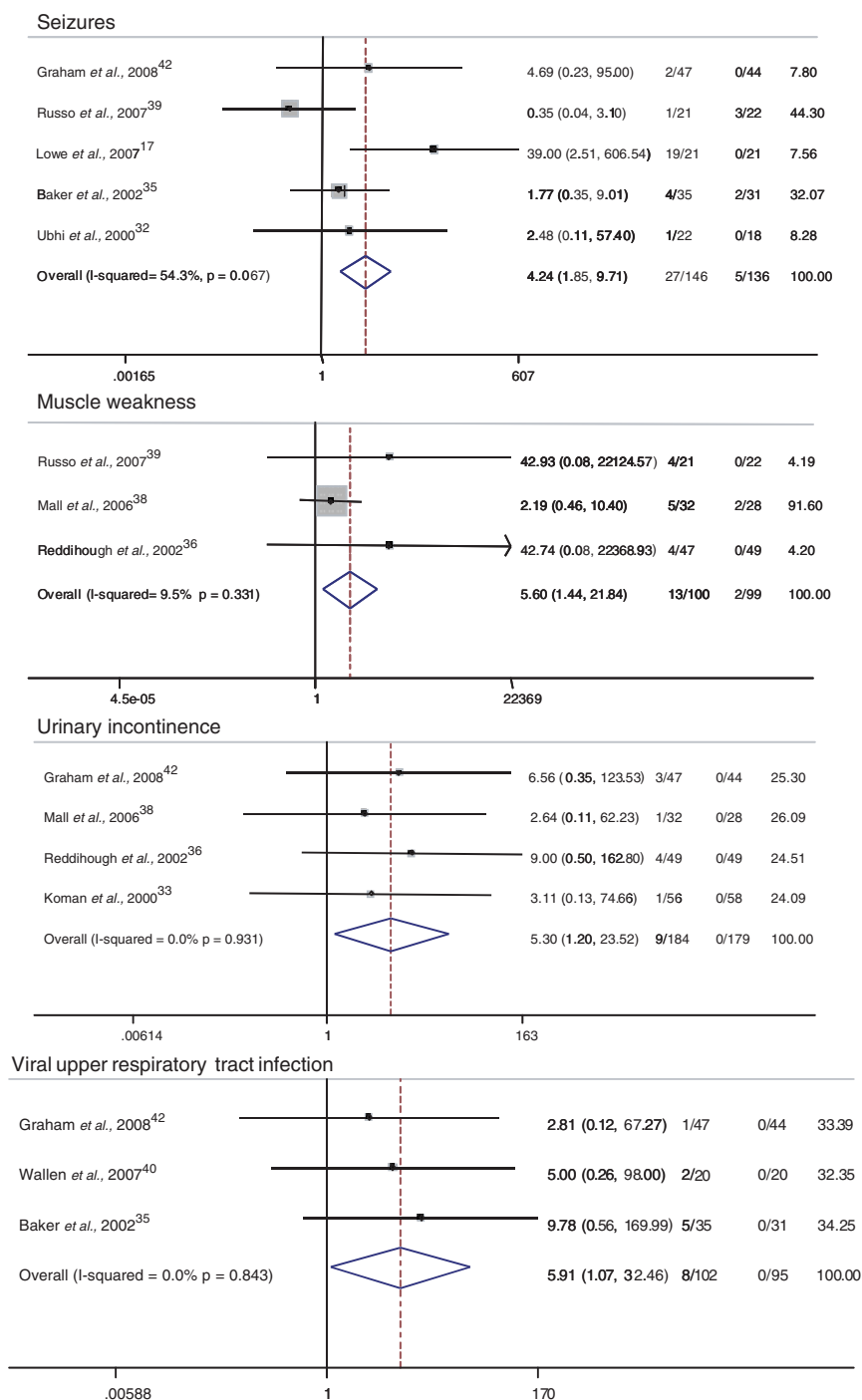


Figure 2 Continued.

Table 2 Mild and moderate adverse effects described exclusively in a single randomized clinical trial

Adverse effect	Author, year	Toxin	Control	k	RR	95% CI	
Malaise	Koman <i>et al.</i> , 1994 ³¹	0/6	2/6	0.5	0.20	0.01	3.46
				0.1	0.05	0.00	24.55
Inflammation	Corry <i>et al.</i> , 1997 ²³	0/10	2/10	0.5	0.20	0.01	3.71
				0.1	0.05	0.00	25.52
Callus in feet	Koman <i>et al.</i> , 2000 ³³	1/56	0/58	0.5	3.11	0.13	74.66
				0.1	11.39	0.02	7302.89
Knee pain	Koman <i>et al.</i> , 2000 ³³	0/56	1/58	0.5	0.35	0.01	8.30
				0.1	0.09	0.00	60.35
Leg pain	Koman <i>et al.</i> , 2000 ³³	1/56	0/58	0.5	3.11	0.13	74.66
				0.1	11.39	0.02	7302.89
Asthenia	Baker <i>et al.</i> , 2002 ³⁵	4/35	0/31	0.5	8.00	0.44	142.89
				0.1	36.34	0.07	1.9 × 10 ⁴
Chills	Baker <i>et al.</i> , 2002 ³⁵	3/35	1/31	–	2.66	0.29	24.24
Somnolence	Baker <i>et al.</i> , 2002 ³⁵	2/35	0/31	0.5	4.44	0.22	89.16
				0.1	18.61	0.03	1.0 × 10 ⁴
Pollakiuria	Mall <i>et al.</i> , 2006 ³⁸	1/32	0/28	0.5	2.63	0.11	62.23
				0.1	9.63	0.02	6118.26
Fainting	Russo <i>et al.</i> , 2007 ³⁹	1/21	0/22	0.5	3.14	0.14	72.96
				0.1	11.52	0.02	7259.86
Unspecified hospitalization	Russo <i>et al.</i> , 2007 ³⁹	0/21	3/22	0.5	0.15	0.01	2.73
				0.1	0.03	0.00	17.83
Depression	Russo <i>et al.</i> , 2007 ³⁹	2/21	0/22	0.5	5.23	0.27	102.87
				0.1	21.99	0.04	1.2 × 10 ⁴
Death	Graham <i>et al.</i> , 2008 ⁴²	2/47	0/44	0.5	4.69	0.23	95.00
				0.1	19.67	0.04	1.1 × 10 ⁴

k, Continuity correction factors; RR, relative risk; 95% CI, 95% confidence interval.

use of botulinum toxin type A. Known causes of these deaths were respiratory arrest, myocardial infarction in a randomized clinical trial, cerebrovascular accident, pulmonary embolism and pneumonia. All these occurred between 1 hour and 120 days after toxin injection.⁴⁹ The direct cause of a death report related to botulinum toxin type A was shown to be anaphylaxis,⁵⁰ and one death was attributable to herpes simplex encephalopathy in a large prospective study ($n=207$) with four-year follow-up.²¹ Why were no deaths observed in previous randomized clinical trials? We believe that the answer is related to the person–time follow-up. The Graham *et al.* study⁴² has the highest person–time follow-up (see Figure 3), thus explaining perhaps why two deaths were observed. A similar discussion is possible with the Lowe *et al.* study,¹⁷ where convulsions are reported but the authors state that ‘none were considered to be related to botulinum toxin type A’.¹⁷ Regarding the safety of botulinum toxin type A, we think that the deaths reported in the

randomized clinical trial should be contextualized within the previous severe cases reported,^{49,50} and not only assessed with statistical methods. The consequence is that we doubt the innocuousness of botulinum toxin type A.

From an epidemiologic perspective findings obtained in the randomized clinical trials fulfil more causal criteria than the FDA registries of adverse effects. With this premise, the two deaths were related the toxin, but the study authors indicate that, based on autopsy results, the deaths were not related. A very important dilemma emerges from these inconsistent results: Are pathology results sufficient to define causality? Are autopsy findings more relevant than results of a randomized clinical trial? These questions do not have an unequivocal answer and they merit further debate. If we accept that pathology defines causality, we are adopting a ‘naturalist’ theory to disease. This is characterized by the assumption of an objective and value-free approach to health-disease phenomena.⁵¹

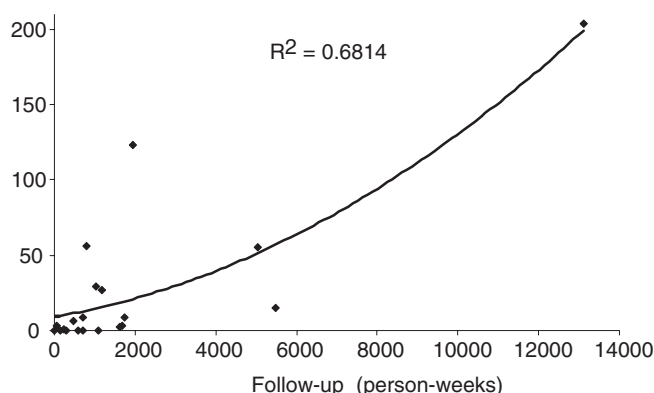


Figure 3 Total adverse effects according to follow-up of randomized clinical trials included in the meta-analysis ($n=19$). Data are approximations based on information of published papers. The study by Barwood *et al.*⁴⁶ does not report follow-up time.

However, if we accept that findings of a randomized clinical trial are valid we allow that new (previously unknown) causal determinants arise. This approach tends to follow a ‘normativist’ approach, in which contextual variables are also relevant.⁵² Moreover, the evidence-based medicine principles privilege findings from randomized clinical trials (phase III).⁵³ With this design, patient selection, treatment randomization, blinding and other characteristics are associated with internal validity and a high capacity to attribute causality.^{53,54} For this reason it is reasonable to attribute some adverse effects to the use of botulinum toxin type A.

This review has some important limitations related to the restriction to randomized clinical trials. This kind of study has a higher capacity to infer causal relationships, but may be inappropriate when: (1) patients involved in clinical studies are relatively more healthy, without comorbidity, than users in daily practice; (2) participants do not belong to particularly vulnerable groups, such as infants (<2 years old); (3) the sample size is small, thereby reducing the probability of observing rare adverse effects; (4) the duration of follow-up is short and delayed consequences may not be observed; and (5) the evaluated treatment interacts with other drugs. These characteristics are present in the randomized clinical trials included in this meta-analysis. Meanwhile, inclusion of other designs has limited capacity to infer a causal

relationship between botulinum toxin type A and adverse effects.⁵⁴ In this sense, this review could be considered a robust evaluation of botulinum toxin type A safety, which should be accompanied by the evaluation of studies with observational designs. Moreover, only a fraction of randomized clinical trials adequately reported adverse effects (14 of 20 in this systematic review). Safety topics tend to have little relevance in studies that explore efficacy. For this reason we think that the findings reported here are underestimated. Another limitation is related to the exclusion of two randomized clinical trials written in Polish and Serbian.^{24,25} We were unable to assess whether these studies fulfilled our inclusion criteria, but the abstracts do not report adverse effects. The first study included 67 individuals (follow-up time: 12 months) and the second 16 patients (follow-up time: 16 weeks) with cerebral palsy. With these characteristics, we think that the impact on our estimators is not significant.

In summary, the limited yet robust evidence available suggests that botulinum toxin type A has a good short-term safety profile. However, the two deaths reported by Graham *et al.*⁴² invite us to better select the potential patients who could use botulinum toxin type A.

Comorbidity requires special attention. Some evidence suggests that subjects with epilepsy^{23,32} or immunological disorders such as HIV infection,⁵⁵ should not be exposed to high doses of

botulinum toxin type A. Additional analysis of data from national and international adverse drug reaction monitoring centres are required to enhance our understanding of this topic. Further use of botulinum toxin type A should be strictly monitored using specific pharmaco-epidemiological surveillance systems to prevent those doubts unresolved by this review.

Clinical messages

- Children with cerebral palsy experience a greater number of botulinum toxin type A-related adverse effects than other users.
- Respiratory tract infection, bronchitis, pharyngitis, asthma, muscle weakness, urinary incontinence, falls, seizures, fever, and unspecified pain are related to the use of botulinum toxin type A by children with cerebral palsy.
- The possible relationship between botulinum toxin type A, seizures and death requires additional study.

Author contributions

Drs Albavera-Hernández, Rodríguez and Idrovo had full access to all of the data in the study and take responsibility for the integrity and accuracy of the data analysis. AJI: Study concept and design. CAH, JMR, AJI: Acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; administrative, technical, or material support; study supervision. AJI: Statistical analysis.

Competing interests

Dr Idrovo reported receiving research support from Beaufour Ipsen, Mexico.

Funding

This study was sponsored by National Institute of Public Health in Mexico.

References

- 1 Koman LA, Paterson Smith B, Shilt JS. Cerebral palsy. *Lancet* 2004; **363**: 1619–31.
- 2 Mense S. Neurological basis for the use of botulinum toxin in pain therapy. *J Neurol* 2004; **251**(suppl 1): 1–7.
- 3 Dressler D, Hallett M. Immunological aspects of Botox®, Dysport® and Myobloc TM/Neurobloc. *Eur J Neurol* 2006; **13**(suppl 1): 11–15.
- 4 Dressler D, Benecke R. Pharmacology of therapeutic botulinum toxin preparations. *Disabil Rehabil* 2007; **29**: 1761–68.
- 5 Boyd RN, Hays RM. Current evidence for the use of botulinum toxin type A in the management of children with cerebral palsy: a systematic review. *Eur J Neurol* 2001; **8**(suppl 5): 1–20.
- 6 Naumann M, Jankovic J. Safety of botulinum toxin type A: a systematic review and meta-analysis. *Curr Med Res Opin* 2004; **20**: 981–90.
- 7 Park ES, Rha D. Botulinum toxin type A injection for management of upper limb spasticity in children with cerebral palsy: A literature review. *Yonsei Med J* 2006; **47**: 589–603.
- 8 Lannin N, Scheinberg A, Clark K. AACPDm systematic review of the effectiveness of therapy for children with cerebral palsy after botulinum toxin A injections. *Dev Med Child Neurol* 2006; **48**: 533–39.
- 9 Naumann M, Albanese A, Heinen F, Molenaers G, Relja M. Safety and efficacy of botulinum toxin type A following long-term use. *Eur J Neurol* 2006; **13**(suppl 4): 35–40.
- 10 Howell K, Selber P, Graham HK, Reddihoough D. Botulinum neurotoxin A: an unusual systemic effect. *J Paediatr Child Health* 2007; **43**: 499–501.
- 11 Feinstein AR. *Clinical epidemiology. The architecture of clinical research*. WB Saunders Company, 1985.
- 12 Ioannidis JPA, Evans SJW, Gotzsche PC *et al*. Better reporting of harms in randomized trials: An extension of the CONSORT statement. *Ann Intern Med* 2004; **141**: 781–88.
- 13 Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. *Stat Med* 1999; **18**: 2693–708.
- 14 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177–88.
- 15 Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med* 2004; **23**: 1351–75.
- 16 Rameckers EA, Speth LA, Duysens J, Vles JS, Smits-Engelsman BC. Kinematic aiming

- task: measuring functional changes in hand and arm movements after botulinum toxin-A injections in children with spastic hemiplegia. *Am J Phys Med Rehabil* 2007; **86**: 538–47.
- 17 Lowe K, Novak I, Cusick A. Repeat injection of botulinum toxin A is safe and effective for upper limb movement and function in children with cerebral palsy. *Dev Med Child Neurol* 2007; **49**: 823–29.
 - 18 Steenbeek D, Meester-Delver A, Becher JG, Lankhorst GJ. The effect of botulinum toxin type A treatment of the lower extremity on the level of functional abilities in children with cerebral palsy: Evaluation with goal attainment scaling. *Clin Rehabil* 2005; **19**: 274–82.
 - 19 Scholtes VA, Dallmeijer AJ, Knol DL *et al.* Effect of multilevel botulinum toxin a and comprehensive rehabilitation on gait in cerebral palsy. *Pediatr Neurol* 2007; **36**: 30–39.
 - 20 Kawamura A, Campbell K, Lam-Damji S, Fehlings D. A randomized controlled trial comparing botulinum toxin A dosage in the upper extremity in children with spasticity. *Dev Med Child Neurol* 2007; **49**: 331–37.
 - 21 Koman LA, Brashear A, Rosenfeld S *et al.* Botulinum toxin type A neuromuscular blockade in the treatment of equinus foot deformity in cerebral palsy: A multicenter, open-label clinical trial. *Pediatrics* 2001; **108**: 1062–71.
 - 22 Polak F, Morton R, Ward C, Wallace CA, Doderlein L, Siebel A. Double-blind comparison study of two doses of botulinum toxin A injected into calf muscles in children with hemiplegic cerebral palsy. *Dev Med Child Neurol* 2002; **44**: 551–55.
 - 23 Corry IS, Cosgrove AP, Walsh EG, McClean D, Graham HK. Botulinum toxin A in the hemiplegic upper limb: A double-blind trial. *Dev Med Child Neurol* 1997; **39**: 185–93.
 - 24 Józwiak M, Harasymczuk P, Cierniewska-Gorzela K. The use of botulinum toxin in the treatment of spastic hip joint instability in children with cerebral palsy [Article in Polish]. *Chir Narzadow Ruchu Ortop Pol* 2007; **72**: 205–09.
 - 25 Dimitrijević L, Stanković I, Zivković V, Mikov A, Colović H, Janković I. Botulinum toxin type A for the treatment of spasticity in children with cerebral palsy [Article in Serbian]. *Vojnosanit Pregl* 2007; **64**: 513–18.
 - 26 Scholtes VA, Dallmeijer AJ, Knol DL *et al.* The combined effect of lower-limb multilevel botulinum toxin type A and comprehensive rehabilitation on mobility in children with cerebral palsy: a randomized clinical trial. *Arch Phys Med Rehabil* 2006; **87**: 1551–58.
 - 27 Hazneci B, Tan AK, Guncikan MN, Dincer K, Kalyon TA. Comparison of the efficacies of botulinum toxin A and Johnstone pressure splints against hip adductor spasticity among patients with cerebral palsy: a randomized trial. *Mil Med* 2006; **171**: 653–56.
 - 28 Bottos M, Benedetti MG, Salucci P, Gasparroni V, Giannini S. Botulinum toxin with and without casting in ambulant children with spastic diplegia: a clinical and functional assessment. *Dev Med Child Neurol* 2003; **45**: 758–62.
 - 29 Flett PJ, Stern LM, Waddy H, Connell TM, Seeger JD, Gibson SK. Botulinum toxin A versus fixed cast stretching for dynamic calf tightness in cerebral palsy. *J Paediatr Child Health* 1999; **35**: 71–77.
 - 30 Fehlings D, Rang M, Glazier J, Steele C. An evaluation of botulinum toxin A injection to improve upper extremity function in children with hemiplegic cerebral palsy. *J Pediatr* 2000; **137**: 331–37.
 - 31 Koman LA, Mooney III JF, Smith BP, Goodman A. Management of cerebral palsy with botulinum toxin A: Report of a preliminary randomised, double blind trial. *J Pediatr Orthop* 1994; **14**: 299–303.
 - 32 Ubhi T, Bhakta BB, Ives HL, Allgar V, Roussounis SH. Randomised double blind placebo controlled trial of the effect of botulinum on walking in cerebral palsy. *Arch Dis Child* 2000; **83**: 481–87.
 - 33 Koman LA, Mooney III JF, Smith BP, Walker F, Leon JM. Botulinum toxin type A neuromuscular blockade in the treatment of lower extremity spasticity in cerebral palsy: A randomized, double-blind, placebo-controlled trial. *J Pediatr Orthop* 2000; **20**: 108–15.
 - 34 Boyd RN, Dobson F, Parrott J *et al.* The effect of botulinum toxin type A and a variable hip abduction orthosis on gross motor function: a randomized controlled trial. *Eur J Neurol* 2001; **8**(suppl. 5): 109–19.
 - 35 Baker R, Jasinski M, Maciag-Tymecka I *et al.* Botulinum toxin treatment of spasticity in diplegic cerebral palsy: A randomized, double-blind, placebo-controlled, dose-ranging study. *Dev Med Child Neurol* 2002; **44**: 666–75.
 - 36 Reddihough DS, King JA, Coleman GJ *et al.* Functional outcome of botulinum toxin A injections to the lower limbs in cerebral palsy. *Dev Med Child Neurol* 2002; **44**: 820–27.
 - 37 Ackman JD, Russman BS, Thomas SS *et al.* Comparing botulinum toxin A with casting for treatment of dynamic equinus in children with

- cerebral palsy. *Dev Med Child Neurol* 2005; **47**: 620–27.
- 38 Mall V, Heinen F, Siebel A *et al.* Treatment of adductor spasticity with botulinum toxin type A in children with cerebral palsy: a randomized, double-blind, placebo-controlled study. *Dev Med Child Neurol* 2006; **48**: 10–13.
- 39 Russo RN, Crotty M, Miller MD, Murchland S, Flett P, Haan E. Upper-limb botulinum toxin A injection and occupational therapy in children with hemiplegic cerebral palsy identified from a population register: a single-blind, randomized, controlled trial. *Pediatrics* 2007; **119**: e1149–58.
- 40 Wallen M, O'Flaherty SJ, Waugh MCA. Functional outcomes of intramuscular cerebral palsy: a randomized controlled trial. *Arch Phys Med Rehabil* 2007; **88**: 1–10.
- 41 Bjornson K, Hays R, Graubert C *et al.* Botulinum toxin for spasticity in children with cerebral palsy: a comprehensive evaluation. *Pediatrics* 2007; **120**: 49–58.
- 42 Graham HK, Boyd R, Carlin JB *et al.* Does botulinum toxin A combined with bracing prevent hip displacement in children with cerebral palsy and 'hips at risk'? *J Bone Joint Surg Am* 2008; **90**: 23–33.
- 43 Sutherland DH, Kaufman KR, Wyatt MP, Chambers HG, Mubarak SJ. Double blind study of botulinum A toxin injections into the gastrocnemius muscle in patients with cerebral palsy. *Gait Posture* 1999; **10**: 1–9.
- 44 Love SC, Valentineb JP, Blair EM, Price CJ, Cole JH, Chauvel PJ. The effect of botulinum toxin type A on the functional ability of the child with spastic hemiplegia a randomized controlled trial. *Eur J Neurol* 2001; **8**(suppl 5): 50–58.
- 45 Detrembleur C, Lejeune TM, Renders A, Van den Bergh PYK. Botulinum toxin and short-term electrical stimulation in the treatment of equinus in cerebral palsy. *Mov Disord* 2002; **17**: 162–69.
- 46 Barwood S, Baillieu C, Boyd R *et al.* Analgesic effects of botulinum toxin A: a randomized, placebo controlled clinical trial. *Dev Med Child Neurol* 2000; **42**: 116–21.
- 47 Kay RM, Rethlefsen SA, Fern-Buneo A, Wren TAL, Skaggs DL. Botulinum toxin as an adjunct to serial casting treatment in children with cerebral palsy. *J Bone Joint Surg* 2004; **86A**: 2377–84.
- 48 Speth LAWM, Leffers P, Janssen-Potten YJM, Vles JSH. Botulinum toxin A and upper limb functional skills in hemiparetic cerebral palsy: A randomized trial in children receiving intensive therapy. *Dev Med Child Neurol* 2005; **47**: 468–73.
- 49 Coté TR, Mohan AK, Polder JA, Walton MK, Braun MM. Botulinum toxin type A injections: adverse events reported to the US Food and Drug Administration in therapeutic and cosmetic cases. *J Am Acad Dermatol* 2005; **53**: 407–15.
- 50 Li M, Goldberger BA, Hopkins C. Fatal case of BOTOX-related anaphylaxis? *J Forensic Sci* 2005; **50**: 169–72.
- 51 Boorse C. Health as a theoretical concept. *Philos Sci* 1977; **44**: 542–73.
- 52 Khushf G. An agenda for future debate on concepts of health and disease. *Med Health Care Philos* 2007; **10**: 19–27.
- 53 Worrall J. Evidence in medicine and evidence-based medicine. *Philosophy Compass* 2007; **2**: 981–1022.
- 54 Stricker BH, Psaty BM. Detection, verification, and quantification of adverse drug reactions. *BMJ* 2004; **329**: 44–47.
- 55 Noguera-Julian A, Pérez-Dueñas B, Fortuny-Guasch C, López-Casas J, Póo P. Evolución y tratamiento de la encefalopatía subaguda progresiva por virus de inmunodeficiencia humana en el niño. Utilidad de la toxina botulínica. *Rev Neurol* 2004; **38**: 239–43.