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To cite this article: Markus Naumann & Joseph Jankovic (2004) Safety of botulinum toxin type A: a systematic review and meta-analysis, Current Medical Research and Opinion, 20:7, 981-990, DOI: [10.1185/030079904125003962](https://doi.org/10.1185/030079904125003962)

To link to this article: <http://dx.doi.org/10.1185/030079904125003962>



Published online: 12 May 2004.



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REVIEW

Safety of botulinum toxin type A: a systematic review and meta-analysis

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Key words: Adverse events – Botulinum toxin type A – Randomized controlled trials – Safety – Systematic review – Tolerability

SUMMARY

Objective: To define quantitatively the safety and tolerability profile of botulinum toxin type A (BTX-A) across all common therapeutic indications. The review was limited to the evaluation of the safety profile of one preparation of BTX-A (BOTOX®) because distinct formulations of BTX-A are associated with different clinical profiles, requiring separate consideration for an analysis of safety.

Research design and methods: We identified randomized controlled trials of BTX-A through searches of the MEDLINE, EMBASE, and Cochrane Controlled Trial databases for the years 1966–2003. Studies were double-blind, randomized, crossover, or of parallel group design. The search strategy included the terms 'botulinum toxin', 'therapeutic use', 'randomized controlled trial', 'controlled clinical trial', 'randomized clinical trial', and 'placebo controlled trial'. Only randomized controlled trials of at least 7 days duration that reported adverse events were included in the analysis.

Main outcome measure: Safety was assessed by means of a meta-analysis of the number and frequency of adverse events.

Results: Thirty-six studies involving 2309 subjects met the inclusion criteria. These reported on 1425 subjects receiving BTX-A treatment. No study reported any severe adverse events. The meta-analysis of any mild to moderate adverse events showed a rate of roughly 25% in the BTX-A-treated group (353/1425 patients) compared with 15% in the control group (133/884 patients, $p < 0.001$). Focal weakness was the only adverse event that occurred significantly more often with BTX-A treatment than control.

Conclusion: The results of this meta-analysis and experience from long-term, open-label investigations demonstrate that the formulation of BTX-A evaluated here has a favorable safety and tolerability profile across a broad spectrum of therapeutic uses.

Introduction

Botulinum toxin type A (BTX-A) is used therapeutically in a vast array of clinical disorders¹⁻³. The therapeutic effects of BTX-A occur through temporary chemodenervation caused by injection into the local

target muscle or skin. This minimizes the likelihood of systemic effects. BTX-A has been subjected to rigorous clinical evaluation in numerous randomized, controlled trials and open-label studies across a broad range of therapeutic indications. However, there is little aggregated information regarding the overall safety and

* BOTOX is a registered trademark of Allergan, Inc. (Irvine, CA)

tolerability profile of BTX-A therapy in established and emerging therapeutic indications for BTX-A. As BTX-A becomes more widely used across a broad range of approved and non-approved uses, it is important to understand its safety and tolerability as drawn from collective clinical experience.

The objective of this systematic review was to define quantitatively the safety and tolerability profile of BTX-A as reported in the clinical setting for approved and unapproved uses. This evaluation was limited to the safety and tolerability profile of BTX-A; therefore, clinical efficacy, the burden of disease, prevalence, epidemiology, cost, and other variables that are not specifically related to safety were not included in the study selection, data extraction, and assessment.

Methods

Distinct formulations of BTX-A are associated with different profiles^{4,5}. For this reason, this review was limited to the evaluation of BOTOX (Allergan Inc., Irvine, CA), excluding other formulations of type A toxin, such as DYSPORT (Ipsen Ltd, Slough, UK). In addition, we excluded studies that used formulations of BOTOX created prior to the imposition of strict manufacturing standards by the US Food and Drug Administration (FDA). Thus, only studies that used BOTOX sourced from Allergan, Inc (Irvine, CA) were included. Inclusion of studies in this systematic review and meta-analysis was based on study design, participants, interventions, and outcome measures as described below. We did not include type B botulinum toxin in this analysis.

Study Selection

This review included data from randomized, controlled trials using either placebo or an active comparator. Studies were either double-blind, randomized, crossover, or parallel group in design, and met the criteria for Class I or Class II evidence⁶. For this review, patients of all ages, either naive or not to BTX-A, were considered. Any concomitant therapies were accepted, except when noted as exclusion criteria in individual studies. This review considered BTX-A or placebo interventions. In some of the therapeutic areas, alternative active comparators were considered. For example, comparison with serial casting was considered an acceptable control treatment for spasticity studies. For studies of anal fissure, topical creams were considered acceptable as the comparator therapy. BTX-A was only administered as an injection. Results of the

intent to treat population are presented. Many of these applications are not licensed indications for BTX-A use in Europe and the US.

Search Criteria

Published studies of BTX-A were identified through searches of the MEDLINE, EMBASE, and Cochrane Controlled Trial databases for the years 1966–2003. The search strategy included the terms 'botulinum toxin', 'therapeutic use', 'randomized controlled trial', 'controlled clinical trial', 'double-blind trial', 'randomized clinical trial', and 'placebo controlled trial'.

Expanded search terms (MeSH terms):

- Botulinum toxins
- Botulinum toxin type A
- Botulin\$.tw
- Botox.tw
- Or/1-5
- Botulinum toxin type A/tu (therapeutic use)

Outcome Measures

The outcome measures for this review were the count and frequency (as shown by percentage of subjects) of adverse reactions and complications. This evaluation was limited to the safety profile of BTX-A; therefore, clinical efficacy, the burden of disease, prevalence, epidemiology, cost, and other variables not specifically related to safety were not included in the study selection, data extraction, and assessment. This review did not consider any measures of efficacy because the range in therapeutic indications and efficacy outcome variables was so diverse.

Studies were grouped according to the following therapeutic areas or indications: dystonias/movement disorders, which included torticollis, cervical dystonia, essential tremor, writer's cramp, tic disorders, and miscellaneous movement disorders; cosmetic use; gastrointestinal tract (achalasia, anal fissure) and urological (detrusor hyper-reflexia) disorders; glandular (hyperhidrosis) disorders; low back pain and headache; and spasticity/cerebral palsy, including spasticity after stroke.

Data extraction and synthesis

Characteristics of included studies and safety/adverse event outcomes were extracted and entered into Review Manager (RevMan) version 4.1, the software developed by the Cochrane Collaboration for performing meta-

Table 1. Included studies

Therapeutic indication	Total dose range (U)*	Controls used	Number of studies	BOTOX (N)	Control (N)	Total (N)
Dystonia/movement disorders	50–300	Saline or vehicle	9	214	169	383
GI/urology	20–100	Saline. Nitroglycerine ointment was used in 1 anal fissure study	7	106	99	205
Glandular (hyperhidrosis)	6–50	Saline or vehicle	3	262	106	368
Pain/headache	25–200	Saline or vehicle	5	136	100	236
Spasticity/cerebral palsy†	25–280	Saline, vehicle or serial casting	9	245	229	474
Cosmetic	6–20	Saline or vehicle	3	464	191	655
<i>Totals</i>			36	1427	894	2321

*Total dose was not reported in all studies

†For studies in young children with cerebral palsy a dose per kilogram was reported. This ranged from 2.8 to 16 U/kg

analyses⁷. Studies were pooled, and the pooled data were analyzed. Dichotomous data were used to calculate risk difference estimates with 95% confidence intervals (CI) using a random-effects model⁸. The number-needed-to-harm (NNH) was derived from the analysis. This was done for total mild to moderate adverse events and for several of the most commonly occurring individual adverse events reported in the included studies. Studies were weighted according to the reciprocal of their variance (calculated as the square of the standard error given in the individual studies). For the studies in which no adverse events were reported in either the BOTOX or placebo treatment groups, non-zero approximations of zero were used by the RevMan software.

Results

The initial search identified 186 relevant published papers. Initial review of these papers excluded 33 papers that were not research reports. The remaining 153 published papers were screened for the following inclusion criteria:

- Controlled trials of BTX-A
- Inclusion of placebo or other control group for comparison
- Reporting of safety and adverse event data

Based on the above inclusion/exclusion criteria, 65 papers were excluded:

- 22 review articles or subgroup analyses
- 21 papers on nonrandomized, controlled trials
- 4 papers on botulinum toxin type B
- 18 papers that concerned studies in which all groups were treated with botulinum toxin: studies comparing doses, preparations, and injection sites

Of the remaining 88 studies, 52 were excluded because the studies did not report adverse events, or the studies used BTX-A formulations other than BOTOX.

Thirty-six studies met all of the study design and methodological quality criteria for inclusion in the analysis^{9–44}.

The characteristics of the 36 studies included in the analysis are shown in Table 1. In total, 2309 subjects in 36 studies were analyzed. Of these, 1425 patients received BTX-A and 884 patients received placebo. None of the included studies reported any treatment-related severe adverse events (as defined by the original investigators). The frequency of any mild to moderate adverse events (as defined by the original investigators) was significantly greater in the BTX-A-treated group compared with the control group (Figure 1): 353/1425 (24.7%) BTX-A-treated patients versus 133/884 (15.0%) in the control group ($p < 0.001$). The adjusted, weighted-risk difference between BTX-A and control was 9%, indicating that the NNH is approximately 11.

Comparisons of specific adverse events in the BTX-A and control groups are shown in Figures 2–7. As expected, focal weakness was reported with significantly greater frequency by the BTX-A-treated patients suffering from blepharospasm and cervical dystonia compared with controls (Figure 2). There were no significant differences in the frequency of pain or reaction at the injection site between the BTX-A and control groups (Figure 3). The frequency of headache was not significantly different between the two groups (Figure 4). The frequency of back pain, neck pain, or soreness as adverse events was also not significantly different between the BTX-A and control groups (Figure 5). Furthermore, there was no significant difference in the incidence of ptosis between treated and control groups (Figure 6). Finally, there was no significant difference between BTX-A and control groups in the occurrence of ‘other’ adverse events (Figure 7). None of the included studies reported the occurrence of any systemic adverse events.

Comparison: 01 Comparison of adverse events in Botox and control treatment groups
Outcome: 01 Total mild to moderate adverse events

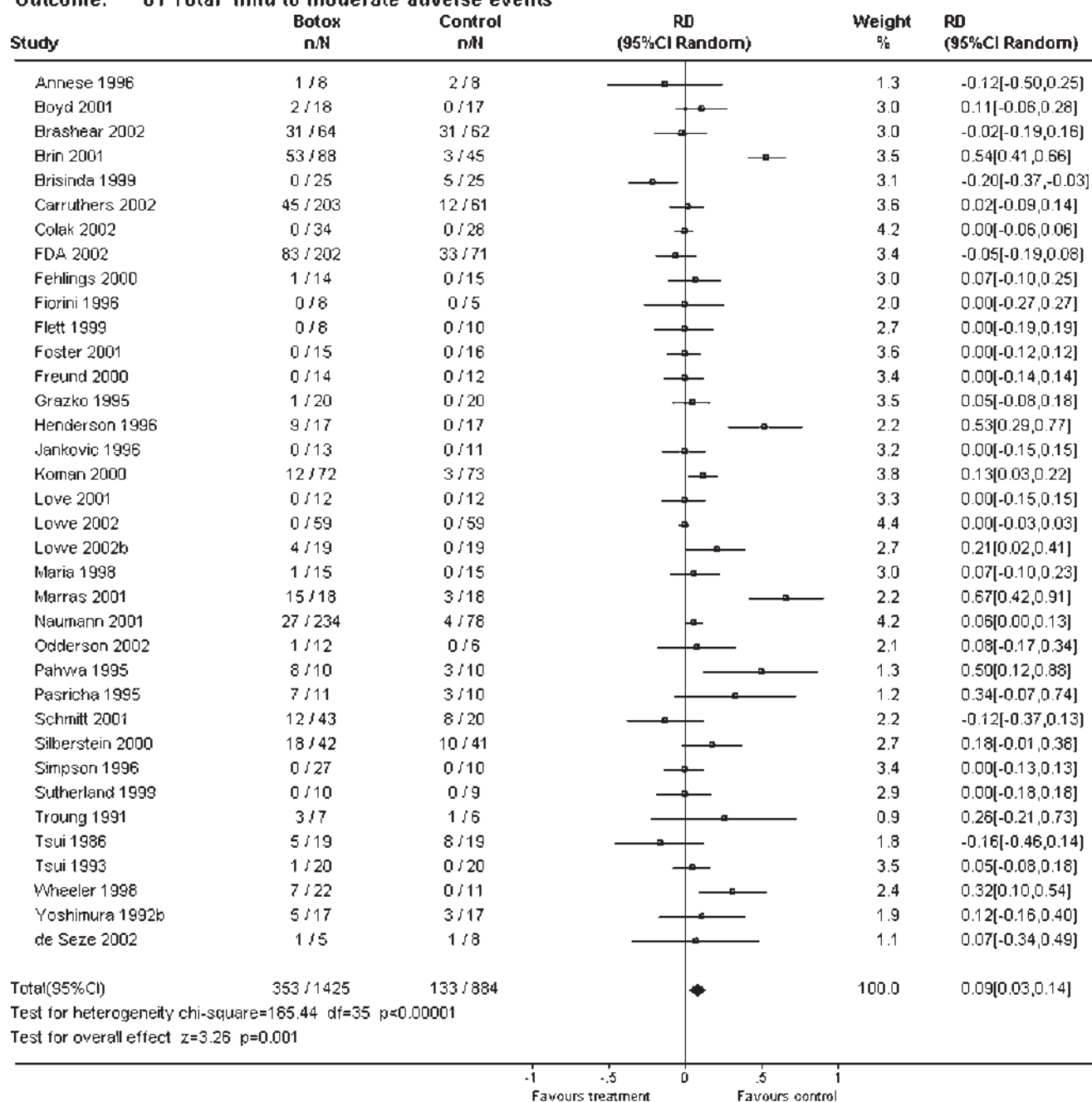


Figure 1. Analysis of all mild to moderate adverse events

Discussion

The results of this analysis of the safety of BTX-A across a wide range of therapeutic uses indicated that, overall, BTX-A is quite safe and generally well tolerated, as no serious or severe adverse events were noted. Few, if any, therapeutic agents have been evaluated in as many different therapeutic applications as BTX-A. Furthermore, to the best of our knowledge, no systematic review has ever assessed the aggregate safety or efficacy of a single agent applied to comparably diverse uses – ranging from elective cosmetic indications

to serious, disabling conditions such as achalasia or cerebral palsy. Accordingly, the perceptions of patients about side effects and the willingness of patients and physicians to tolerate these side effects relative to the perceived or actual benefits of therapy are likely to vary substantially across the range of therapeutic uses included in our analysis.

Virtually no systemic adverse events were reported in any of the studies included in this analysis. It is possible that low frequency and mild systemic AEs were reported numerically within a given study but captured as ‘other’. There have been no published reports of anaphylaxis or

Comparison: 01 Comparison of adverse events in Botox and control treatment groups
Outcome: 02 Focal weakness

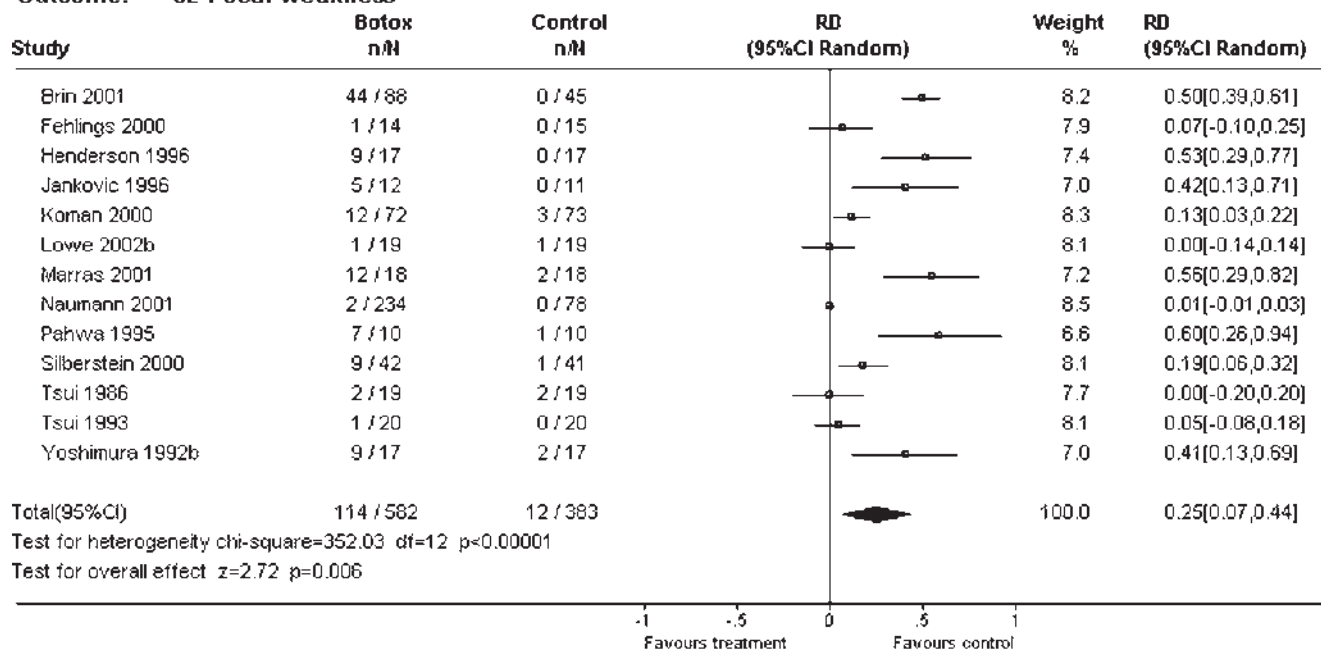


Figure 2. Analysis of focal weakness

Comparison: 01 Comparison of adverse events in Botox and control treatment groups
Outcome: 03 Injections site pain or reaction

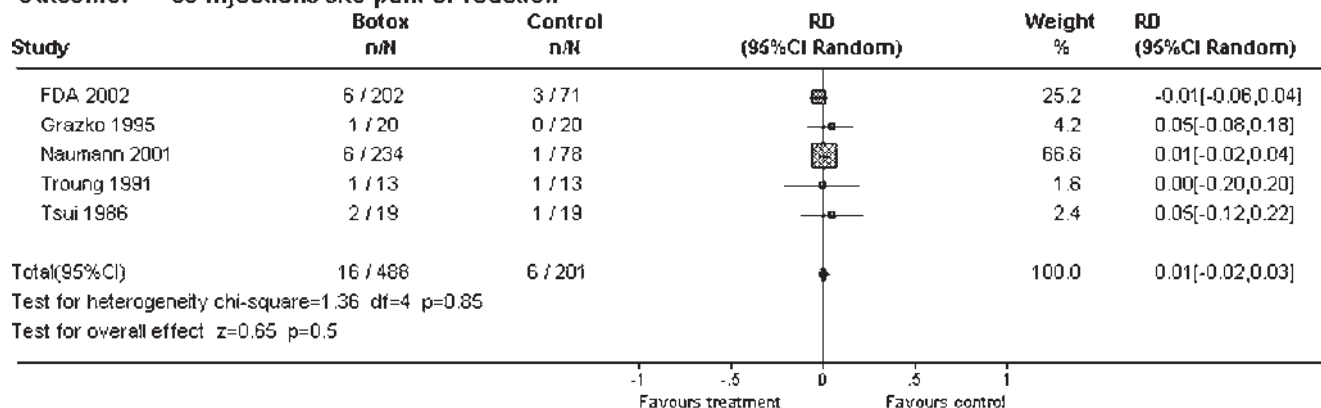


Figure 3. Analysis of pain or reaction at injection site

Comparison: 01 Comparison of adverse events in Botox and control treatment groups
Outcome: 05 Headache

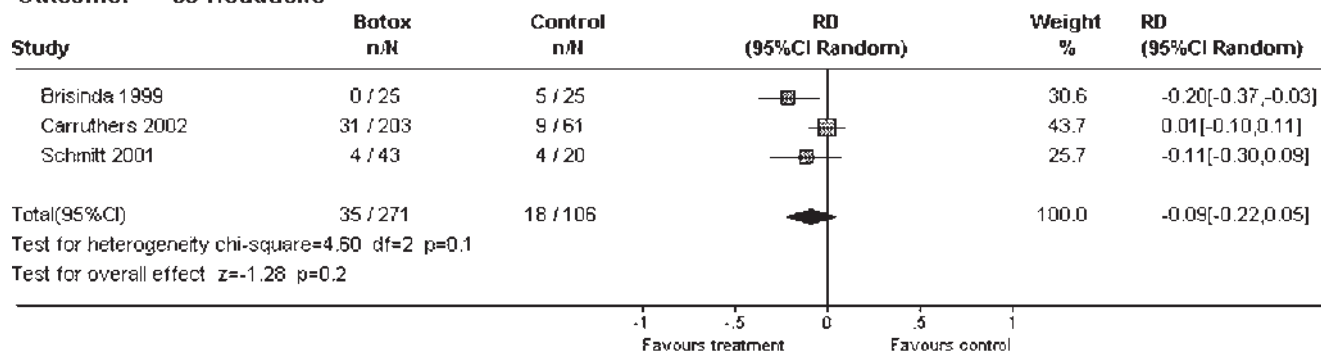


Figure 4. Analysis of headache

Comparison: 01 Comparison of adverse events in Botox and control treatment groups

Outcome: 06 Back or neck pain

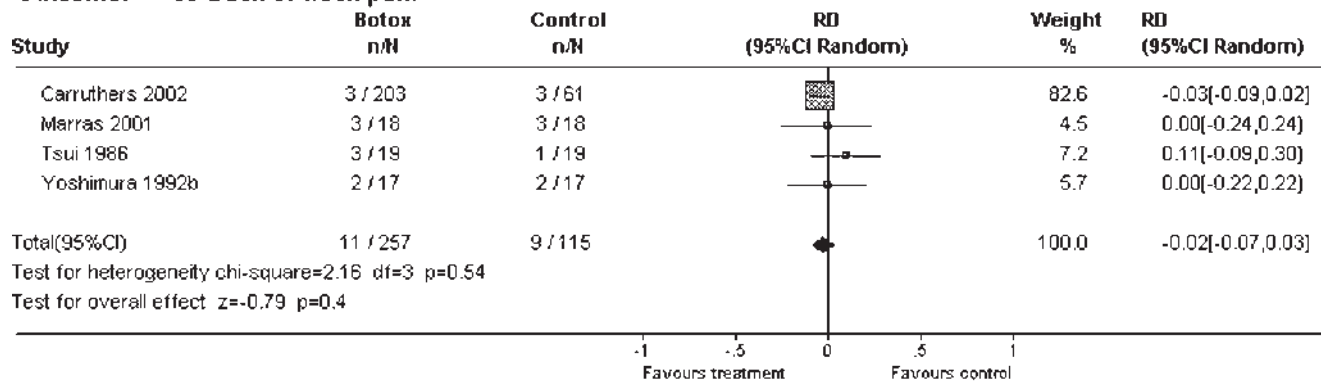


Figure 5. Analysis of back or neck pain or soreness

Comparison: 01 Comparison of adverse events in Botox and control treatment groups

Outcome: 07 Ptosis

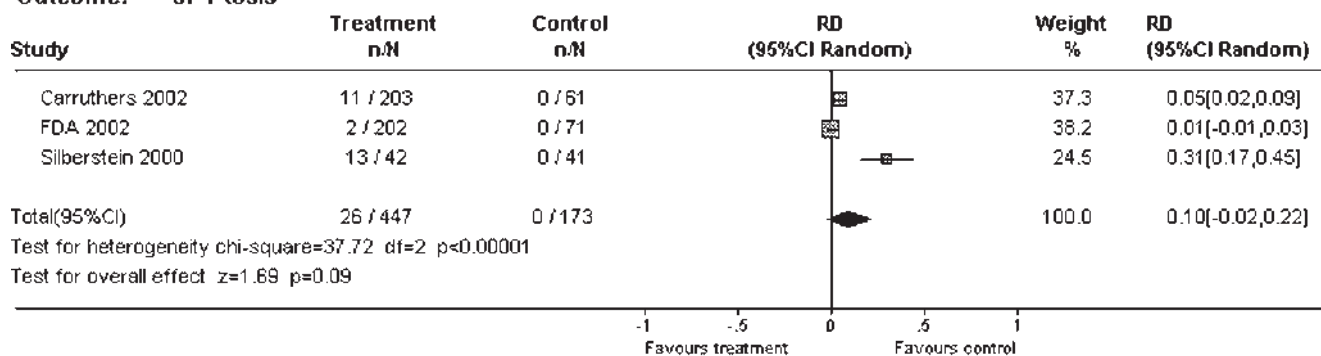


Figure 6. Analysis of ptosis

Comparison: 01 Comparison of adverse events in Botox and control treatment groups

Outcome: 04 Other

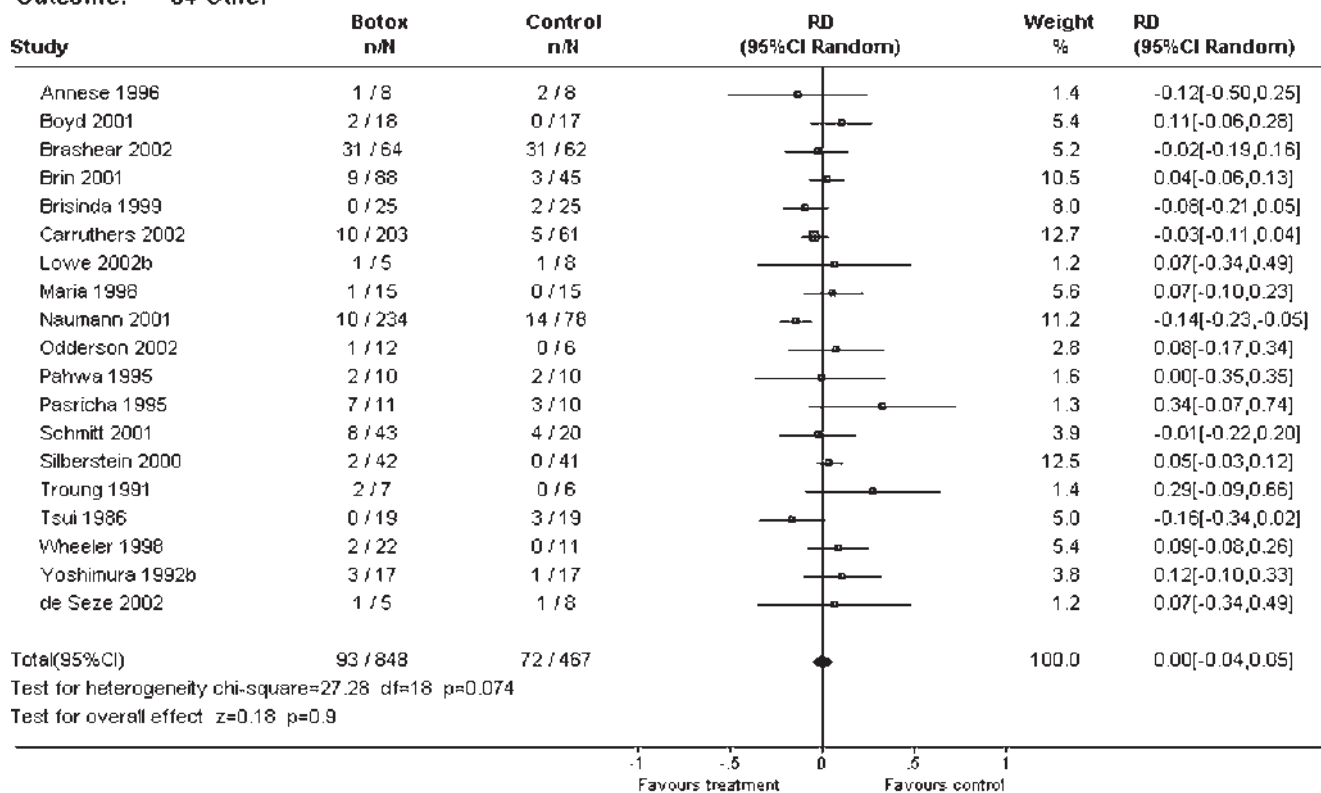


Figure 7. Analysis of other adverse events

other rare but serious systemic adverse events associated with BTX-A treatment, suggesting that the findings from the meta-analysis reflect clinical experience. The greater overall prevalence of any reported adverse event in BTX-A-treated patients compared with control patients appeared to be attributable to the greater frequency of focal weakness in BTX-A-treated patients.

Focal Adverse Events Associated with Treatment

Focal weakness is an expected effect of BTX-A treatment that is very much a function of the mechanism of action of neurotoxin therapy. Indeed, in some of its therapeutic applications, local muscle weakness is either the desired outcome of treatment or the way in which the therapeutic benefit is achieved. However, depending on the site of injection and the particular therapeutic use, focal weakness may be considered an undesirable adverse event. In particular, the highest frequency of focal weakness occurred in the studies in which BTX-A was used to treat essential tremors, especially hand tremor^{14,29}. Functional impairment due to focal weakness appears to be dose-dependent¹⁴, and this transient focal weakness is more likely to be perceived as troublesome when it occurs in the hands compared with other sites of the body in which fine motor function would not be noticeably affected. It is important to note, also, that Jankovic *et al.* reported that although finger weakness was noted by 40–50% of BTX-A-treated patients, none of the patients perceived the weakness as interfering with their functioning or activities of daily living, nor did any of the patients cite weakness as a reason for not continuing in the open-label continuation of the study²⁹. Lastly, all of the essential tremor studies concluded that focal weakness may be able to be reduced by optimizing the dose, distributing doses over the sites injected, and using proper injection techniques while preserving the tremorolytic benefits of therapy. Indeed, Jankovic and other investigators no longer inject the finger extensor muscles in patients with essential tremor.

Ptosis is the clinical manifestation of focal weakness in the management of blepharospasm, headache, glabellar lines, and other conditions requiring peri-orbital injections. Several studies have shown transient ptosis occurs in 8.4–13.4% of patients treated with BTX-A for blepharospasm^{45–47}. However, pre-tarsal injections have been shown to decrease the frequency of ptosis in blepharospasm treatment^{48,49}.

Safety and Tolerability of Other Commonly Used Agents

It is helpful to consider the results of this analysis of BTX-A adverse events in the context of the safety profiles of

other commonly used therapeutic agents. For example, as a benchmark of safety, one can consider the rate of adverse events caused by a commonly used class of drugs, the non-steroidal anti-inflammatory drugs (NSAIDs)^{50,51}. It is well established that NSAIDs cause ulcer and other gastrointestinal injuries. For gastric ulcers alone, NSAID use increases the average risk of developing them above that of controls by 3.6 and 6.8% with < 2 weeks and > 4 weeks of use, respectively. Using these estimates, the NNH to produce 1 gastric ulcer is 28 and 13 for < 2 weeks or > 4 weeks, respectively^{50,51}. The NNH is a reflection of the safety of treatment, compared with that of control, and it indicates the number of people who would have to be treated in order for one person to be harmed (by adverse events).

In our analysis of BTX-A, there were no serious or severe adverse events reported in any of the 36 included trials. Therefore, it is not possible to calculate the NNH for adverse events of the same magnitude or intensity to contrast with those caused by NSAIDs. The NNH for any mild to moderate adverse event in our analysis of BTX-A was estimated to be roughly 11. Obviously, one needs to consider the specific nature of the adverse events as well as how frequently they occur. For example, gastric ulcer is a much more serious adverse event than temporary ptosis or focal weakness. Accordingly, it is imperative to interpret the results of safety analyses in light of the frequency of occurrence of adverse events, as well as the seriousness and clinical implications of the adverse events.

A recent systematic review of the efficacy and safety of gabapentin for the treatment of a variety of types of pain followed a similar approach to our analysis⁵². Data pooled from randomized, placebo-controlled trials in a total of 256 patients treated with gabapentin and 197 patients treated with placebo indicated that the most commonly reported adverse events were dizziness (24.6 vs 5.1% for gabapentin and placebo), somnolence (20 vs 5.6%), gastrointestinal complaints (13.2 vs 5.6%), sedation (9.3 vs 0%), ataxia (7.4 vs 0%), and peripheral edema (6.6 vs 2.0%)⁵². In contrast with the adverse events reported in our aggregate analysis, the adverse events of gabapentin are systemic and would be considered somewhat more troublesome than the intensity of the adverse events produced by BTX-A. Overall, any adverse event was reported by 54.9% of gabapentin-treated patients compared with 27.6% of placebo-treated patients in one randomized, controlled trial, and by 72% of patients in another randomized, controlled trial^{53,54}. The estimated NNH in the latter trial was 3.7⁵⁴; thus, simply on the basis of the frequency of occurrence, without regard to the seriousness of the adverse events, one might conclude that a systemic medication such as gabapentin produces adverse events with a substantial frequency.

However, it is impossible to evaluate the risks of these adverse events relative to the therapeutic benefits without considering the clinical context in which these agents are used. In addition, factors such as other available treatment options, impact on quality of life, and potential complications and costs of observed adverse events of treatment are important considerations when evaluating the overall safety and tolerability profile of a specific treatment.

Long-term Safety of BTX-A

None of the randomized, controlled trials included in our analysis assessed the long-term safety and adverse events profile of BTX-A. Data obtained from placebo-controlled trials are usually only available for relatively short-term studies, perhaps up to 2 years, whereas a considerable amount of longer-term safety data are available from prospective and retrospective surveillance evaluations, but these usually suffer from lack of a control group⁵⁵. This is particularly true for BTX-A therapy for blepharospasm and cervical dystonia, two of the most important indications for BTX-A therapy. However, information derived from uncontrolled observations of repeated BTX-A therapy over a number of years can provide some insights into the safety and tolerability of long-term BTX-A use.

Hsiung *et al.*⁵⁶ evaluated the long-term efficacy and safety of BTX-A used for a variety of different movement disorders in a retrospective analysis of 235 patients who received a total of 2616 treatment cycles over a 10-year period. The study population included patients with cervical dystonia, hemifacial spasm, and blepharospasm. It was found that 9.1% of patients had primary resistance (defined as < 25% improvement after 2–3 consecutive treatments), and 7.5% of patients developed secondary resistance over a 10-year period.

A recent study by Jankovic *et al.*⁵⁷ indicated that antibody formation with the current formulation of BOTOX was six-fold lower than that reported with an older formulation of the same product. The current BOTOX formulation contains 5 ng neurotoxin complex protein per 100 units of activity⁵⁷. This is an 80% reduction in protein from the older formulation, which contained 25 ng complex protein per 100 units of activity. The reduced protein load of increasingly refined preparations of BTX-A, therefore, appears to be associated with reduced antibody formation. Adverse events, mostly minor, were reported by 27% of patients, occurring over 4.5% of treatment cycles. At least one adverse event occurred most frequently in blepharospasm patients (61%), followed by hemifacial spasm patients (30%), and cervical dystonia patients (16%). The overall rate of 27% for any adverse event is

remarkably consistent with the overall rate of 25.2% (365/1446) for mild to moderate adverse events in BTX-A-treated patients in our analysis of adverse events in shorter-duration randomized, controlled trials.

This consistency between the observed long-term safety and tolerability in clinical practice and our more rigorous analysis of safety under controlled conditions suggests that mild adverse events are likely to persist over long-term, repeated treatment cycles. Furthermore, the greater prevalence of adverse events in patients with blepharospasm compared with cervical dystonia observed by Hsiung *et al.*⁵⁶ is not incompatible with the pattern that we noted for more frequent adverse events in hand or head tremor. This could be related to injections into relatively smaller muscles at sites that are more immediately noticeable to patients.

Tan and Jankovic reported the long-term safety and tolerability of BTX-A therapy for oromandibular dystonia in 202 patients treated for a mean of 4.4 years⁵⁸. In this study, 31.5% of patients reported at least one side effect in at least one treatment cycle over the follow-up period. This figure is better understood by considering the number of adverse events reported per treatment cycle. The overall rate of adverse events was 135 in 1213 treatment visits. Thus, 11.1% of visits were associated with a complication. Dysphagia (10.2% of visits) and dysarthria (0.9%) were the two most common problems. Generally, these adverse events were temporary, with a mean duration of symptoms of 9 days. The investigators note that this adverse event profile represents a substantial improvement over their preliminary experience, in which 49% of patients experienced adverse events, and they attributed this improvement to long-term experience and improvements in injection technique⁵⁸.

DeFazio *et al.* carried out a retrospective analysis of the safety and tolerability of BTX-A therapy in 65 patients who had received BTX-A injections for primary hemifacial spasm regularly over a period of at least 10 years⁵⁹. The overall rate of reported adverse events was 37% (24/65) during the first year of treatment and 12% (8/65) during the tenth year. The reduction in the frequency of adverse events was statistically significant ($p = 0.02$). The most frequently reported adverse events were upper lid ptosis (23% in year 1; 8% in year 10) and focal muscle weakness (11% in year 1; 5% in year 10)⁵⁹. The investigators attributed the substantial reduction in the rate of adverse events over the 10-year duration of treatment to clinical experience and improved injection technique.

It is important to remember that our analysis of placebo-controlled trials and review of long-term safety is limited to one specific formulation of BTX-A; therefore, the results may not apply to other formulations or toxin types because of differences in dosing, potency, vehicle and dilution scheme, and possibly other clinical properties⁶⁰. In addition, there are limitations to the

clinical interpretation of these findings. The meta-analysis reports on the intent to treat population which will define a minimum rate of adverse events that might be expected in clinical practice. Furthermore, experience from placebo-controlled, double-blind studies and long-term open-label studies does not offer a true representation of rare but potentially serious adverse events, such as those which occur in fewer than 1 in 1000 patients.

Conclusions

BTX-A therapy has an excellent safety and tolerability profile across a wide range of cosmetic and therapeutic uses including facial rejuvenation, a variety of dystonias, spasticity, pain and headache, and smooth muscle and glandular disorders. A systematic review of adverse events extracted from randomized controlled trials in a total of 2309 patients, treated with either BTX-A (1425 patients) or a control (884 patients) indicates that the overall rate of adverse events was 25% in BTX-A-treated patients compared with 15% in control groups. The reported adverse effects were temporary, mild to moderate in intensity, non-systemic, and related to the mechanism of action. Focal weakness was the only adverse event that was more frequent in BTX-A patients compared with control. The rate of adverse events derived from this analysis of controlled clinical trials was consistent with the safety and tolerability profile observed in uncontrolled long-term clinical use for as long as 10 years. It is likely that clinical experience and optimized injection technique can further reduce the rate of adverse events associated with BTX-A therapy.

Acknowledgments

This study was supported by an unrestricted grant from Allergan, Inc., Irvine, California.

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 Paper CMRO-2635, Accepted for publication: 14 April 2004
 Published Online: 12 May 2004
 doi:10.1185/030079904125003962