Effect of preventive treatment with botulinum toxin type A on acute headache medication usage in migraine patients

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CRD summary
This review assessed the effects of botulinum toxin type-A (BoNT-A) on the amount of drug relief used for migraines. The analysis indicated a 57% reduction in medication use in the 8- to 12-week period after receiving BoNT-A. The search was limited, there was no quality assessment, and the analysis was based on dissimilar studies. The conclusions should therefore be viewed with caution.

Authors' objectives
To assess the preventive effects of botulinum toxin type A (BoNT-A, marketed as BOTOX) on the amount of acute headache medication used for migraines.

Searching
MEDLINE and EMBASE were searched from 1993 to 2003, while published congress proceedings were searched from 1998 to 2003. No search terms were provided.

Study selection
Study designs of evaluations included in the review
The study designs eligible for inclusion were not explicitly stated. However, the study had to be at least 8 to 12 weeks in duration, as the author stated that this was the usual reported length of efficacy of BoNT-A.

Specific interventions included in the review
Studies of BoNT-A administered as a preventive treatment for migraines were eligible for inclusion. Doses of BoNT-A were 25, 50 and 75 units (U) in the two studies for which dosage information was available.

Participants included in the review
Studies conducted in populations of migraine patients or in subsets of migraine patients were eligible for inclusion. Those assessing patients with chronic tension type headache or other headache types were excluded. The participants included in the primary studies were those with 'chronic migraine' or 2 to 8 migraine attacks per month, or headache patients identified as high triptan users.

Outcomes assessed in the review
Studies that quantified the amount of acute headache medication usage before and after treatment with BoNT-A were eligible for inclusion.

How were decisions on the relevance of primary studies made?
The author did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The author did not state that they assessed validity.

Data extraction
The author did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data on study design, assessments, outcome variables and patient populations were extracted. The class of acute headache medication used was extracted whenever possible.
Methods of synthesis
How were the studies combined?
The mean percentage change in acute headache medication usage was calculated in a pooled analysis. The pooled estimate was weighted according to the sample size of each individual study.

How were differences between studies investigated?
The differences between the studies were not formally investigated, though some limited discussion was presented.

Results of the review
Four studies were eligible for inclusion in the review. There were two randomised placebo-controlled trials involving 153 participants, 57 of which were allocated to receive BoNT-A, an open-label study with 50 patients and a retrospective analysis of 60 participants.

The pooled analysis of the four trials showed that the weighted mean reduction (plus or minus standard deviation) in acute headache medication use was 57% (+/- 15.88). However the studies included in the analysis varied substantially. Study 1 was a randomised placebo-controlled trial with participants receiving 50 U BoNT-A. The primary outcome used in the pooled analysis was a 73% reduction in overall acute medication use for the BoNT-A arm. Study 2 was also a randomised placebo-controlled trial with participants receiving 25 or 75 U BoNT-A (only the 25 U group were considered in the pooled analysis). The primary outcome used in the analysis was a 38% decrease in days of medication use for the BoNT-A arm. Study 3 was a retrospective analysis of patients that received BoNT-A. The primary outcome used in the pooled analysis was a 75% reduction in acute medication use for those receiving BoNT-A. Study 4 was an open-label study of two treatments administered over a 6-month period. The primary outcome used in the pooled analysis was a 48% reduction in triptan medication costs.

Cost information
The author stated that the direct medical costs were 2 to 5 times greater for people suffering from migraines because of physician visits and pharmacotherapy, and that effective migraine treatments have been shown to lower the number of physician visits and emergency care required.

Authors' conclusions
The pooled analysis indicated a 57% reduction in acute headache medication use in the 8- to 12-week period after treatment with BoNT-A. Effective migraine prevention can result in cost-savings which could offset the total cost of treatment with BoNT-A.

CRD commentary
The review question was clear in terms of the intervention, outcome and participants of interest. Two electronic databases were searched, but the search strategy was not provided and it was unclear whether any language restrictions were applied. Unpublished data were sought from one source, but no assessment of potential publication bias was attempted. However, formal publication assessments do have limitations when the number of studies is small. It was not stated how the studies were selected or the data extracted, so these processes could not be assessed for the presence of bias.

A pooled analysis of the four trials was presented. This included three different study designs, and heterogeneous patient populations and interventions. Despite pooling these four studies statistically, no formal attempts were made to investigate any statistical heterogeneity that might be present. The author acknowledged some of the differences between the studies included in the pooled analysis, and the directions of the treatment effects were consistent between the studies.

The author's conclusions appeared to follow from the evidence presented in the individual studies. However, the search was limited and there was no quality assessment of the individual studies. The studies included in the pooled analysis appeared to be heterogeneous, particularly in terms of study designs and outcomes reported. Reducing the results to a
single summary estimate by pooling was inappropriate, and the conclusions should be viewed with due caution.

**Implications of the review for practice and research**

**Practice:** The author stated that BoNT-A may be a cost reasonable option for the prevention of acute headache medication use, especially in patients with chronic headache and higher acute medication use.

**Research:** The author stated that further larger controlled trials are required to confirm the efficacy and safety of BoNT-A for the treatment of migraines. Additional prospective studies evaluating the costs (direct and indirect) of using BoNT-A as migraine therapy are also needed.

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