Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: a meta-analysis

Jackson JL, Kuriyama A, Hayashino Y

CRD summary
The authors concluded that botulinum toxin A compared to placebo may be associated with benefit for chronic daily headaches and chronic migraines, but not episodic migraine or chronic tension headaches. Despite some issues with the included trials, which the authors acknowledged, this was a generally thorough analysis and the authors’ conclusions seem reasonable and reflect the uncertainty surrounding the evidence.

Authors' objectives
To assess the effects of botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched between 1966 and March 2012. The search strategy was reported. Reference lists of published systematic reviews and retrieved articles were searched manually and medical librarians supplemented the searches (no further details were provided).

Study selection
Randomised controlled trials (RCTs) that assessed the effects of botulinum toxin A injections on the frequency and severity of headaches in adults were eligible for inclusion. Eligible trials had a duration of at least four weeks. Patients could receive additional prophylactic and analgesic treatments. The primary outcome was patient-reported headache frequency per month (measures of headache frequency or headache indices). Other outcomes included patient reported headache intensity/severity, duration, global improvement/relief, analgesics used and adverse events.

Included trials were conducted in USA, Brazil, Egypt, Europe, Thailand and India. Most patients were female (76%). Mean age was 42.1 years. Mean trial duration was 19 weeks. Headaches were categorised as episodic (<15 headaches per month) and chronic (≥15 headaches per month) and as migraine and tension headaches. The maximum botulinum toxin A dose ranged from 16U to 300U. Injection schedules ranged from once to three injections at 90-day intervals (range four to 58 injections). Active comparisons included topiramate, amitriptyline, valproate and methylprednisolone.

The authors stated that they followed Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. They did not state explicitly how many reviewers screened studies for inclusion.

Assessment of study quality
Trial quality was assessed independently by two reviewers according to the Cochrane Risk of Bias tool and Jadad eight-point scale of randomisation, allocation concealment, blinding, incomplete outcome data addressed, no selective outcome reporting, no other bias, industry sponsorship and use of intention-to-treat analysis. Discrepancies were resolved by consensus.

Data extraction
At least two reviewers independently extracted or calculated means and variances for continuous headache outcome data at all time points. Dichotomous outcome data were abstracted at all time points (if there was at least 50% clinical improvement) to calculate relative risks (RRs) and 95% confidence intervals (CIs). Where trials had more than one treatment group, these were combined.

Discrepancies were resolved by consensus.

Methods of synthesis
A random-effects model was used to pool relative risks and 95% CIs. Mean differences and variances in headache frequency were pooled to calculate weighted mean differences (WMDs) and 95% CIs. Other measures of headache

were pooled to calculate standardised mean differences (SMDs) and 95% CIs. Robustness of the random-effects model was assessed using the methods of Higgins and by performing a non-informative random-effects Bayesian analysis.

Heterogeneity was visually assessed using Galbraith plots and statistically assessed using Q and $I^2$ statistics. Potential sources of statistical heterogeneity were investigated using stratified analysis and meta-regression. The effects of quality criteria on the results were investigated. Sensitivity analyses were conducted to assess the effects of population characteristics, study methods and treatment regimens.

Publication bias was assessed using the methods of Peters for dichotomous data and Egger for continuous data.

**Results of the review**

Twenty-seven placebo-controlled RCTs (5,313 participants reported and 5,423 calculated, range 21 to 705) and four active-controlled RCTs (210 participants) were included in the review. Jadad scores were reported to range from 2 to 8, but this did not seem to tally with the Cochrane Risk of Bias criteria. Drop-out rates ranged from 0% to 44%.

Compared to placebo, botulinum toxin A injections were associated with a statistically significant reduction in the frequency of chronic daily headaches (WMD -2.06 per month, 95% CI -3.56 to -0.56; $I^2=28.2\%$, three RCTs) and chronic migraine (WMD -2.30 per month, 95% CI -3.66 to -0.94; $I^2=32.2\%$, five RCTs). There were no differences compared to placebo in the number of episodic migraines per month and/or chronic tension headaches (16 RCTs) and there was some evidence of statistical heterogeneity.

Compared to active comparators, botulinum toxin A was associated with a significantly greater reduction in average headache severity in patients with chronic tension-type headaches (one RCT). No other outcomes were statistically different compared to active comparators.

Botulinum toxin A was statistically significantly more effective than placebo in achieving 50% improvement in chronic migraine headaches (RR 2.21, 95% CI 1.30 to 3.78; $I^2=0\%$, two RCTs). There were no differences for other types of headache.

Sensitivity analyses did not significantly alter the results. Reanalysis using the Higgins distribution and a non-informative Bayesian model showed that none of the results were statistically significant.

Patients who received botulinum toxin A were more likely to experience adverse events. There was a placebo effect (placebo patients reported substantial improvements in headaches over time).

There was no evidence of publication bias.

**Authors' conclusions**

Botulinum toxin A was not associated with greater benefit compared to placebo in the prophylactic treatment of episodic migraine or chronic tension type headaches. Botulinum toxin A may be associated with improvements in chronic daily and chronic migraine headaches, but these improvements had limitations.

**CRD commentary**

The review question and supporting inclusion criteria were clearly defined. A satisfactory number of sources were searched for relevant literature. There was potential for missed data as unpublished data were not sought; formal assessment found no evidence of publication bias. The authors performed data extraction and quality assessment in duplicate, but it was unclear whether this was true for study selection so reviewer error and bias could not be ruled out. Appropriate criteria were used to assess the risk of bias and trial quality, but the results appeared to be confounding: trials generally received high Jadad scores and poor or unclear ratings on the Cochrane Risk of Bias tool.

The authors acknowledged the small number of trials for each headache type and the short duration of the trials. There was evidence of clinical and methodological heterogeneity among trials and the authors made some attempts to investigate the sources. The authors stated that the active comparator trials were underpowered and not designed as equivalence trials. In general, comprehensive statistical analyses were undertaken.

Despite some issues with the included trials, this was a generally thorough analysis. The authors’ conclusions seem
reasonable and reflect the uncertainty surrounding chronic daily and chronic migraine headaches.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated a need for more research to assess the effects of botulinum toxin A on different headache types.

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