

Shuhendler AJ, Lee S, et al. Efficacy of Botulinum Toxin Type A for the Prophylaxis of Episodic Migraine Headaches: A Meta-analysis of Randomized, Double-Blind, Placebo-Controlled Trials. *Pharmacotherapy* 2009;29(7):784-791.

Design: Meta-analysis of randomized trials

PICOS:

- **Patients:** patients with a history of episodic migraine headaches (<15 headaches per month)
- **Interventions:** Botulinum toxin A (BTX) injections, either low-dose (<100 U) or high dose (<100 U)
- **Comparison:** placebo injections
- **Outcomes:** Mean change in headache frequency (number of episodes per month) at intervals of 30, 60, and 90 days after injection of botulinum toxin or placebo
- **Study types:** Randomized, placebo-controlled, double-blind trials
 - o Studies involving subgroup analyses, nonrandomized studies, single-blind studies, and studies using a different outcome scale were excluded

Study type and selection:

- Databases were PubMed, Google Scholar, and the Cochrane Library from inception to October 2007
- Two reviewers independently selected articles with differences resolved by consensus or by a third reviewer who served as an adjudicator
- Quality was scored on a scale with a maximum score of 32, encompassing 27 questions about reporting, sources of bias, external validity, and statistical power
 - o A score below 50% was considered weak, 50-69% fair, 70-79% good, and 80-100% very good
- Analyses were stratified by dose (high dose was ≥ 100 U, low dose <100 U) of BTX and by number of days after first administration of BTX (30, 60, and 90 days)
- The standardized mean difference between BTX and placebo was used as the measure of effectiveness; this summarizes the number of standard deviations by which BTX differs from placebo in headache frequency reduction (>0.8 SD is generally considered a “large” effect; 0.5-0.8 SD is “medium,” and 0.2-0.5 is a “small” effect)
- 8 studies, consisting of 1601 patients with a mean age of 43, were used in the meta-analysis, each with a “fair” quality rating
- The largest effect size in any meta-analysis was 0.10 SD for high dose BTX 30 days after administration; however, the 95% confidence interval included the null value, rendering the effect both clinically and statistically non-significant
- The effect sizes across all dosing levels and timing of assessment were homogeneous, making it feasible to estimate an overall effect for all studies

combined; this effect was 0.05 SD in favor of BTX, with a confidence interval which includes the null value; again, both clinical and statistical significance are lacking between BTX and placebo

- Some studies (Relja 2007) reported separately on placebo responders and non-responders (that is, some studies used a 30 day placebo run-in phase after randomization); even after possible differences between placebo responders and non-responders were accounted for, BTX remained no more effective than placebo

Authors' conclusions:

- The placebo effect in studies of BTX is very large, and BTX was not better than placebo at any dose or any duration in reducing frequency of headaches in patients with episodic migraine
- There were several different dosing levels in several of the included studies; a dose-response effect was not apparent, making it further unlikely that BTX differs from placebo
- Several studies administered BTX to muscles involved in facial expression; this would make blinding vulnerable to failure
 - o Because unblinding would bias the treatment effect in favor of BTX, the lack of clinical and statistical treatment differences is further underscored
- Although headache frequency is not decreased by BTX, it remains possible that it may reduce duration or severity of migraines

Comments:

- Figure 1 shows both "high" and "low" doses in the same forest plots; these occurred when more than one dose was administered by one investigator, and both doses were in the same dosing range specified for the meta-analysis
 - o E.g., analysis 4.1.1 of low-dose BTX at 30 days includes high, medium, and low doses for Elkind 2006; the doses used by Elkind were 50 U, 25 U, and 7.5 U respectively; all three doses were less than the 100 U defined as low-dose for purposes of the meta-analysis
- A random-effects model was used to combine the data (although a fixed-effect model would also have been appropriate)
 - o Random-effects models give more weight than fixed-effect models to small studies
 - o Some of the smaller studies were also the ones with the greater estimates of effect size (e.g., Barrientos in analyses 4.1.1, 5.1.1, and 6.1.1 had an effect size of 0.47 SD in favor of BTX)
 - o The fact that the random-effects analysis still yielded a trivial effect size, in spite of granting more weight to studies with greater effect sizes, further supports the conclusions of the authors that BTX does not decrease headache frequency more effectively than placebo
- None of the studies was high quality; all were scored as only fair quality

- In general, study quality is inversely related to estimated effect size; although it is possible that high-quality studies would show a greater effect of BTX, this would be an unexpected result
- Although only three databases (all in English) were searched, it would require a very large number of highly positive unbiased studies from alternative databases to change the estimate of the effect of BTX to something clinically and statistically significant

Assessment: High quality for good evidence that BTX is not more effective than placebo for reducing the frequency of episodic migraine headaches

References:

Elkind AH, O'Carroll P, et al. A Series of Three Sequential, Randomized, Controlled Studies of Repeated Treatments With Botulinum Toxin Type A for Migraine Prophylaxis. *J Pain* 2006;7:688-696.

Relja M, Poole AC, et al. A multicentre, double-blind, randomized, placebo-controlled, parallel group study of multiple treatments of botulinum toxin type A (BoNTA) for the prophylaxis of episodic migraine headaches. *Cephalgia* 2007;27:492-503.