

To the editor:

Dr. Jackson and colleagues (1) pooled data from five randomized trials to estimate the effect of botulinum toxin on the frequency of chronic migraine headache. Two of these trials, Aurora 2010 (2) and Diener 2010 (3), were reported separately as the PREEMPT 1 and PREEMPT 2 trials, respectively. Aurora and Diener believe that blinding was maintained despite of the potential for unblinding due to the physical changes attributable to the intervention; Jackson et al appear to agree and rate the blinding of both studies as adequate.

Aurora and Diener argue that the presence of a placebo response suggests that the blind was maintained, since participants in the placebo group could have been unblinded by the lack of physical changes, inducing a nocebo efficacy effect. The placebo group would fail to improve, it is argued, if it knows that it has received placebo. As an argument that blinding was maintained, this is equivocal. However, the purpose of blinding is to avoid biased reporting of trial outcomes; as an argument that the PREEMPT trials prevented such bias, the presence of a symptomatic response in the placebo group is unpersuasive. When participants in the experimental group observe the visible signs of having received the active drug, their reporting of headache symptoms is likely to be influenced by these observations. Rather than rating the blinding of the PREEMPT trials as adequate, it is more appropriate to rate the blinding as “unclear.” There is some risk of bias in the PREEMPT trials, making the effectiveness of botulinum toxin for chronic migraine headache as uncertain as its effectiveness for other headache conditions.

1. Jackson JL, Kuriyama A, Hayashino Y. Botulinum Toxin A for Prophylactic Treatment of Migraine and Tension Headaches in Adults. A Meta-analysis. *JAMA* 2012;307(16):1736-1745.
2. Aurora SK, Dodick DW, et al. Onabotulinumtoxin A for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalalgia* 2010;30(7):793-803.
3. Diener HC, Dodick DW et al. Onabotulinumtoxin A for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia* 2010;30(7):804-814.

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