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LETTER TO THE EDITOR

Reply: OnabotulinumtoxinA should be considered in medication overuse withdrawal in patients with chronic migraine

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Sir,

We thank Prof. Dressler for his interest in our study and his honesty to report that he is shareholder of Allergan, the manufacturer of the drug tested in our trial, and that he holds patents on botulinum toxin and botulinum toxin therapy (Dressler, 2019).

His letter offers us the opportunity to correct some misconceptions with respect to the perceived efficacy of botulinum toxin A (BTA) in chronic migraine with medication overuse (CM + MO). It also enables us to correct some apparent misunderstandings with respect to the study design and to present new additional evidence, further supporting the conclusion that BTA does not afford any additional clinical benefit over withdrawal in patients with CM + MO.

Professor Dressler suggests that BTA is an effective treatment for chronic migraine. We would like to put this claim into perspective. While statistically significant, the greater reduction in headache days with BTA versus placebo was clinically hardly relevant: 1.8 days from 19.9 days at baseline (<10%) (Aurora *et al.*, 2010; Diener *et al.*, 2010; Dodick *et al.*, 2010; May and Schulte, 2016). Moreover, unblinding due to BTA-induced removal of facial wrinkling might well have biased outcome. Up to 90% of participants had correctly guessed their treatment in similar trials, mainly because of the cosmetic effect (Australian Government, 2011; Wollmer *et al.*, 2012). In a recent Cochrane review, the efficacy of BTA was disputed because of the large and unexplained heterogeneity in the studies (Herd *et al.*, 2018).

To avoid unblinding, we administered 17.5 units of BTA in the forehead of participants in the placebo group. This is very low compared to the 155 units used in the PREEMPT studies (Aurora *et al.*, 2010; Diener *et al.*, 2010). We are not aware of any published evidence that such low doses may afford clinically relevant improvement. In fact, 17.5 units is significantly lower than the lowest dose ever reported for headache (Jackson *et al.*, 2012; Herd *et al.*, 2018), psychiatric disorders (Wollmer *et al.*, 2012), peripheral neuropathy (Attal *et al.*, 2016), or regular cosmetic purposes (Durand *et al.*, 2016). In animal studies, low doses were clearly less effective (Zhang *et al.*, 2016) or not effective at all (Antonucci *et al.*, 2008; Lawrence *et al.*, 2012) on putative therapeutic modes of action. In conclusion, there is no evidence that seven injections with in total 17.5 units BTA in the forehead might have caused a clinically relevant reduction in headache days. Moreover, if such low doses were indeed effective, why then should we continue to treat patients with 31 injections totalling a 9-fold higher dose?

In his letter, Professor Dressler seems also mistaken with the study design and patient number. To clarify, all 179 participants were advised to stop all headache medication and were randomly allocated (1:1) to receive BTA (n = 90; 31 injections; in total 155 units) or placebo (n = 89; seven injections with a total of 17.5 units BTA in the forehead and 24 injections with saline elsewhere). Importantly, blinding was well kept. BTA did not afford any additional clinical benefit over withdrawal alone (Pijpers *et al.*, 2019).

The effect of withdrawal in our study was similar to that in other studies, showing similar proportions of patients reverting from chronic to episodic headache (Rossi *et al.*, 2006; Munksgaard *et al.*, 2012) or with at least 50% reduction in headache days (Zeeberg *et al.*, 2006; Rossi *et al.*, 2011; Munksgaard *et al.*, 2012). In a recent randomized,

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controlled, clinical trial, patients with mainly CM + MO had 6.7 fewer migraine days after withdrawal (Carlsen *et al.*, 2018). In a recent review, it was recommended to implement withdrawal in the care of patients with CM + MO (Diener *et al.*, 2019). In summary, withdrawal is now recognized as a highly cost-effective therapy (Jellestad *et al.*, 2019) leading to substantial reduction of headache days in most patients (Munksgaard *et al.*, 2012; Pijpers *et al.*, 2016; Carlsen *et al.*, 2018; Diener *et al.*, 2019; Jellestad *et al.*, 2019).

Data availability

The trial is registered at the Netherlands trial registry, #3440, www.trialregister.nl. The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: Support from the Netherlands Organisation for Scientific Research (NWO), VIDI 91711319 and the Dutch Brain Foundation for the submitted work. No author has financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years. No other relationships or activities that could appear to have influenced the submitted work.

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