

Commentary

BTX-A for persistent myofascial TMD pain: Interpreting a small clinical trial with negative results

In this issue *Pain*, Ernberg et al. [1] present the results from a randomized double-blind placebo controlled crossover trial assessing the therapeutic effects of botulinum toxin A (BTX-A) for the treatment of persistent myofascial TMD pain. Their conclusion that, “results do not indicate a clinically relevant effect of BTX-A in patients with persistent myofascial TMD pain” [1], begs the question: does this mean that BTX-A is not an effective treatment for persistent myofascial pain? Or, stated another way, is this a definitive study? More importantly, what can we conclude from the results reported and what does this paper add to the literature?

It is difficult to conclusively prove a treatment is not effective, especially with a single clinical trial that involved a small numbers of subjects. A great deal more precision is required in order to prove conclusively that the observed outcome is not going to reach a minimal clinical significance, given an increased sample size. A larger sample is often therefore required to “prove” the null hypothesis, but this would be set against diminishing returns on the investments of time and money required to do so. Small studies can also have inherent difficulties with generalizability because it is unlikely that the subjects recruited for the study represent the intended sample and that the clinicians providing the intervention represent those who typically provide patient care. These problems are the norm with research investigating outcomes of novel treatments and is one reason why meta-analyses were developed. With the current state of the literature, which includes four controlled studies with inherent limitations, we seem to be at an intermediate stage. So, should more, larger studies be performed or should this application of BTX-A be abandoned? What about the option of designing future research to assess treatment equivalence, with an emphasis on assessment of benefit:risk ratio of treatment?

My interpretation of the available research data leads me to the two following conclusions:

- (1) In addition to the methods used by Ernberg et al., future trials involving botulinum toxin need to be double blind in nature and assessment of the outcome of the concealment process reported. The design and rigor of clinical trials for TMDs have improved over recent years [2], which is particularly pertinent to this situation. Three double-blind studies reported no significant differences [1,3,4] whilst the only single-blind study reported positive effects [5], similar to those previously reported in non-randomized reports on the topic. Furthermore, there is a sense that with BTX-A

treatment, both the subjects and examiner(s) are able to determine group assignment, because of perceived and/or observed motor effects. Continuing that argument, one can suggest that it is impossible to perform such a study with adequate blinding and therefore single blind and unblinded studies should be given equal consideration when synthesizing results.

To address this potential source of bias, there needs to be an assessment of the outcome of the concealment process in the design of this study. Although Ernberg et al. did not design assessment of concealment into their study, they were able to present data that suggests that adequate concealment was maintained [1]. Taken together with a previous study that failed to report their assessment of concealment, which determined that neither the examiner nor the subjects were able to determine group allocation status [3], I am therefore inclined to only consider results of double blind studies. In other words, the trend of finding no positive treatment benefit is more convincing. This research has implications for clinical trials assessing the use of botulinum toxin for the management of pain in general, which further supports the need to perform studies with the highest level of rigor possible.

- (2) BTX-A treatment does not seem to be an effective option for all patients with persistent myofascial TMD pain. Generally, it is more difficult to demonstrate a positive treatment effect in recalcitrant stages of disorders, which may explain the lack of response observed in the multiple domains thought to be important in patient care. Therefore, I can imagine that the inclusion of subjects with recalcitrant myofascial TMD pain may obscure the positive benefits experienced by other subjects. With small numbers of subjects, performing subgroup analysis is meaningless, making the existing data incapable of proposing, with confidence, that the use of BTX-A earlier within the care-pathway may be a better treatment option. As other efficacious treatment options for myofascial TMD pain are readily available and well-established, superficially this seems like an illogical application for BTX-A. However, the benefit:risk ratio comparison of such approaches to care are not known. Given that pain reduction has consistently been reported with BTX-A treatment of muscles associated with hyperactivity, such as multiple sclerosis spasticity and dystonia, it seems likely that there are subgroups of TMD pain patients that may benefit

from such treatment. Therefore, future studies investigating this treatment approach need to be large enough for subgroup analysis to occur, such as with an equivalence trial. Alternatively, the subject sample needs to be enriched with particular subgroups thought to be more responsive to BTX-A treatment.

The authors and the journal's editors should also be lauded for having the foresight to publish a clinical trial that concludes no net benefit. These efforts help to reverse the potential publication bias of positive studies and allow such data to be available for future meta-analyses, in which more comprehensive research studies, with larger patient samples, will be included.

Conflict of interest statement

The author received drug and pharmacy support from Allergan for previous research on this topic. No current conflicts of interest to report.

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