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Comment on: Efficacy of botulinum toxin type A for treatment of persistent myofascial TMD pain: a randomized, controlled, double-blind multicenter study, by Ernberg, Hedenberg-Magnusson, List, and Svensson

To the Editor,

Given the limited options available for the treatment of myofascial temporomandibular disorder (TMD) pain and the recent U.S. Food and Drug Administration approval of the use of botulinum toxin A (BTX-A) for chronic migraine, the randomized controlled clinical trial reported by Ernberg et al. [4], is most welcome. Nevertheless, we find their conclusions overly conservative because although their abstract concludes, "These results do not indicate a clinical [sic] relevant effect of BTX-A in patients with persistent myofascial TMD pain," the study was limited in the same way as previous research on BTX-A for TMD [5,8]—it was underpowered.

Over 40 years ago, Jack Cohen [1,2] began a revolution in the use of power analysis in behavioral and clinical research. He asked then, how many good ideas (ie, those with meaningful effect sizes but insufficient sample sizes) had been rejected over the last 50 years by the bias to favor the minimization of type I over type II error rates in statistical decision making? We write to question whether a potential treatment effect may have been missed as a result of an apparent misunderstanding in the way these rates are determined and interpreted.

Ernberg et al. [4] determined a priori that a sample of 18 subjects was sufficient to detect a 30% reduction in the rating of spontaneous pain, given type I and type II error rates of 5% and 10%, respectively. Although that power calculation is correct for the main effect of time, it is only correct in the test of the interaction effect, clearly the most relevant to this situation, if we assume that the change under the control condition were zero. Stated differently, although this study planned to detect a 30% improvement from baseline after active treatment, it actually required that the active treatment provide 30% more improvement from baseline than did the control treatment. In fact, there was improvement after control treatment, and our calculations indicate that the actual statistical power with 21 subjects was considerably less than 90%—the power of the Student *t* test of the difference between treatment conditions was about 54% at 1 month and 75% at 3 months. Although the obtained effect sizes were smaller than planned, there was approximately 0.5 SD more improvement in the active than control treatment at 1 month, and 0.6 SD more at 3 months. To put these effect sizes in context, 3 clinical trials [3,9,10] have shown an advantage in the use of stabilization splints over nonoccluding splints of no more than 0.25 SD. Thus, this, and 2 other studies of BTX-A efficacy in TMD [5,8] produce effects that are at least twice as strong as those seen in placebo-controlled trials of stabilization splints.

Thus, although these data showed that the active treatment produced a potentially meaningful and greater reduction in pain than the control treatment, the *P* level associated with that statistical test was .11; that is, trending in the expected direction, but not statistically significant. Our analyses indicate that relatively few additional subjects would have been needed to reject the null hypothesis of no time by treatment interaction at the .05 level—24 and 32 subjects, respectively, for power of 80% and 90%. At worst, then, we find the results reported here to be inconclusive because although a relevant effect size was evident, a slightly larger sample was needed to detect that effect. "Size is everything" [7] when drawing conclusions from clinical trials.

Potential efficacy was also suggested by the counts of clinically significant reductions in pain report under the 2 conditions. When patients reported a large (50%) reduction in pain, BTX-A was at least twice as likely to have been the treatment (at 1 month). Like many useful treatments, BTX-A appeared to be effective in only a minority of cases (depending on the follow-up interval, about 6 of 21). The task may then be to focus efforts on identifying patients who derive a benefit from BTX-A (eg, patients with hyperactivity in the masticatory muscles). This is particularly important in TMDs and other musculoskeletal pain conditions that are likely to have multiple underlying mechanisms, in which "monism of experience...does not translate into singularity of causes" [6]. Because this study used a general sample of myofascial TMD patients, treatment effects could have been diluted as a result of heterogeneity in causal mechanisms.

Despite the authors' forthright description of methodological caveats in their discussion section, their final words leave the reader with a conclusion that is consistent with the significance level, but not with either the effect size or the power of the study. (We limit ourselves here to analyses related to differences in the report of usual pain). Rather than stating "BTX-A is not efficacious...in patients with persistent myofascial TMD pain," they could have stated, with considerable justification, that their study was not sufficiently powered to rule out the presence of clinically significant effects of BTX-A.

As the authors note, evidence for the efficacy of most TMD treatments is limited. TMD patients need more effective and safe treatment options, and treatments may need to be tailored to underlying mechanisms. It would be a shame then, if conclusions drawn from insufficiently powered clinical trials were responsible for limiting future research on treatments that may benefit some TMD sufferers.

References

[1] Cohen J. The statistical power of abnormal-social psychological research: a review. J Abnorm Soc Psychol 1962;65:145–53.
[2] Cohen J. Statistical power analysis for the behavioral sciences. 1st ed. Hillsdale, NJ: Erlbaum; 1969.
[3] Dao TT, Lavigne GJ, Charbonneau A, Feine JS, Lund JP. The efficacy of oral splints in the treatment of myofascial face pain of the jaw muscles: a controlled clinical trial. Pain 1994;56:85–94.
[4] Ernberg M, Hedenberg-Magnusson B, List T, Swensson P. Efficacy of botulinum toxin type A for treatment of persistent myofascial TMD pain: a randomized, controlled, double-blind multicenter study. Pain 2011; 152:1988–96.
[5] Guarda-Nardini L, Manfredini D, Salamone M, Salmaso L, Tonello S, Ferronato G. Efficacy of botulinum toxin in treating myofascial pain in bruxers: a controlled placebo pilot study. J Cranio 2008;26:1–10.
[6] Merskey H. Distortion of the biopsychosocial approach. Pain 2005;113:240–2.
[7] Moore RA, Gavaghan D, Tramèr MR, Collins SL, McQuay HJ. Size is everything—large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. Pain 1998;78: 209–16.
[8] Nixdorf DR, Heo G, Major PW. Randomized controlled trial of botulinum toxin A for chronic myogenous orofacial pain. Pain 2002;99:465–73.
[9] Raphael KG, Marbach JJ. Widespread pain and the effectiveness of oral splints in myofascial face pain. J Am Dent Assoc 2001;132:305–16.

[10] Rubinoff MS, Gross A, McCall WD. Conventional and nonoccluding splint therapy compared for patients with myofascial pain dysfunction syndrome. Gen Dent 1987;35:502–6.

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Response to letter by Janal and Raphael

First we would like to thank Drs. Janal and Raphael for their interest in our study and for adding to the debate about the efficacy of botulinum toxins (BTX) for myofascial temporomandibular disorders (TMD).

In their Letter to the Editors, Drs. Janal and Raphael argue that our conclusions are too conservative and that the study is underpowered. They also argue that the patient selection was too heterogeneous and that treatment effects therefore could have been diluted.

In their calculations they come to the conclusion that our study had a power of 54% at 1 month and 75% at 3 months based on the difference in pain intensity between treatments, which is a lower power than we aimed at. In order to be clinically meaningful we believe that there should be a considerable difference between treatments, given the high costs for BTX compared with other treatments, and we therefore chose a difference of 30% pain reduction in our power calculation, which is regarded as clinically relevant [2]. One can always argue that this was a too strict approach.

Although our study showed a larger pain reduction after BTX-A than after normal saline, this difference was not statistically significant. Because of this we therefore decided to interpret our findings with caution. In addition, and most importantly, the number of subjects with 30% pain reduction at 1 and 3 months, respectively, was not impressive, and not larger for BTX-A than for normal saline (9 vs 7 and 7 vs 4). Based on these findings, at not even 3 times as many patients (n = 63) with the same frequency of responders (27 vs 21 and 21 vs 12) would these figures be significant (McNemars test; $P = .307$ and $P = .081$, respectively). We also believe that we have provided a fair discussion of the limitations of the present study so that other researchers wanting to demonstrate clinical efficacy of the BTX-A can learn from this study.

We agree that our choice of patient selection, that is, not to focus on patients with muscle hyperactivity, can be discussed. In the clinic most patients with myofascial pain improve considerably with conservative treatment, for example, self-care regimen, occlusal splints, and physical therapy. Hence, the biggest challenges are patients whose pain does not resolve or who do not adequately improve after such standard treatment. For them we had hoped that BTX-A could be a useful complement. Thus, although strict diagnostic criteria were used for diagnosis [1], most probably our patient material was heterogeneous with respect to muscle activity. The group also consisted of patients with a high grade of depression (72%) and nonspecific physical symptoms (86%) in addition to persistent pain.

Of the 2 studies that have investigated the effect of BTX-A in bruxism, only 1 used electromyographic (EMG) recordings to asses changes in muscle activity. However, whereas a significant reduction in masseter muscle EMG activity was reported after BTX-A compared with normal saline, as well as compared with the temporalis muscle, pain was unfortunately not assessed [4]. In the other study, there is ambiguity about the diagnosis of bruxism because it was based on patient report and clinical signs. Nevertheless, the patients that received BTX-A showed a better global treatment effect compared with those randomized to placebo [3]. These findings suggest that there might be a role for BTX-A in patients with myofascial pain and muscle hyperactivity, but this was not the group we selected for our study. Furthermore, it should be noted that the relationship between bruxism and craniofacial pain is still under considerable debate [5].

Both the relatively low number of patients included in our study and the very select group of patients having persistent myofascial pain and treated at specialist clinics are discussed under limitations of the study.

References

[1] Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandib Disord 1992;6:301–55.
[2] Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. Pain 2000;88:287–94.
[3] Guarda-Nardini L, Manfredini D, Salamone M, Salmaso L, Tonello S, Ferronato G. Efficacy of botulinum toxin in treating myofascial pain in bruxers: a controlled placebo pilot study. Cranio 2008;26:126–35.
[4] Lee SJ, McCall Jr WD, Kim YK, Chung SC, Chung JW. Effect of botulinum toxin injection on nocturnal bruxism: a randomized controlled trial. Am J Phys Med Rehabil 2010;89:16–23.
[5] Svensson P, Jadidi F, Arima T, Baad-Hansen L, Sessle BJ. Relationships between craniofacial pain and bruxism. Review. J Oral Rehabil 2008;35:524–47.

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