LETTERS

DOI 10.1002/art.42291

Reply

To the Editor:

We thank Dr. Braillon and Drs. Block and Pincus for their comments on our recent article.

The first comment concerned the generalizability of our results. In The Netherlands, duloxetine is not registered for use in patients with OA-related pain and therefore is not a common treatment for general practitioners (GPs) to prescribe for OA-related pain (1). In our cluster-randomized trial, patients were eligible when acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) did not reduce symptoms of pain or if these medications had side effects or were contraindicated. Treatment with duloxetine is not indicated for all patients with OA. For our trial, GPs asked their patients to participate based on their medical records to avoid introducing bias. The indication for prescribing duloxetine was difficult to assess based on the medical records, especially with regard to presence of pain. GPs could only examine for the presence of certain exclusion criteria, like comorbidities or use of certain medications, in the medical records. Therefore, the number of patients suitable for inclusion was much lower than the 4,748 patients registered with OA in the GPs’ medical records. Only 205 patients were eligible for the trial, and only 133 (65%) of these patients who were suitable for the intervention participated in the trial. Despite these limitations, we believe our trial included a representative sample of patients for whom duloxetine can be prescribed.

The second remark addressed the results of our trial in the context of current prescription practices of duloxetine and future research. Our results showed only small, not clinically relevant effects in the outcome parameters. Based on the 95% confidence intervals, we even could rule out the presence of a clinically relevant effect for the complete group of patients with OA. This result is in accordance with a more recent meta-analysis on the efficacy and safety of antidepressants for low back pain and OA, which also demonstrated no effect of duloxetine for OA-related pain, although the investigators could not rule out the possibility of a relevant effect (2). We note that pain in OA is multifactorial (3) and can consist of nociceptive pain from the joint or from alterations in central pain processing, and duloxetine may only be beneficial for a specific subtype of OA. A possible disadvantage of a pragmatic trial can be that the effect of the intervention is not found, because it is predominantly found in a specific phenotype of OA (4). For this reason, we specified a subgroup analysis a priori. We hypothesized that the effect of duloxetine would be predominantly found in patients with symptoms of central sensitization. In this subgroup analysis, we did not observe this effect (in fact, the estimate was about the same as in the total group); however, this finding was based on smaller numbers and we could not rule out a clinically relevant effect. For this reason, we advised a more extensive study of duloxetine’s effectiveness in this specific subgroup.

The final comment addressed the side effects of duloxetine. The current American College of Rheumatology guidelines conditionally recommend the use of duloxetine for patients with knee, hip, and/or hand OA and specifically mention issues about the tolerability of duloxetine (5). In our trial, the presence of side effects from duloxetine was high; during follow-up, 57% of the patients who quit taking duloxetine had stopped because of the presence of side effects. No serious adverse events occurred during our trial. Furthermore, 39% (28 of 72) of the eligible patients declined to participate because of fear of side effects, indicating a concern among patients.

So that an effective treatment is not withheld from patients, research is needed to assess if and for which subgroup duloxetine may be useful, rather than prescribing duloxetine to all patients with OA who have moderate or worse pain and who do not respond satisfactorily to paracetamol or oral NSAIDs or cannot use such medications. However, the tolerability and risks of serious side effects should be considered when assessing the use of duloxetine for OA-related pain.

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