In Response

To the Editor:

We would like to thank van der Kooij and his colleagues for their interest in our paper and for taking the time to express their concerns regarding efficacy and safety concerns of opioids use in chronic low back pain (CLBP) patients.

The letter to the editor by van der Kooij et al. raised potential concern about the Oxymorphone and its U.S. Food and Drug Administration (FDA)-withdrawal. Oxymorphone (Opana ER) was first approved in 2006 for the management of moderate-to-severe pain. In 2012, Endo replaced the original formulation of Opana ER with a new formulation intended to make the drug resistant to physical and chemical manipulation for abuse by snorting or injecting (1). The FDA declined company's request to include labelling describing potentially abuse-deterrent properties for Opana ER due to insufficient data. In addition to this, injection abuse of reformulated Opana ER has been associated with a serious outbreak of human immunodeficiency virus (HIV) and hepatitis C, as well as cases of a serious blood disorder (thrombotic micro angiopathy). Randomized clinical trials published by Katz et al (2) and Hale et al (3) used the original oxymorphone form instead of the new formulation and observed that in both the trials oxymorphone shown significant pain reduction compared to placebo (30% pain reduction). Hence, in the present network meta-analyses, we included oxymorphone to avoid the missing information on all opioids used in CLBP.

The second concern by van der Kooij et al was about the efficacy outcomes and the ranking probability of oxymorphone based on the effectiveness in pain reduction. They also reported that oxymorphone does not show a clinically relevant benefit in systematic review of CLBP.

In chronic pain clinical trials, different efficacy outcomes were used like mean change in pain intensity, 30% pain reduction and 50% pain reduction from baseline to follow-up (4). The supportive systematic review on efficacy of opioids mentioned by van der Kooij et al used mean change in pain intensity as efficacy outcome and the opioids showed a small change in pain intensity compared with placebo (mean differences [MD] –8.98; 95% CI –11.71 to –6.25; 13 trials, n = 3071) and this MD was less than minimal perceptible threshold (10 mm points on 100 MM VAS scale) (4). In such circumstances, the initiative on methods, measurement, and pain assessment in clinical trials (IMMPACT) recommended responder analyses (proportion of patients showing clinical meaningful pain reduction from base line) as efficacy outcome in chronic pain clinical trials when trials show small treatment effect sizes (i.e., standardized MD) between the treatment groups (5). Responder analyses is useful to determine whether a subgroup of patients may experience meaningful or even substantial benefits even though the overall MD is small. In the present study, we considered both 30% and 50% of pain reduction from baseline to follow-up as efficacy outcomes. Separate network meta-analyses were done for both 30% and 50% of pain reduction efficacy outcomes. The opioids were ranked according to 30% and 50% efficacy outcomes and oxymorphone showed the highest probability.

Further van der Kooij et al discouraged the prescribing of opioids as recommended by Olivera et al (6). The study by Olivera et al (6) is an overview of current clinical practice guidelines for patients with nonspecific low back pain. The study recommended that use of opioids should be discouraged due to the small benefit on pain intensity in CLBP as well as potential side effects (6). In contrast to this, the majority of the existing guidelines (13 out of 15; 87%) recommended weak opioids for the management of CLBP for short term, if there is no improvement with nonsteroidal antiinflammatory drugs or other treatments.

Van der Kooij et al also raised concern about the safety outcome used in our study. In the present study, we considered total withdrawal due to any reason from the trial as safety outcome. It covers the patients who withdrew from the study due to lack of efficacy or adverse events or any other reason. The same was reported in methodology.

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References

1. Food and drug administration. Oxymorphone (marketed as Opana ER) Information. www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/oxymorphone-marketed-opana-er-information. 2017. Accessed on 04-20-2021.
2. Hale ME, Ahdieh H, Ma T, Rauck R, Oxymorphone ER Study Group. Efficacy and safety of OPANA ER (oxymorphone extended release) for relief of moderate to severe chronic low back pain in opioid-experienced patients: A 12-week, randomized, double-blind, placebo-controlled study. *J Pain* 2007; 8:175-184.
3. Katz N, Rauck R, Ahdieh H, et al. A 12-week, randomized, placebo-controlled trial assessing the safety and efficacy of oxymorphone extended release for opioid-naive patients with chronic low back pain. *Curr Med Res Opin* 2007; 23:117-128
4. Tucker HR, Scaff K, McCloud T, et al. Harms and benefits of opioids for management of non-surgical acute and chronic low back pain: A systematic review. *Br J Sports Med* 2020; 54:664-2018-099805.
5. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005; 113:9-19.
6. Oliveira CB, Maher CG, Pinto RZ, et al. Clinical practice guidelines for the management of non-specific low back pain in primary care: An updated overview. *Eur Spine J* 2018; 27:2791-2803.