Review of: "Methadone: from Chronic Non-Oncological pain and primary Management Of Opioid Hyperalgesia to Disassuefaction Of Painkillers Abuse"

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Potential competing interests: The author(s) declared that no potential competing interests exist.

The manuscript presented by the authors is interesting and allows us to focus on many issues related to the use of methadone both in chronic pain and in the treatment of opioid addiction.

The study can be published after a series of improvements to the text and a careful revision of the English.

I would recommend the following modifications:

1. The Methods section needs to be expanded by better indicating the inclusion and exclusion criteria of the articles. Is there an article flow?
2. I believe it is necessary to give a more defined structure to the Discussion section, providing it with two or three subparagraphs with a first part dedicated to the pharmacology of methadone (pharmacodynamics and pharmacokinetics) and to explain its role in the mechanisms of tolerance and opioid-induced hyperalgesia. The last subsection could be dedicated to clinical uses.
3. The part in which the authors describe the situation regarding the use of methadone in the United States and its repercussions could be shortened.
4. The focuses used by the authors are very useful and well done. I would recommend inserting another one dedicated to the procedure to be followed when a patient on methadone therapy must undergo the treatment of acute pain, above all in the perioperative period, especially postoperative. In these cases, clinical practice tells us that the needs of such patients tend to be underestimated, whereas on the contrary a targeted postoperative analgesic therapy should be set up. On this topic it would be good to remember that the perioperative phase is a very vulnerable time for these patients. Indeed, the literature (1) recommends that for moderate to severe pain, peripheral, regional, and neuraxial analgesia or PCA with opioids may be appropriate. Postoperatively, patients should be closely monitored for pain control as well as for side effects such as sedation, euphoria, opioid-induced constipation, and respiratory depression (Ward E N, Quaye A NA, Wilens T E. Opioid Use Disorders: Perioperative Management of a Special Population. Anesth Analg. 2018; 127(2): 539–547. doi:10.1213/ANE.0000000000003477).