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Reply

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We thank the authors for their gracious comments on our article [2] and their interest in this line of research.

The authors state that ‘While the use of opioids represents an important and necessary option for the management of chronic pain, the risk benefit ratio of the approach is narrow owing to its significant potential for side effects, adverse events, dependency, and abuse’.

We would rather emphasize that opioid use does not represent a first-line treatment for the management of many types of chronic noncancer pain, and based on the lack of high-quality evidence demonstrating its efficacy, effectiveness and long-term safety, opioid therapy may be unhelpful [1]. Nonetheless, the prescription rates of opioids have increased by 300 percent over the past 20 years in the United States [4] and risen seven-fold from 2000 to 2010 in the United Kingdom [6]. Independently of any cultural and race difference, attitudes towards the use of opioids vary across countries. In the United States, a per capita use of opioids is double that of the United Kingdom; three times of that in the Netherlands; and 26 times of that in Japan [5; 3].

The multiple aspects of pain from intensity to affective components to emotional and physical functioning require attention for optimal pain management. In our review, we focused on placebo analgesia as an example of descending pain modulatory mechanisms in animals and humans with a thoughtful discussion of potential benefits and limitations. The authors state that ‘despite potential positive aspects, this approach is controversial for several reasons: 1) limited data demonstrating that the strategy is possible, 2) some clinicians consider the use of placebos (in any application) unethical and unacceptable to patients, and 3) behavioral pharmacotherapeutics is not implementable in the real word’.

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1) Limited data demonstrating that the strategy is possible

Dose-extending placebos and/or subclinical dose of painkillers that are blended with treatments in accordance with reinforcement learning principles are effective in reducing pain in laboratory settings by boosting endogenous pain modulatory mechanisms [2]. To translate this knowledge into the real-world settings, further research is warranted to explore specific requirements. First, initial safety, feasibility and optimization studies are necessary to address the following questions: a. Is the rationale for the study design scientifically and ethically sound? b. Is there sufficient evidence to justify the inclusion of placebos in the therapeutic regimens (safety, feasibility, primary and secondary outcomes and sample size)?

Second, confirmatory efficacy studies should address the following aspects: a. Have safety, feasibility and dose optimization been confirmed for the clinical condition under evaluation? b. Have potential biases been minimized?; Are treatment as usual (TAU) control groups included?; c. Are open label placebos as effective as phase IV post-marketing treatments?

2) Some clinicians consider the use of placebos (in any application) unethical and unacceptable to patients

We illustrated clinicians' attitudes towards the use of placebos, reviewing several surveys in different clinical contexts. We noticed a substantial difference between what is currently perceived about the placebo use and the proposed use of dose-extending placebos. Last but not least, any attempt to address the questions above must be performed in an ethically acceptable manner that involves training patients and health care providers. We provided guidance on ethical aspects that require a careful and thoughtful analysis. The informed consent should incorporate the pre-authorized use of dose-extending placebo and post-treatment debriefing and health practitioners should be trained to prepare consents that are clear and understandable to any patients. We believe ethical objections to placebo use even under these strict conditions would be irrational.

3) Behavioral pharmacotherapeutics is not implementable in the real world

Manufacturing blister packs, placebos or tablets with subclinical doses of medication is not the real implementation issue when research is performed in line with regulations and policies for human research and with adequate resources. Clinical aspects such as opioid-related drug tolerance, escalating doses, opioid-related hyperalgesia, and secondary addiction may represent a challenge.

The implementation of dose-extending placebo use to activate endogenous pain modulatory systems that would otherwise be silent represents not only a potential innovative pain management approach practice but is also in line with the urgent demand for inter- and multi-disciplinary strategies to face chronic pain.

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References

1. Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, Dana T, Bougatsos C, Deyo RA. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med.* 2015; 162(4):276–286. [PubMed: 25581257]
2. Colloca L, Enck P, DeGrazia D. Relieving pain using dose-extending placebos: a scoping review. *Pain.* 2016; 157(8):1590–1598. [PubMed: 27023425]
3. Deyo RA, Von Korff M, Duhrkoop D. Opioids for low back pain. *BMJ.* 2015; 350:g6380. [PubMed: 25561513]
4. Sullivan MD, Howe CQ. Opioid therapy for chronic pain in the United States: promises and perils. *Pain.* 2013; 154(Suppl 1):S94–S100. [PubMed: 24036286]
5. Zerzan JT, Morden NE, Soumerai S, Ross-Degnan D, Roughead E, Zhang F, Simoni-Wastila L, Sullivan SD. Trends and geographic variation of opiate medication use in state Medicaid fee-for-service programs, 1996 to 2002. *Med Care.* 2006; 44(11):1005–1010. [PubMed: 17063132]
6. Zin CS, Chen LC, Knaggs RD. Changes in trends and pattern of strong opioid prescribing in primary care. *Eur J Pain.* 2014; 18(9):1343–1351. [PubMed: 24756859]