

Opioid-induced hyperalgesia method is a clinically relevant issue

Laxmaiah Manchikanti

Anesthesiology and Perioperative Medicine, University of Louisville, Kentucky, USA

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The manuscript by Mercadante *et al.* (1) on opioid-induced hyperalgesia after rapid titration with intravenous morphine: switching and re-titration to intravenous methadone is not only interesting, but also provides clinically relevant information. As evidenced by multiple publications, opioid-induced hyperalgesia is no longer an extraneous research phenomenon. Its clinical relevance and importance are increasingly recognized (2,3). While it has proven to be a problem in chronic non-cancer long-term opioid therapy, now it is increasingly clear that opioid hyperalgesia does not spare those suffering with acute pain or cancer pain. Further, the literature shows that it can happen soon after opioid therapy initiation. Opioid hyperalgesia should not be confused with opioid tolerance, allodynia, and withdrawal-associated hyperalgesia, rather it is a distinct phenomenon in all types of pain with all types of opioids at all durations.

Mercadante *et al.* (1) provide us with illustrations of opioid-induced hyperalgesia with morphine in acute settings, in a surprisingly high proportion of patients (i.e., 12 of 81). They also provide evidence that switching and re-titration through intravenous methadone is a feasible method -- even though methadone has been associated with adverse consequences (including deaths) and is not available in an intravenous form in many countries (4,5).

Preclinical research has illustrated that chronic administration of opioids caused hyperalgesic response (6). While the evidence

is overwhelming in reference to opioid-induced hyperalgesia in rats and other animals, the research in humans is still ongoing. Even then, the mechanism of opioid-induced hyperalgesia in acute settings, or, for that matter, chronic settings, is still puzzling with emergence of multiple hypotheses. The emerging literature might appear to be complicating an already confusing picture. To date, we still do not understand why some individuals suffer from opioid-induced hyperalgesia while others do not, even when larger chronic doses of opioids are used. However, this becomes most puzzling when we consider acute pain and the acute administration of opioids. As the authors describe, this is a state of a paradoxical response whereby a patient who is receiving opioids for the treatment of pain might actually become more sensitive to certain painful stimuli. The pain experienced might be the same or even different pain from the original underlying painful condition (7). Even though the precise molecular mechanism is not yet understood, it is generally believed to occur due to neuroplasty changes in the peripheral and central nervous systems leading to sensitization of pronociceptive pathways. But, these mechanisms do not explain because the conditions described here are related to acute pain without disease progression and long-term high dose opioid therapy.

Thus, a clear understanding of the important mechanistic underpinnings and clinical ramifications of opioid hyperalgesia continue to elude the medical community, with significant implications for diagnosis and management.

Mercadante *et al.* (1) attempt to explain the practical issues involved in managing this unusual and difficult phenomenon. While the study results are preliminary, continued research will be helpful and also helps to lay the foundation for large-scale randomized, double-blind placebo controlled trials.

No potential conflict of interest.

Corresponding to: Laxmaiah Manchikanti, MD. Chairman of the Board and Chief Executive Officer, ASIPP and SIPMS; Medical Director, Pain Management Center of Paducah; Associate Clinical Professor, Anesthesiology and Perioperative Medicine, University of Louisville, Kentucky, 2831 Lone Oak Road, Paducah, KY 42003, USA. Tel: 270-554-8373 ext. 101; Fax: 270-554-8987. E-mail: drlm@thepainmd.com.

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