

Opioid-induced hyperalgesia: a qualitative systematic review

Angst MS, Clark JD. *Anesthesiology* 2006; 104:570-87.

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Abstract: Opioids are the cornerstone therapy for the treatment of moderate to severe pain. Although common concerns regarding the use of opioids include the potential for detrimental side effects, physical dependence, and addiction, accumulating evidence suggests that opioids may yet cause another problem, often referred to as *opioid-induced hyperalgesia*. Somewhat paradoxically, opioid therapy aiming at alleviating pain may render patients more sensitive to pain and potentially may aggravate their preexisting pain. This review provides a comprehensive summary of basic and clinical research concerning opioid-induced hyperalgesia, suggests a framework for organizing pertinent information, delineates the status quo of our knowledge, identifies potential clinical implications, and discusses future research directions.

Comments:

Strengths/Uniqueness: This paper represents an admirable attempt to summarize a large body of evidence from disparate sources on a very complex topic. The search strategy and inclusion criteria are well described.

Weaknesses: The article does not mention the experimental and clinical evidence for the role of opioid metabolites in the development of opioid-induced hyperalgesia (OIH). Also, a more detailed discussion of peripheral and central sensitization to chronic pain as a factor in increased pain perception would have been appropriate, since some of the underlying mechanisms are in common with those for OIH.

Relevance to Palliative Care: Despite abundant animal data, there is limited evidence to confirm the existence of clinically relevant opioid-induced hyperalgesia (OIH). Perhaps the most compelling evidence comes from case reports of patients with allodynia on high dose opioids. Strategies to address OIH include opioid dose reduction, opioid rotation, and possibly the use of NMDA antagonists. Available evidence suggests that phenantrene opioids (e.g. morphine, hydromorphone, oxycodone) may be more likely to cause OIH than piperidine opioids (e.g. fentanyl) or methadone. In the situation of pain that fails to respond to increasing doses of opioid, it would be reasonable to include OIH in the differential diagnosis, along with opioid tolerance, peripheral and central sensitization, delirium, somatization of psychological distress, and addiction.