Pain SIG Research Review

Topic: Opioid-Induced Hyperalgesia

Introduction: The long-term use of opioids to treat chronic pain is problematic for several reasons. One concern with the long-term use of opioids is the development of opioid-induced hyperalgesia (OIH). OIH is associated with a lower pain threshold and occurs in some individuals who use opioids. Hyperalgesia could be a barrier to recovery for some patients with chronic pain.

General Literature Overview: Several studies suggest that OIH may be caused by long-term use of opioids. OIH is more common in patients with opioid abuse than with chronic pain and OIH is reversible when opioid use is tapered. Some authors question the validity of OIH based on the quality of evidence and inconsistent findings found in the literature. The impact of OIH on outcomes for patients receiving physical therapy services is unknown; however, it is possible that interventions provided by a physical therapist may be less effective for patients with OIH.

Articles:

1. Chu L, Clark D, Angst M. Opioid Tolerance and Hyperalgesia in Chronic Pain Patients After One Month of Oral Morphine Therapy: A Preliminary Prospectie Study. J Pain. 2006;7(1):43-48
2. Hooten WM, Lamer TJ, Twyner C. Opioid-Induced Hyperalgesia in Community-Dwelling Adults with Chronic Pain. Pain. 2015;156(6):1145-1152
3. Chu L, Darcy N, Brady C, Zamora K, et al. Analgesic tolerance without demonstrable opioid-induced hyperalgesia: A double-blinded, randomized, placebo-controlled trial of sustained-release morphine for treatment of chronic nonradicular low-back pain. Pain. 2012;(153)8;1583-1592
4. Compton P, Halabicky O, Aryal S, Badiola I. Opioid Taper is Associated with Improved Experimental Pain Tolerance in Patients with Chronic Pain: An Observational Study. Pain Ther 2022;11(1):303-313
5. Higgins C, Smith BH, Matthews K. Evidence of opioid-induced hyperalgesia in clinical populations after chronic opioid exposure: a systematic review and meta-analysis. Br J Anaesth. 2019;122(6):114-126
6. Fishbain D, Pulikal A. Does Opioid Tapering in Chronic Pain Patients Result in Improved Pain or Same Pain vs Increased Pain at Taper Completion? A Structured Evidence-Based Systematic Review. Pain Med. 2019; 20(11):2179-2197

7. Svensson C. Opioid-induced hyperalgesia: is it a clinically relevant phenomenon?. Int J Pharm Pract. 2022; Ahead of Print

- Chu L, Clark D, Angst M. Opioid Tolerance and Hyperalgesia in Chronic Pain Patients After One Month of Oral Morphine Therapy: A Preliminary Prospectie Study.

There is accumulating evidence that opioid therapy might not only be associated with the development of tolerance but also with an increased sensitivity to pain, a condition referred to as opioid-induced hyperalgesia (OIH). However, there are no prospective studies documenting the development of opioid tolerance or OIH in patients with chronic pain. This preliminary study in 6 patients with chronic low back pain prospectively evaluated the development of tolerance and OIH. Patients were assessed before and 1 month after initiating oral morphine therapy. The cold pressor test and experimental heat pain were used to measure pain sensitivity before and during a target-controlled infusion with the short-acting μ opioid agonist remifentanil. In the cold pressor test, all patients became hyperalgesic as well as tolerant after 1 month of oral morphine therapy. In a model of heat pain, patients exhibited no hyperalgesia, although tolerance could not be evaluated. These results provide the first prospective evidence for the development of analgesic tolerance and OIH by using experimental pain in patients with chronic back pain. This study also validated methodology for prospectively studying these phenomena in larger populations of pain patients.

- Hooten WM, Lamer TJ, Twyner C. Opioid-Induced Hyperalgesia in Community-Dwelling Adults with Chronic Pain.

The hyperalgesic effects of long-term opioid use in community-dwelling adults with chronic pain have not been widely reported. Therefore, the primary aim of this study was to determine the associations between opioid use and heat pain (HP) perception in a sample of community-dwelling adults with chronic pain. The study cohort involved 187 adults (85 opioid and 102 nonopioid) with chronic pain consecutively admitted to an outpatient interdisciplinary pain treatment program. Heat pain perception was assessed using a validated quantitative sensory test method of levels. An effect of opioid use was observed for nonstandardized (P = 0.004) and standardized (P = 0.005) values of HP 5-0.5 in which values of the opioid group were lower (more hyperalgesic) compared with those of the nonopioid group. HP 5-0.5 is a measure of the slope of the line connecting HP 0.5 (HP threshold) and HP 5 (intermediate measure of HP tolerance). In univariable (P = 0.019) and multiple variable (P = 0.003) linear regression analyses (adjusted for age, sex, body mass index, work status, pain diagnosis, pain severity, depression, and pain catastrophizing), opioid use was associated with lower (more hyperalgesic) nonstandardized values of HP 5-0.5. Similarly, in univariable (P = 0.004) and multiple variable (P = 0.011) linear regression analyses (adjusted for work status, pain diagnosis, pain severity, depression, and pain catastrophizing), opioid use was associated with lower standardized values of HP 5-0.5. In this sample of community-dwelling adults, these

observations suggest that long-term opioid use was associated with hyperalgesia independent of other clinical factors known to influence HP perception.

- Chu L, Darcy N, Brady C, Zamora K, et al. Analgesic tolerance without demonstrable opioid-induced hyperalgesia: A double-blinded, randomized, placebo-controlled trial of sustained-release morphine for treatment of chronic nonradicular low-back pain.

Although often successful in acute settings, long-term use of opioid pain medications may be accompanied by waning levels of analgesic response not readily attributable to advancing underlying disease, necessitating dose escalation to attain pain relief. Analgesic tolerance, and more recently opioid-induced hyperalgesia, have been invoked to explain such declines in opioid effectiveness over time. Because both phenomena result in inadequate analgesia, they are difficult to distinguish in a clinical setting. Patients with otherwise uncomplicated low-back pain were titrated to comfort or dose-limiting side effects in a prospective, randomized, double-blind, placebo-controlled clinical trial using sustained-release morphine or weight-matched placebo capsules for 1 month. A total of 103 patients completed the study, with an average end titration dose of 78 mg morphine/d. After 1 month, the morphine-treated patients developed tolerance to the analgesic effects of remifentanil, but did not develop opioid-induced hyperalgesia. On average, these patients experienced a 42% reduction in analgesic potency. The morphine-treated patients experienced clinically relevant improvements in pain relief, as shown by a 44% reduction in average visual analogue scale pain levels and a 31% improvement in functional ability. The differences in visual analogue scale pain levels (P = .003) and self-reported disability (P = .03) between both treatment groups were statistically significant. After 1 month of oral morphine therapy, patients with chronic low-back pain developed tolerance but not opioid-induced hyperalgesia. Improvements in pain and functional ability were observed.

- Compton P, Halabicky O, Aryal S, Badiola I. Opioid Taper is Associated with Improved Experimental Pain Tolerance in Patients with Chronic Pain: An Observational Study.

Introduction: The degree to which opioid-induced hyperalgesia contributes to the pain experience of patients with chronic pain remains relatively undescribed. The objective of this pilot study was to determine if experimental pain responses improve in patients with chronic pain as they undergo a planned opioid taper. **Methods:** This was a prospective observational study. Seven patients with chronic neuropathic pain on at least 120 mg morphine equivalents/day were enrolled. The participants were followed over the course of an individualized opioid taper to a lower dose. Measures of experimental pain sensitivity, including indicators of central pain modulation, were collected on a biweekly basis; in addition, measures of function and quality of life were collected monthly. The effect of opioid taper on pain responses and functional outcomes over time were examined using longitudinal mixed-effects regression modeling and general linear regression modeling with regularization as a function of baseline dose, end dose, and taper rate. **Results:** In this small sample of patients undergoing highly individualized and

variable opioid taper, the opioid taper was significantly associated with improved pain responses to the cold-pressor test, with the pain threshold on average increasing by 1.14 s every 6 weeks (p = 0.0084, 95% confidence interval [CI] for 6-week change 0.3039-2.0178) and pain tolerance on average increasing by 2.87 s every 6 weeks (p = 0.0026, 95% CI for 6-week change 1.02-4.7277). Taper-related changes in central pain modulation were not observed, although conditioned modulation trended toward improvement by the completion of opioid taper. Similarly, no declines in function and quality of life were observed with the opioid taper, suggesting stability despite decreased opioid dose. **Conclusions:** Opioid taper was associated with improvements in experimental pain responses without a decline in function and quality of life, suggestive of diminished opioid-induced hyperalgesia in this clinical sample.

-Higgins C, Smith BH, Matthews K. Evidence of opioid-induced hyperalgesia in clinical populations after chronic opioid exposure: a systematic review and meta-analysis.

Background: Opioid-induced hyperalgesia (OIH) is well documented in preclinical studies, but findings of clinical studies are less consistent. The objective was to undertake a systematic review and meta-analysis of studies examining evidence for OIH in humans after opioid exposure. **Methods:** Systematic electronic searches utilised six research databases (Embase, Medline, PubMed, CINAHL Plus, Web of Science, and OpenGrey). Manual 'grey' literature searches were also undertaken. The Population, Interventions, Comparators, Outcomes, and Study design (PICOS) framework was used to develop search strategies, and findings are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. Data synthesis and subgroup analyses were undertaken using a random effects model (DerSimonian-Laird method). **Results:** A total of 6167 articles were identified. After abstract and full-text reviews, 26 articles (involving 2706 participants) were included in the review. There was evidence of OIH, assessed by pain tolerance, in response to noxious thermal (hot and cold) stimuli, but not electrical stimuli. There was no evidence of OIH when assessing pain detection thresholds. OIH was more evident in patients with opioid use disorder than in patients with pain, and in patient groups treated with N-methyl-d-aspartate receptor antagonists (primarily evidenced in methadone-maintained populations). **Conclusions:** OIH was evident in patients after chronic opioid exposure, but findings were dependent upon pain modality and assessment measures. Further studies should consider evaluating both pain threshold and pain tolerance across a range of modalities to ensure assessment validity. Significant subgroup findings suggest that potential confounders of pain judgements, such as illicit substance use, affective characteristics, or coping styles, should be rigorously controlled in future studies.

-Fishbain D, Pulikal A. Does Opioid Tapering in Chronic Pain Patients Result in Improved Pain or Same Pain vs Increased Pain at Taper Completion? A Structured Evidence-Based Systematic Review.

Objective: To support or refute the hypothesis that opioid tapering in chronic pain patients (CPPs) improves pain or maintains the same pain level by taper completion but does not increase pain. **Methods:** Of 364 references, 20 fulfilled inclusion/exclusion criteria. These studies were type 3 and 4 (not controlled) but reported pre/post-taper

pain levels. Characteristics of the studies were abstracted into tabular form for numerical analysis. Studies were rated independently by two reviewers for quality. The percentage of studies supporting the above hypothesis was determined. **Results:** No studies had a rejection quality score. Combining all studies, 2,109 CPPs were tapered. Eighty percent of the studies reported that by taper completion pain had improved. Of these, 81.25% demonstrated this statistically. In 15% of the studies, pain was the same by taper completion. One study reported that by taper completion, 97% of the CPPs had improved or the same pain, but CPPs had worse pain in 3%. As such, 100% of the studies supported the hypothesis. Applying the Agency for Health Care Policy and Research Levels of Evidence Guidelines to this result produced an A consistency rating. **Conclusions:** There is consistent type 3 and 4 study evidence that opioid tapering in CPPs reduces pain or maintains the same level of pain. However, these studies represented lower levels of evidence and were not designed to test the hypothesis, with the evidence being marginal in quality with large amounts of missing data. These results then primarily reveal the need for controlled studies (type 2) to address this hypothesis.

-Svensson C. Opioid-induced hyperalgesia: is it a clinically relevant phenomenon?

The potential for the development of opioid-induced hyperalgesia (OIH) provokes debate about whether long-term treatment with opioids is advisable and effective. If OIH develops during acute administration, will continuation of opioids actually make the pain worse? Hence, it is not surprising that OIH is part of the rationale used to promote deprescribing opioids in patients with chronic pain. But is there evidence that OIH is a clinically relevant phenomenon? This Commentary examines the evidence for OIH in randomized clinical trials in both the acute and chronic settings. Of critical importance in such an assessment is a trial design capable of differentiating OIH, tolerance, withdrawal-mediated pain sensitivity and worsening of the disease. However, studies published to date that purport to give evidence of OIH via experimentally induced pain all lack the rigour needed to differentiate these phenomena. Patient-reported measures of pain and analgesic consumption in these trials are not consistent with the presence of clinically significant OIH. At present, there is insufficient evidence from well-designed clinical trials that OIH is a clinically relevant phenomenon. Hence, while there are other reasons to avoid long-term use of opioids, the potential for the development of hyperalgesia during chronic opioid treatment is not a sound rationale for deprescribing these drugs in patients with chronic pain.

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