

# The Journal of Pain

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### REVIEW ARTICLES

#### 233 **Methadone in Pain Management: A Systematic Review**

Verina Hanna and Helen Senderovich

This systematic review provides a summary of published randomized controlled trials that investigated the effectiveness of methadone in the management of pain. Adequate analgesia can be challenging, as pharmacological options are not necessarily effective for all types of pain and are associated with adverse effects. Methadone is increasingly being considered in the management of both cancer-related and noncancer-related pain. Evidence demonstrates that methadone in postprocedural pain and in cancer-related pain may be dependent on the procedure and cancer type, respectively. Side effects experienced were generally similar to the comparison drug, and lower cost was a benefit to using methadone.

#### 246 **Chronic Opioid Therapy: A Scoping Literature Review on Evolving Clinical and Scientific Definitions**

Yun Shen, Hemita Bhagwandass, Tychell Branchcomb, Sophia A. Galvez, Ivanna Grande, Julia Lessing, Mikela Mollanazar, Natalie Ourhaan, Razanne Oueini, Michael Sasser, Ivelisse L. Valdes, Ashmita Jadubans, Josef Hollmann, Michael Maguire, Silken Usmani, Scott M Vouri, Juan M Hincapie-Castillo, Lauren E. Adkins, and Amie J Goodin

The management of chronic noncancer pain with chronic opioid therapy (COT) is controversial. There is a lack of consensus on how COT is defined, resulting in unclear clinical guidance. This scoping review identifies and evaluates evolving COT definitions throughout the published clinical and scientific literature. This study summarized the most common, current definition criteria for COT and recommends adoption of consistent definition criteria to be utilized in practice and research. The most recent literature trends toward shorter duration criteria overall, suggesting that COT definition criteria are increasingly stringent.

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#### ON THE COVER

Oxylipins are lipid peroxidation products that participate in nociceptive, inflammatory, and vascular responses to injury. Effects of oxylipins depend on tissue-specific differences in accumulation of precursor polyunsaturated fatty acids, and the expression of specific enzymes to transform the precursors. There has been a knowledge gap in the way these molecules operate in nociception. This study applied a systems-based approach to characterize oxylipin precursor fatty acids, and expression of genes coding for proteins involved in biosynthesis, transport, signaling and inactivation of pro- and antinociceptive oxylipins in pain circuit tissues. The findings reported here advance the understanding of molecular lipidomic systems linking oxylipins and their precursors to nociceptive and inflammatory signaling pathways in rats. See Domeniello, et al, Page 275.

## ORIGINAL REPORTS

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### **Transcranial Direct Current Stimulation Accelerates The Onset of Exercise-Induced Hypoalgesia: A Randomized Controlled Study**

Jana Borovskis, Rocco Cavaleri, Felicity Blackstock, and Simon J Summers

Exercise-induced hypoalgesia (EIH) describes acute reductions in pain that occur following exercise. Current evidence suggests that the magnitude of EIH is small-to-moderate at best, warranting exploration of novel avenues to bolster these effects. Transcranial direct current stimulation (tDCS) has been shown to relieve pain and represents a promising intervention that may enhance EIH. This study aimed to determine whether anodal tDCS of the primary motor cortex can augment EIH in healthy individuals experiencing experimentally-induced musculoskeletal pain. Findings show that active tDCS accelerates the onset of EIH in healthy individuals experiencing experimentally-induced pain. This may represent a promising means of enhancing adherence to exercise protocols. However, larger randomized controlled trials in persistent pain populations are required to confirm the clinical impact of these findings.

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### **Molecular Pathways Linking Oxylipins to Nociception in Rats**

Anthony F. Domenichiello, Matthew R. Sapio, Amelia J. Loydpierson, Dragan Maric, Taichi Goto, Mark S. Horowitz, Gregory S. Keyes, Zhi-Xin Yuan, Sharon. F. Majchrzak-Hong, Andrew J. Mannes, Michael J. Iadarola, and Christopher E. Ramsden

Oxylipins are lipid peroxidation products that participate in nociceptive, inflammatory, and vascular responses to injury. Effects of oxylipins depend on tissue-specific differences in accumulation of precursor polyunsaturated fatty acids, and the expression of specific enzymes to transform the precursors. There has been a knowledge gap in the way these molecules operate in nociception. This study applied a systems-based approach to characterize oxylipin precursor fatty acids, and expression of genes coding for proteins involved in biosynthesis, transport, signaling and inactivation of pro- and antinociceptive oxylipins in pain circuit tissues. The findings reported here advance the understanding of molecular lipidomic systems linking oxylipins and their precursors to nociceptive and inflammatory signaling pathways in rats.

## **300 Median Nerve Stimulation as a Nonpharmacological Approach to Bypass Analgesic Tolerance to Morphine: A Proof-of-Concept Study in Mice**

Ming Tatt Lee, Yi-Hung Chen, Ken Mackie, and Lih-Chu Chiou

Analgesic tolerance to opioids contributes to the opioid crisis by increasing the quantity of opioids prescribed and consumed. Thus, there is a need to develop non-opioid-based pain-relieving regimens as well as strategies to circumvent opioid tolerance. This research examined the efficacy of median nerve electrostimulation in morphine-tolerant mice with neuropathic pain induced by chronic constriction injury (CCI) of the sciatic nerve. Findings show that daily treatments of MNS-PC6 for a week (but not electrostimulation at a nonmedian nerve-innervated location) post-CCI induction significantly suppressed established mechanical allodynia in CCI-mice in an orexin-1 and cannabinoid-1 receptor-dependent fashion. This study provides a proof of concept for utilizing peripheral nerve stimulating devices for pain management in opioid-tolerant patients.

## **313 Pain Intensity as a Lagging Indicator of Patient Improvement: Longitudinal Relationships With Sleep, Psychiatric Distress, and Function in Multidisciplinary Care**

John A. Sturgeon, Dale Langford, David Tauben, and Mark Sullivan

Despite a common assumption that reductions in chronic pain intensity must precede improvements in other pain-relevant domains, there has been limited empirical inquiry into the temporal ordering of improvements in chronic pain treatment. Cross-lagged models using retrospective clinical data examined relationships between average pain intensity and symptoms of psychological distress, difficulties with sleep initiation and maintenance, and disability in treatment-seeking patients with chronic pain who demonstrated improvement in pain intensity. This study shows that reductions in pain intensity may not be the first factors to change in effective chronic pain management. Pain intensity scores are not robust predictors of psychosocial outcomes longitudinally. Instead, other factors such as sleep initiation, psychological distress and disability appear to be important targets for intervention that may promote effective pain reduction.

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### **Longitudinal Transcriptomic Profiling in Carrageenan-Induced Rat Hind Paw Peripheral Inflammation and Hyperalgesia Reveals Progressive Recruitment of Innate Immune System Components**

Taichi Goto, Matthew R. Sapio, Dragan Maric, Jeffrey M. Robinson, Leorey N. Saligan, Andrew J. Mannes, and Michael J. Iadarola

Pain is a common but potentially debilitating symptom, often requiring complex management strategies. To understand the molecular dynamics of peripheral inflammation and nociceptive pain, we investigated longitudinal changes in behavior, tissue structure, and transcriptomic profiles in the rat carrageenan-induced peripheral inflammation model. This study investigated the highly orchestrated biological response during tissue inflammation with precise assessment of molecular dynamics at the transcriptional level. The results identify transcriptional changes that define an evolving inflammatory state in rats. This work provides foundational data for identifying markers of, and potential treatments for, inflammation and pain in patients.

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### **A Cost-effectiveness Analysis of an Internet-delivered Pain Management Program Delivered With Different Levels of Clinician Support: Results From a Randomised Controlled Trial**

Blake F. Dear, Eyal Karin, Rhiannon Fogliati, Joanne Dudeney, Olav Nielssen, Amelia J. Scott, Milena Gandy, Madelyne A. Bisby, Andreea I. Heriseanu, Taylor Hathway, Lauren Staples, Nickolai Titov, and Liz Schroeder

There is growing interest in the potential of internet-delivered pain management programs (PMPs) to increase access to care for people with chronic pain. However, very few economic evaluations of these interventions have been reported. Using existing data, the current study examined the cost-effectiveness of an internet-delivered PMP for a mixed group chronic pain patients provided with different levels of clinician support. These findings suggest that carefully developed and administered internet-delivered PMPs, provided with different levels of clinician support, can be highly cost effective for patients with a broad range of pain conditions. The same general pattern of results was found when more stringent clinical outcomes were employed.

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