

The Journal of Pain

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Volume 14, Number 4, April 2013

Editorials

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What Does It Mean to Call Chronic Pain a Brain Disease?

Mark D. Sullivan, Alex Cahana, Stuart Derbyshire,
and John D. Loeser

Multiple investigators have recently asked whether neuroimaging has shown that chronic pain is a brain disease. In this editorial piece, the authors consider the clinical implications of seeing chronic pain as a brain disease. They argue that "disease" is a clinical concept and that conceiving of chronic pain as a brain disease can have negative consequences for research and clinical care of patients with chronic pain.

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Pain Measurement and Brain Activity: Will Neuroimages Replace Pain Ratings?

Michael E. Robinson, Roland Staud, and Donald D. Price

Although brain imaging may offer considerable insight into the neural mechanisms of pain, including relevant causes and correlations, brain images cannot and should not replace self-report. Only the latter assesses the *experience* of pain, which is not identical to neural activity. Brain imaging may help to explain pain, but replacing self-report with brain imaging data would be philosophically and scientifically misguided and potentially harmful to pain patients.

ON THE COVER

A novel, high-definition, transcranial direct current stimulation technique that is capable of a focal and targeted stimulation has been shown to provide a reduction in overall perceived pain in fibromyalgia patients. This image demonstrates placement of electrodes and electric field distribution. See Villamar, et al, page 371.

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Critical Review

338 The Infancy of Infant Pain Research: The Experimental Origins of Infant Pain Denial

Elissa N. Rodkey and Rebecca Pillai Riddell

Skepticism toward infant pain characterized much of 20th century research and clinical practice, with infant surgery routinely conducted with minimal or no anesthesia into the 1980s. This review article examines the history of 19th and early 20th century infant pain research, tracing how the widely accepted belief that infants could not feel pain developed in the period prior to the growing acceptance of infant pain. Four interrelated causes are posited to help explain the tolerance of infant pain denial until recent times.

Original Report

351 Abuse Rates and Routes of Administration of Reformulated Extended-Release Oxycodone: Initial Findings From a Sentinel Surveillance Sample of Individuals Assessed for Substance Abuse Treatment

Stephen F. Butler, Theresa A. Cassidy, Howard Chilcoat, Ryan A. Black, Craig Landau, Simon H. Budman, and Paul M. Coplan

Abuse of opioid analgesics is a growing source of morbidity and mortality in the United States. Some abuse involves modifying the original formulation of the product, or tampering. The intention of tampering is to achieve rapid release of the drug through alternative routes of administration, such as inhalation, injection, and smoking. This article presents preliminary findings indicating that 8 outcome measures of abuse of a reformulated extended-release oxycodone were lower than those for original extended-release oxycodone; this was particularly true for nonoral routes of administration that require tampering.

Commentary

359 **Is There Support for Abuse-Deterrent and Tamper-Resistant Opioid Formulations?**

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Original Reports

363 **Anxiety and Depression Are Associated With Migraine and Pain in General: An Investigation of the Interrelationships**

Lannie Ligthart, Marloes M. J. G. Gerrits, Dorret I. Boomsma, and Brenda W. J. H. Penninx

There is a well-established comorbidity between migraine and anxiety and depression (A/D). This report investigates whether this relationship is specific for migraine and A/D or whether other types of pain are also consistently associated with A/D. The authors conclude that anxiety and depressive disorders are consistently associated with pain, regardless of anatomical site, and that these disorders may be important factors in the co-occurrence of different pain disorders. Awareness of this comorbidity and a better understanding of the underlying mechanisms may facilitate adequate treatment of both types of conditions.

371 **Focal Modulation of the Primary Motor Cortex in Fibromyalgia Using 4×1-Ring High-Definition Transcranial Direct Current Stimulation (HD-tDCS): Immediate and Delayed Analgesic Effects of Cathodal and Anodal Stimulation**

Mauricio F. Villamar, Pakorn Wivatvongvana, Jayanton Patumanond, Marom Bikson, Dennis Q. Truong, Abhishek Datta, and Felipe Fregni

This research focuses on a novel, high-definition, transcranial direct current stimulation technique capable of a focal and targeted stimulation. Results suggest that this technique provides significant reduction in overall perceived pain in fibromyalgia patients as compared to sham stimulation, irrespective of current polarity. The interventions were well tolerated among patients and may have other applications in research and clinical settings.

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Lack of Correlation Between Opioid Dose Adjustment and Pain Score Change in a Group of Chronic Pain Patients

Lucy Chen, Trang Vo, Lindsey Seefeld, Charlene Malarick, Mary Houghton, Shihab Ahmed, Yi Zhang, Abigail Cohen, Cynthia Retamozo, Kristen St. Hilaire, Vivian Zhang, and Jianren Mao

Despite increasing use of opioid analgesics for chronic pain management, it is unclear whether dose escalation leads to better pain relief during chronic opioid therapy. In this study, clinical data from a 7-year period were retrospectively analyzed, examining the impact of dose adjustment on clinical pain score; gender and age differences in response to therapy; and the influence of clinical pain conditions on the opioid analgesic efficacy. A relationship, or lack thereof, between opioid dose change and clinical pain score in a group of chronic pain patients is indicated. The study also calls for further investigation into the effectiveness of opioid therapy in the management of chronic nonmalignant pain conditions.

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Persistent Peripheral Inflammation Attenuates Morphine-Induced Periaqueductal Gray Glial Cell Activation and Analgesic Tolerance in the Male Rat

Lori N. Eidson and Anne Z. Murphy

Morphine is among the most prevalent analgesics prescribed to treat chronic pain. However, prolonged morphine treatment results in the development of analgesic tolerance. This research tests the hypothesis that morphine-induced increases in ventrolateral periaqueductal gray (vlPAG) glial cell activity contribute to the development of morphine tolerance. Conclusions suggest that vlPAG glia are modulated by a persistent pain state and implicate vlPAG glial cells as possible regulators of morphine tolerance.

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Use of ClinicalTrials.gov to Estimate Condition-Specific Nocebo Effects and Other Factors Affecting Outcomes of Analgesic Trials

M. Soledad Cepeda, Victor Lobanov, and Jesse A. Berlin

ClinicalTrials.gov is a registry and results database of federally and privately supported clinical trials conducted worldwide. The authors questioned: what are the characteristics of pain trials; how frequently are trials stopped and why; what is the magnitude of attrition due to lack of efficacy or adverse events; and whether the withdrawal rates depend on pain syndrome. To facilitate this, the authors developed a system called Sherlock that automatically downloads data from ClinicalTrials.gov into a relational database. The ClinicalTrials.gov registry provides researchers with a snapshot of a specific field and allows them to observe changes over time in trial design, including numbers of subjects accrued, and can inform clinical trial design.

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Mere Intention to Perform Painful Movements Elicits Fear of Movement-Related Pain: An Experimental Study on Fear Acquisition Beyond Actual Movements

Ann Meulders and Johan W. S. Vlaeyen

The fear-avoidance model advanced pain-related fear as an important vulnerability factor for the development of chronic musculoskeletal pain. This study demonstrates that the mere intention to perform a painful movement prior to the actual painful movement itself can come to elicit conditioned fear responses. This indicates that actual movement may not be necessary to elicit pain-related fear responses, maintaining chronic pain-related fear, avoidance, and disability.

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Does Opiate Use in Traumatically Injured Individuals Worsen Pain and Psychological Outcomes?

Colleen M. Trevino, Terri deRoos-Cassini, and Karen Brasel

The purpose of this research was to investigate the percent of trauma patients still using opiates, their pain levels, and psychological outcomes—4 months posttrauma—in 101 participants. Seventy-nine percent of participants developed chronic pain 4 months after the initial traumatic injury. Of those who developed chronic pain, 26% were still using opiates. Those using narcotics at 4 months posttrauma had more pain, life interference, depression, and anxiety. The conclusion notes that narcotic pain medication must be used carefully in traumatically injured patients with chronic pain, especially in those individuals with comorbid psychological pathology.

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