

# The Journal of Pain

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### Critical Review

#### 1137 Adverse Event Reporting in Clinical Trials of Intravenous and Invasive Pain Treatments: An ACTION Systematic Review

Mark R. Williams, Andrew McKeown, Zachary Pressman, Matthew Hunsinger, Kendrick Lee, Paul Coplan, Ian Gilron, Nathaniel P. Katz, Michael P. McDermott, Srinivasa N. Raja, Bob A. Rappaport, Michael C. Rowbotham, Dennis C. Turk, Robert H. Dworkin, and Shannon M. Smith

This review article investigated adverse events (AE) reporting in clinical trials of intravenous and invasive pain treatments published in six major anesthesiology and pain journals between 2000–2003 and 2006–2012. The authors examined whether AE reporting improved following publication of the 2004 CONSORT recommendations and also comprehensively reviewed AE assessment using the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks AE reporting recommendations. The report concludes that little improvement has been made since the 2004 guidelines. Better assessment and reporting of treatment AEs is necessary to understand the full clinical impact of intravenous and invasive treatments.

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#### ON THE COVER

Stimulation-evoked antinociception from the anterior pretectal nucleus (APtN) activates two descending inhibitory pathways, one relaying in the ipsilateral lateral paragigantocellular nucleus (LPGi) and another relaying sequentially in the contralateral deep mesencephalic (DpMe) and pedunculopontine tegmental (PPTg) nuclei. The images show the locations of an electrode track in the APtN and injection site into the DpMe, PPTg and LPGi. See Genaro and Prado, Page 1156.

## Original Reports

1150

### **Reducing Opioid Misuse: Evaluation of a Medicaid Controlled Substance Lock-In Program**

Asheley Cockrell Skinner, Chris Ringwalt, Rebecca B. Naumann, Andrew W. Roberts, Leslie A. Moss, Nidhi Sachdeva, Mark A. Weaver, and Joel Farley

Opioid misuse, abuse, and overdose are public health concerns. Medicaid Lock-In Programs (MLIPs) are designed to prevent overutilization of controlled substances by Medicaid patients. However, despite widespread use, there is little information on their impact. Using North Carolina Medicaid claims data from October 2008 through June 2013, this report examined changes in Medicaid-reimbursed opioid prescriptions. Enrollment in this MLIP reduced both the likelihood that patients would present a claim for an opioid prescription, and the number of opioid prescriptions patients secured each month. In conclusion, MLIPs may constitute a successful strategy for reducing the misuse, abuse, and diversion of prescription opioids. However, further research is needed to examine the program's potential unintended consequences.

1156

### **Neural Correlates of the Antinociceptive Effects of Stimulating the Anterior Pretectal Nucleus in Rats**

Karina Genaro and Wiliam A. Prado

Stimulation-evoked antinociception from the anterior pretecal nucleus (APtN) activates mechanisms that descend to the spinal cord through the dorsolateral funiculus, but the encephalic route followed by the descending pathways from the APtN is not completely known. This study evaluated changes in the Wistar rat tail-flick test following lidocaine-induced neural block or N-methyl-D-aspartate receptor-induced neurotoxic lesion of the deep mesencephalic nucleus, tegmental pedunculo-pontine nucleus, or lateral paragigantocellular nucleus.

1164

### **Involvement of Opioid Receptors and $\alpha_2$ -Adrenoceptors in Inhibitory Pain Modulation Processes: A Double-Blind Placebo-Controlled Crossover Study**

Lechi Vo, Sean Hood, and Peter D. Drummond

In healthy humans, high-frequency electrical stimulation (HFS) of the forearm not only evokes local signs of central sensitization but also triggers broader ipsilateral inhibitory influences on pain, akin to a lateralized form of conditioned pain modulation. Paradoxically, some inhibitory influences are augmented by  $\alpha_2$ -adrenoceptor blockade. To determine whether opioid peptides mediate inhibitory effects after HFS, naltrexone was co-administered orally with the  $\alpha_2$ -adrenoceptor antagonist yohimbine in 16 healthy subjects. The findings imply involvement of opioid peptides in an ipsilateral analgesic response that complements the more generalized form of conditioned pain modulation. HFS not only evokes local signs of central sensitization but also triggers a broader ipsilateral anti-nociceptive mechanism mediated by opioid receptors. Dysfunction of this lateralized pain modulation process might contribute to painful unilateral disorders such as migraine or complex regional pain syndrome.

**1174** **Child and Family Antecedents of Pain During the Transition to Adolescence: A Longitudinal Population-Based Study**

Emily Incledon, Meredith O'Connor, Rebecca Giallo, George A. Chalkiadis, and Tonya M. Palermo

Persistent pediatric pain is associated with poorer physical and psychosocial functioning in children, as well as immediate and long-term societal costs. Onset typically occurs in early adolescence, suggesting that late childhood is a key window for identifying potential intervention targets before pain symptoms become entrenched. This study used population-based data from a longitudinal study and found that frequency of previous pain and sleep difficulties were important predictors. This work highlights the importance of early intervention for persistent pain in childhood, given that pain complaints in late childhood tend to persist into early adolescence.

**1183** **A Role for Bradykinin Signaling in Chronic Vulvar Pain**

Megan L. Falsetta, David C. Foster, Collynn F. Woeller, Stephen J. Pollock, Adrienne D. Bonham, Constantine G. Haidaris, and Richard P. Phipps

Chronic vulvar pain is alarmingly common in women of reproductive age and is often accompanied by psychological distress, sexual dysfunction, and a significant reduction in quality of life. To date, the origins of localized provoked vulvodynia (LPV) are poorly understood and treatment manages pain symptoms but does not resolve the root causes of disease. This work indicates LPV has inflammatory origins, although additional studies are needed to understand LPV pain. Bradykinin signaling is one of the most potent inducers of inflammatory pain; this study reports that bradykinin receptors are expressed at elevated levels in LPV patients. The authors also determined that bradykinin activates NF $\kappa$ B signaling (a major inflammatory pathway), while inhibition of NF $\kappa$ B successfully ablates this response. These data suggest that therapeutic agents targeting bradykinin sensing and/or NF $\kappa$ B may represent new, more specific options for LPV therapy.

**1198** **Participant Preferences for Pharmacologic Chronic Pain Treatment Trial Characteristics: An ACTION Adaptive Choice-Based Conjoint Study**

Shannon M. Smith, Jennifer S. Gewandter, Rachel A. Kitt, John D. Markman, Janet A. Vaughan, Penney Cowan, Ernest A. Kopecky, Richard Malamut, Alesia Sadosky, Leslie Tive, Dennis C. Turk, and Robert H. Dworkin

Barriers to clinical trial recruitment can delay study completion, potentially resulting in increased costs and an unrepresentative sample. In the current study of 150 participants with chronic pain, the authors used a computerized adaptive choice-based conjoint (ACBC) survey which included eight characteristics that may affect enrollment in pharmacologic pain treatment trials. Three characteristics had the largest relative importance in participants' trial preferences: (1) invasiveness of required laboratory procedures; (2) ability to continue current pain medications; and (3) payment for study participation. Understanding the preferences of potential participants is an important step toward enhancing enrollment in pain treatment trials. These findings may help to improve enrollment into analgesic clinical trials and in turn accelerate the development of new pain treatments.

1207

**The Effect of Perceived Injustice on Appraisals of Physical Activity: An Examination of the Mediating Role of Attention Bias to Pain in a Chronic Low Back Pain Sample**

Zina Trost, Dimitri Van Ryckeghem, Whitney Scott, Adam Guck, and Tine Vervoort

A growing body of research suggests that perceptions of injustice contribute to detrimental physical and psychological outcomes, both among individuals with recent injury and chronic pain conditions. Outcomes associated with elevated injustice perception have included greater self-reported pain and disability, higher pain behavior, and poorer outcomes following rehabilitation treatment. This article identifies significant associations between perceived injustice, biased attention to pain, and appraisals of common physical activities among individuals with chronic low back pain. These findings suggest targets for intervention as well as directions for future research regarding individuals with high perceptions of injustice related to pain.

1217

**Perceived Injustice Is Associated With Pain and Functional Outcomes in Children and Adolescents With Chronic Pain: A Preliminary Examination**

Megan M. Miller, Eric. L. Scott, Zina Trost, and Adam T. Hirsh

Chronic pain is prevalent in children/adolescents and contributes to high healthcare utilization. Research suggests injustice perceptions about pain are important in adult patients and are a possible treatment focus. The authors conducted a preliminary evaluation of the psychometric properties of the Injustice Experiences Questionnaire (IEQ) and the relationship between perceptions, pain, and functioning in chronic pain patients. Patients completed measures assessing pain intensity, injustice perceptions, catastrophizing, overall functional disability, emotional functioning, social functioning, and school functioning. The IEQ demonstrated good reliability and validity. This initial investigation suggests that injustice perceptions can be reliably and validly measured and are tied to important clinical outcomes in children/adolescents. Future studies that replicate and extend these results are necessary to determine the extent to which injustice perceptions are an important target for intervention.

## **1227**     **Disease-Related, Nondisease-Related, and Situational Catastrophizing in Sickle Cell Disease and Its Relationship With Pain**

Vani A. Mathur, Kasey B. Kiley, C. Patrick Carroll,  
Robert R. Edwards, Sophie Lanzkron,  
Jennifer A. Haythornthwaite, and Claudia M. Campbell

Catastrophizing is a potent psychological modulator of pain across several chronic pain populations. Despite evidence that patients with sickle cell disease (SCD) catastrophize more than other patients, prior research indicates that catastrophizing is not related to sickle cell pain after controlling for relevant covariates such as depression. Recent research suggests that catastrophizing should be assessed across pain contexts. The authors measured disease-specific, general non-disease related, and situational catastrophizing and assessed the relationship between these contextual dimensions. Results revealed differential catastrophizing, with patients reporting greater catastrophizing about SCD-specific pain compared to non-SCD pain and laboratory pain. These results demonstrate the relevance of catastrophizing in understanding pain in SCD, and suggest that context-specific anchors may be beneficial in predicting different aspects of the pain experience

## **1237**     **Exploring What Factors Mediate Treatment Effect: Example of the STarT Back Study High-Risk Intervention**

Gemma Mansell, Jonathan C. Hill, Chris Main, Kevin E. Vowles,  
and Daniëlle van der Windt

Lower back pain (LBP) has a wide impact, not only on the sufferer but also on healthcare costs, workplace absence and social support. Identifying factors associated with long-term disability has been the focus of recent research, and evidence suggests a number of psychological factors being predictive of outcome. One potential solution is the idea of providing stratified care based on a person's risk of a poor outcome, such as the STarT Back approach. Mediation analysis was used to investigate what led to the effectiveness of the STarT Back trial, a large primary care-based trial which treated patients consulting with LBP according to their risk of a poor outcome. Change in pain-related distress and pain intensity were found to have a significant mediating effect on the relationship between treatment group allocation and change in disability outcome.. This study adds to the evidence base of treatment mediation studies in pain research and the role of distress in influencing disability outcome in those with complex LBP.

## **Long-Term Changes in Musculoskeletal Pain Sites in the General Population: The HUNT Study**

Ingunn Mundal, Johan Håkon Bjørngaard, Tom I. L. Nilsen, Barbara I. Nicholl, Rolf W. Gråwe, and Egil Andreas Fors

This large population-based prospective research project, a Norwegian prospective cohort study, aimed to (1) study long-term changes in the mean number of musculoskeletal pain sites, relative to the influence of demographic, lifestyle, and morbidity variables, and (2) examine the development of musculoskeletal pain in terms of number of pain sites within individuals over an 11-year period, according to the same risk factors. This research provides an important contribution to the ongoing debate regarding the association between lifestyle, demographic, and psychosocial risk factors, versus the course of multisite chronic pain. The authors also provide discussion on potential directions for clinical relevance and further research in this field.

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