

# The Journal of Pain

Table of Contents

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## Critical Review

807

### Fifteen Years of Explaining Pain: The Past, Present, and Future

G. Lorimer Moseley and David S. Butler

Explaining Pain (EP) refers to a range of educational interventions that aim to change one's understanding of the biological processes thought to underpin pain. It draws on educational psychology and on conceptual change strategies to help patients understand current thought in pain biology. This report attempts to address common misconceptions of EP. The authors provide a systematic review of recent contributions to the field and propose future directions by which care providers might enhance the effects of EP as part of multimodal pain rehabilitation.

## Original Reports

814

### Analgesic Response to Intravenous Ketamine Is Linked to a Circulating microRNA Signature in Female Patients With Complex Regional Pain Syndrome

Sabrina R. Douglas, Botros B. Shenoda, Rehman A. Qureshi, Ahmet Sacan, Guillermo M. Alexander, Marielle Perreault, James E. Barrett, Enrique Aradillas-Lopez, Robert J. Schwartzman, and Seena K. Ajit

Although ketamine is beneficial in treating complex regional pain syndrome (CRPS), a subset of patients respond poorly to therapy. This work investigated treatment-induced microRNA (miRNA) changes and their predictive validity in determining treatment outcome by assessing miRNA changes in whole blood from CRPS patients. Differences in miRNA signatures in responders and poor responders prior to therapy indicate prognostic value. Mechanistic studies on altered miRNAs can provide new insights into disease.

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#### ON THE COVER

Although ketamine is beneficial in treating complex regional pain syndrome (CRPS), a subset of patients respond poorly to therapy. This work investigated treatment-induced microRNA (miRNA) changes and their predictive validity in determining treatment outcome by assessing miRNA changes in whole blood from CRPS patients. This figure represents post-treatment samples, demonstrating that 43 miRNAs differed between responders and poor responders. See Douglas et al, page 814.

825

**Adherence to Analgesics for Cancer Pain: A Comparative Study of African Americans and Whites Using an Electronic Monitoring Device**

Salimah H. Meghani, Aleda M. L. Thompson, Jesse Chittams, Deborah W. Bruner, and Barbara Riegel

Despite well-documented disparities in cancer pain outcomes among African Americans, surprisingly little research exists on adherence to analgesia for cancer pain in this group. This research compared adherence for cancer-related pain over a 3-month period between African Americans and whites using the Medication Event Monitoring System. There were considerable differences between African Americans and whites in the overall dose adherence. Unique predictors of analgesic adherence varied by race; income levels, analgesic side effects, and fear of distracting providers predicted analgesic adherence for African Americans but not for whites.

836

**Psychological Distress Mediates the Relationship Between Pain and Disability in Hand or Wrist Fractures**

Cassie Ross, Ilona Juraskova, Hopin Lee, Luke Parkitny, Tasha R. Stanton, G. Lorimer Moseley, and James H. McAuley

Upper limb fracture is a common musculoskeletal injury that can lead to marked pain-related disability. Unlike with other common painful musculoskeletal conditions, such as low back pain, little consideration has been given to the role of psychological variables in explaining the relationship between pain and disability during early fracture recovery. This cross-sectional study aimed to determine if psychological distress mediates the relationship between pain and disability in acute hand/wrist fractures. Findings suggest that depression and stress, but not anxiety, explain the relationship between pain and disability and may be novel targets for interventions designed to reduce pain-related disability after upper limb fracture.

844

**Symptoms of Depression Are Associated With Opioid Use Regardless of Pain Severity and Physical Functioning Among Treatment-Seeking Patients With Chronic Pain**

Jenna Goesling, Matthew J. Henry, Stephanie E. Moser, Mohit Rastogi, Afton L. Hassett, Daniel J. Clauw, and Chad M. Brummett

In the past 2 decades, there has been a dramatic increase in the use of opioids to treat acute and chronic pain. Recently it has been posited that depression may be a critical factor in the initiation and maintenance of opioids. This study investigated the association among opioid use, pain, and depression in patients evaluated at a university-based outpatient pain clinic. Depression emerged as a moderator of the relationship among opioid use, pain severity, and physical functioning. These findings lend support to the hypothesis that patients may be self-medicating affective pain with opioids.

852

### **Long-Term Outcome of the Management of Chronic Neuropathic Pain: A Prospective Observational Study**

Dwight E. Moulin, A. John Clark, Allan Gordon, Mary Lynch, Patricia K. Morley-Forster, Howard Nathan, Cathy Smyth, Cory Toth, Elizabeth VanDenKerkhof, Ammar Gilani, and Mark A. Ware

Neuropathic pain arising as a result of a lesion or disease affecting the somatosensory system is often a challenging clinical problem due to severe and disabling pain. This prospective observational cohort study addressed the long-term clinical effectiveness of the management of chronic neuropathic noncancer pain at 7 Canadian tertiary pain centers. Patients were treated according to standard guidelines and were followed at 3, 6, 12, 18, and 24 months. Our present treatment modalities provide significant long-term benefit in only about a quarter of neuropathic pain patients managed at tertiary care pain clinics. Opioid therapy may not be beneficial for the long term.

862

### **Age-Related Decline in Cognitive Pain Modulation Induced by Distraction: Evidence From Event-Related Potentials**

Shu Zhou, Olivier Després, Thierry Pebayle, and André Dufour

Pain symptoms are reported by about 50% of older adults and are strongly associated with decreased quality of life. Impaired pain modulation is a risk factor in the development of chronic pain and therefore may contribute to the frequency of chronic pain in the elderly. This study suggests that age-related declines in pain modulation are caused by functional degeneration of frontal cerebral networks, which may contribute to a higher prevalence of chronic pain. Analyzing the impact of frontal network function on pain modulation may assist in the development of more effective targeted treatment plans.

873

### **Race Effects on Conditioned Pain Modulation in Youth**

Matthew C. Morris, Lynn Walker, Stephen Bruehl, Natalie Hellman, Amanda L. Sherman, and Uma Rao

Race and ethnicity shape the experience of pain in adults, with African Americans typically exhibiting greater pain intensity and evoked pain responsiveness than non-Hispanic whites. However, it remains unclear whether there are racial differences in conditioned pain modulation (CPM) and if these are present in youth. This study assessed CPM to evoked thermal pain in 78 healthy youth (ages 10–17 years), 51% of whom were African American and 49% of whom were non-Hispanic whites. African American youth reported lower mean conditioning pain ratings than non-Hispanic white youth, controlling for mean preconditioning pain ratings, which is consistent with stronger CPM. Findings could have implications for the development of personalized chronic pain treatment strategies that are informed by race and ethnicity.

881

### **Topical Tetrodotoxin Attenuates Photophobia Induced by Corneal Injury in the Rat**

Paul G. Green, Pedro Alvarez, and Jon D. Levine

Corneal injury can produce photophobia, an aversive sensitivity to light. Using topical application of lidocaine, a local anesthetic, and tetrodotoxin (TTX), a selective voltage-sensitive sodium channel blocker, the authors assessed whether enhanced aversiveness to light induced by corneal injury in rats was caused by enhanced activity in corneal afferents. Results showed that lidocaine and TTX attenuate photophobia induced by corneal injury. Although corneal toxicity limits use of local anesthetics, TTX may be a safer therapeutic option to reduce the symptom of photophobia associated with corneal injury.

887

### **Pain Among High-Risk Patients on Methadone Maintenance Treatment**

Pauline Voon, Kanna Hayashi, M-J Milloy, Paul Nguyen, Evan Wood, Julio Montaner, and Thomas Kerr

The complexity of treating concurrent pain and opioid dependence among many methadone-maintained individuals presents a major challenge in many clinical settings. Furthermore, recent expert guidelines have called for increased research on the safety of methadone in the context of chronic pain. This study explores the prevalence and correlates of pain among a prospective cohort of people who use illicit drugs in Vancouver, British Columbia, Canada, who reported enrollment in methadone maintenance treatment between 2011 and 2014. This research suggests several areas for clinical intervention, particularly related to patient education and alternative analgesic approaches for MMT patients experiencing pain.

895

### **Bidirectional Association Between Depression and Fibromyalgia Syndrome: A Nationwide Longitudinal Study**

Meng-Han Chang, Ju-Wei Hsu, Kai-Lin Huang, Tung-Ping Su, Ya-Mei Bai, Cheng-Ta Li, Albert C. Yang, Wen-Han Chang, Tzeng-Ji Chen, Shih-Jen Tsai, and Mu-Hong Chen

Several cross-sectional studies have reported a common comorbidity between depression and fibromyalgia syndrome (FMS). However, a bidirectional temporal association between these 2 distinct diseases has rarely been investigated. Using the Taiwan National Health Insurance Research Database, 25,969 patients with FMS and without any psychiatric disorder and 17,142 patients with depression and without FMS were enrolled and separately compared with age- and sex-matched control groups. This work supports a bidirectional temporal association between depression and FMS such that each disease occurring first may increase the risk of the other subsequently. This result may imply a shared pathophysiology between FMS and depression, but further investigation is warranted.

903

**Spontaneous Chronic Pain After Experimental Thoracotomy Revealed by Conditioned Place Preference: Morphine Differentiates Tactile Evoked Pain From Spontaneous Pain**

Ching-Hsia Hung, Jeffrey Chi-Fei Wang, and Gary R. Strichartz

Chronic pain after surgery limits social activity, interferes with work, and causes emotional suffering. A major component of such pain is reported as resting or spontaneous pain with no apparent external stimulus. A broad variety of surgical procedures result in chronic postoperative pain that persists for at least 3 and sometimes 6 months or longer after surgery. Among these procedures, thoracotomy ranks high. In this report, spontaneous pain, a hallmark of chronic postoperative pain, is demonstrated in a rat model of experimental postthoracotomy pain, further validating use of this model for development of analgesics to treat such symptoms. Although stimulus-evoked pain was sensitive to systemic morphine, spontaneous pain was not, suggesting different mechanistic underpinnings.

913

**Neurobiological Phenotypes of Familial Chronic Pain in Adolescence: A Pilot fMRI Study**

Anita Cservenka, Hannah Stein, Anna C. Wilson, and Bonnie J. Nagel

Parental history of chronic pain has been associated with self-reported pain in adolescent offspring. This suggests that there may be neurobiological mechanisms associated with pain heritability. Because emotional circuitry is an important component of pain processing and may also influence cognition, the authors used functional magnetic resonance imaging to examine affective processing and cognitive control. Results indicate that both affective and executive functioning pathways may be important markers related to the intergenerational transmission of pain. This is the first study to examine neurobiological markers in adolescents with a family history of chronic pain. These findings may aid in the identification of neural phenotypes related to vulnerability for the onset of pain in at-risk youth.

926

**Long-Term Effects of Neonatal Morphine Infusion on Pain Sensitivity: Follow-Up of a Randomized Controlled Trial**

Abraham J. Valkenburg, Gerbrich E. van den Bosch, Joke de Graaf, Richard A. van Lingen, Nynke Weisglas-Kuperus, Joost van Rosmalen, Liesbeth J. M. Groot Jebbink, Dick Tibboel, and Monique van Dijk

Short-term and long-term effects of neonatal pain and its analgesic treatment have been topics of translational research over the years. This work aimed to identify the long-term effects of continuous morphine infusion in the neonatal period on thermal pain sensitivity, the incidence of chronic pain, and neurological functioning. This unique long-term follow-up study shows that neonatal continuous morphine infusion has no long-term adverse effects on thermal detection and pain thresholds or overall neurological functioning. These findings will help clinicians to find the most adequate and safe analgesic dosing regimens for neonates and infants.

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