

The Journal of Pain

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Critical Review

157 **Combination Drug Therapy for Chronic Pain: A Call for More Clinical Studies**

Jianren Mao, Michael S. Gold, and Miroslav "Misha" Backonja

Chronic pain is a debilitating condition associated with disease entities that include diabetic neuropathy, postherpetic neuralgia, low back pain, fibromyalgia and neurological disorders. For many practitioners, managing chronic pain is a challenge. Medications are often prescribed in combinations, an approach referred to as combination drug therapy (CDT). Yet many medications have significant side effects. This article calls for more clinical studies to fully understand the mechanisms and clinical application of CDT in chronic pain management.

Focus Article

167 **Learning About Pain From Others: An Observational Learning Account**

Liesbet Goubert, Johan W. S. Vlaeyen, Geert Crombez, and Kenneth D. Craig

Though direct experience and verbal instruction are important sources in the development of pain-related beliefs and behaviors, accumulating evidence indicates that observation of others in pain may be equally as important. This Focus Article discusses evidence on observational learning in the context of pain, highlights its importance for development and management of chronic pain problems, and discusses potential moderators of observational learning. This piece aims to stimulate research on the role of learning about pain from others.

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ON THE COVER

Heart rate and temperature data are demonstrated in a study of the anesthetic ropivacaine, which may help speed recovery after surgery. See Charlet, et al, page 246.

Original Reports

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A Randomized, Placebo-Controlled Phase 3 Trial (Study SB-767905/013) of Alvimopan for Opioid-Induced Bowel Dysfunction in Patients With Non-Cancer Pain

Gordon Irving, Janos Péntzes, Brian Ramjattan, Michael Cousins, Richard Rauck, Egilius L. H. Spierings, Christi S. Kleoudis, Jerry W. Snidow, Amy Pierce, John Wurzelmann, and Eric R. Mortensen

The balance between pain relief provided by opioid analgesics and the side effects caused is important to patients who take opioids for long-term relief of non-cancer pain. The spectrum of signs and symptoms affecting the gastrointestinal (GI) tract associated with opioid use is known as opioid-induced bowel dysfunction. Although the primary endpoint was not met in this study, the magnitude of alvimopan-induced improvements versus baseline—together with previous study results—suggest that a peripherally acting mu-opioid receptor antagonist has the potential to improve opioid-induced constipation.

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A Randomized, Placebo-Controlled Phase 3 Trial (Study SB-767905/012) of Alvimopan for Opioid-Induced Bowel Dysfunction in Patients With Non-Cancer Pain

Jan-Peter Jansen, Daniel Lorch, John Langan, Ben Lasko, Kai Hermanns, Christi S. Kleoudis, Jerry W. Snidow, Amy Pierce, John Wurzelmann, and Eric R. Mortensen

Gastrointestinal side effects are common with opioid medication, and constipation affects about 40% of patients. Alvimopan is a peripherally acting mu-opioid receptor (PAM-OR) antagonist approved in the U.S. for short-term, in-hospital use for patients undergoing bowel resection. This trial was conducted as part of a discontinued clinical program, in which alvimopan was being developed for opioid-induced constipation. These results demonstrate the potential for a PAM-OR antagonist to manage opioid-induced constipation.

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Does Chronic Pain Alter the Normal Interaction Between Cardiovascular and Pain Regulatory Systems? Pain Modulation in the Hypertensive-Monoarthritic Rat

Dora Pinho, Manuela Morato, Marta R. Couto, José Marques-Lopes, Isaura Tavares, and António Albino-Teixeira

Hypertension-associated hypoalgesia is widely recognized in acute pain conditions. In chronic pain states, the relationship between blood pressure and pain sensitivity is still ill-defined. This work addresses this issue, using complete Freund's adjuvant induced monoarthritis in different models of hypertension. This shows the importance of using multiple models of hypertension, and evaluating pain responses by various methods, to better understand the complex interactions between pain and cardiovascular regulatory systems.

205 Median Nerve Small- and Large-Fiber Damage in Carpal Tunnel Syndrome: A Quantitative Sensory Testing Study

Stefano Tamburin, Carlo Cacciatori, Maria Luigia Praitano, Clizia Cazzarolli, Cristina Foscatto, Antonio Fiaschi, and Giampietro Zanette

The involvement of median nerve small and large fibers in carpal tunnel syndrome (CTS) was explored. The authors found a significant correlation between A δ -fiber function and CTS symptoms. Small fiber involvement took place in milder disease stages. These findings could help understanding CTS pathophysiology and reconcile the discrepancy between CTS symptoms and electrodiagnostic data.

213 Reduced Analgesic Effect of Acupuncture-like TENS but Not Conventional TENS in Opioid-Treated Patients

Guillaume Léonard, Christian Cloutier, and Serge Marchand

Evidence from recent animal studies indicates that the analgesic effect of low frequency transcutaneous electrical nerve stimulation (TENS) is reduced in opioid-tolerant animals. This study compared the effect of conventional (high frequency) and acupuncture-like (low frequency) TENS between a group of opioid treated patients and a group of opioid-naïve patients, to determine if cross-tolerance is also present in humans. Results suggest that patients taking opioids regularly are less susceptible to benefit from acupuncture-like TENS, probably because the analgesia induced by acupuncture-like TENS and opioids are mediated by the same receptors (i.e. μ opioid receptors).

222 The Influence of Non-Nociceptive Factors on Hot-Plate Latency in Rats

Amanda Gunn, Erin N. Bobeck, Ceri Weber, and Michael M. Morgan

The hot plate is a widely used test to assess nociception. The effect of non-nociceptive factors (weight, sex, activity, habituation, and repeated testing) on hot plate latency was examined. This manuscript shows that non-nociceptive factors such as body weight, habituation, and repeated testing can alter hot plate latency, but these factors do not alter morphine potency. This analysis concludes that the hot plate test is an easy and reliable method to assess supraspinally organized nociceptive responses.

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Peak and End Effects in Patients' Daily Recall of Pain and Fatigue: A Within-Subjects Analysis

Stefan Schneider, Arthur A. Stone, Joseph E. Schwartz, and Joan E. Broderick

Clinical research often relies on retrospective recall of symptom levels, but the information gleaned is not well understood. The "peak-and-end rule" suggests that the most intense (peak) and final (end) moments of an experience disproportionately influence retrospective judgments, which may bias self-reports. This study examined the extent to which peak and end symptom levels affect day-to-day recall of pain and fatigue. Results suggest that peak- and end-effects create a small bias in recall reports of pain, but not fatigue. However, there are considerable individual differences in susceptibility to peak and end heuristics.

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Prevalence and Characteristics of Chronic Pain in the General Population of Hong Kong

Wing S. Wong and Richard Fielding

For this research, more than 5,000 adults drawn from the general population of Hong Kong completed the Chronic Pain Grade (CPG) questionnaire, providing information on chronic pain and socio-demographic status. Overall, 34.9% reported pain lasting more than 3 months (chronic pain), having an average of 1.5 pain sites; 35.2% experienced multiple pain sites. This report shows that chronic pain is common in the general population of Hong Kong, and the prevalence is highest among women and middle-aged adults.

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Radiotelemetric and Symptomatic Evaluation of Pain in the Rat After Laparotomy: Long-Term Benefits of Perioperative Ropivacaine Care

Alexandre Charlet, Jean-Luc Rodeau, and Pierrick Poisbeau

Relief of acute and long-term postoperative pain is essential to patients undergoing surgery. The authors undertook a controlled procedure of abdominal surgery in the rat and tested the efficacy of a perioperative care with the anesthetic ropivacaine. This study on freely-moving animals with postoperative pain symptoms and altered autonomic/motor function illustrates the importance of preemptive analgesia care with long-acting local anesthetics. Speeding recovery time after surgery using perioperative ropivacaine care is of significant clinical relevance since it may limit the risk of chronic pain and postoperative complications.

257 **Improving Individual Measurement of Postoperative Pain: The Pain Trajectory**

C. Richard Chapman, Gary W. Donaldson, Jennifer J. Davis, and David H. Bradshaw

The purpose of this research was to demonstrate a method for increasing the precision and information yield of postoperative pain assessment. Pain was recorded using a tool that defines an identifiable trajectory pattern. Most patients (63%) demonstrated a negative slope trajectory characterized by a decline in pain intensity over days following surgery. The acute pain trajectory quantifies rate of pain resolution as well as pain intensity and affords more precise measurement.

263 **Formalin-Induced c-fos Expression in the Brain of Infant Rats**

Gordon A. Barr

In the fetal, infant and adult rat, injury induces a well-defined behavioral response and induces c-fos expression in the spinal cord dorsal horn. There is more limited information about the processing of noxious stimulation in the infant brain. Using Fos expression as a marker of neural activity in the rat, this examination shows that the pattern of brain activation is immature at birth but is in place by 14 days of age.

272 **A Randomized Clinical Trial of Acupuncture Versus Oral Steroids for Carpal Tunnel Syndrome: A Long-Term Follow-Up**

Chun-Pai Yang, Nai-Hwei Wang, Tsai-Chung Li, Ching-Liang Hsieh, Hen-Hong Chang, Kai-Lin Hwang, Wang-Sheng Ko, and Ming-Hong Chang

Short-term acupuncture treatment may result in long-term improvement in mild to moderate idiopathic CTS, this article demonstrates. Acupuncture treatment can be considered as an alternative therapy as other conservative treatments for those who do not opt for early surgical decompression.

280 **Intra-Periaqueductal Gray Matter Microinjection of Orexin-A Decreases Formalin-Induced Nociceptive Behaviors in Adult Male Rats**

Hassan Azhdari Zarmehri, Saeed Semnanian, Yaghoub Fathollahi, Elaheh Erami, Roghaieh Khakpay, Hossein Azizi, and Kambiz Rohampour

The antinociceptive effects of intra-periaqueductal gray matter (PAG) administration of orexin-A, 5 minutes prior to formalin injection, was investigated. Results indicate that the antinociceptive effect of orexin in PAG may provide a role for this neurotransmitter in the up-down modulating pain system, and may further support the development of orexin-1 agonists for pain treatment.

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A Randomized Trial of 2 Prescription Strategies for Opioid Treatment of Chronic Nonmalignant Pain

Bruce D. Naliboff, Stephen M. Wu, Beatrix Schieffer, Roger Bolus, Quynh Pham, Ariel Baria, Dixie Aragaki, Walter Van Vort, Frederick Davis, and Paul Shekelle

The use of opioid medications for treating chronic non-cancer pain is growing. However, there is lacking evidence regarding their long-term effectiveness, association with substance abuse, and proper prescribing guidelines. The findings demonstrate that even in carefully selected patients, there is a significant risk of problematic opioid misuse. While there were no statistically significant differences in the primary outcomes between groups, the escalating dose strategy did lead to small improvements in self-reported acute relief from medications without an increase in opioid misuse, compared with the stable dose strategy.

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Effects of the N-Methyl-D-Aspartate Receptor on Temporal Summation of Second Pain (Wind-up) in Irritable Bowel Syndrome

QiQi Zhou, Donald D. Price, Christopher S. Callam, Michael A. Woodruff, and G. Nicholas Verne

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder in which the pathophysiological mechanisms of pain and hypersensitivity are not well understood. This work further elucidates mechanisms of somatic hypersensitivity in a subset of IBS patients. Results also support an etiologic basis for abnormal NMDA receptor mechanisms in some IBS patients. Future studies are needed to determine if NMDA receptor antagonists may be used to treat IBS patients.

Letter to the Editor

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Negative Emotional Constructs Relevant to Pain: Unique Variability, Content Overlap, and Interrelations: A Comment on Mounce, Keogh, and Eccleston (2010)

Linda M. G. Vancleef, Madelon. L. Peters, and Johan W. S. Vlaeyen

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