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CRITICAL REVIEW

489 **The Blind Leading the Not-So-Blind: A Meta-Analysis of Blinding in Pharmacological Trials for Chronic Pain**

Ben Colagiuri, Louise Sharpe, and Amelia Scott

Patient blinding is a critical feature of double-blind placebo-controlled randomized controlled trials (RCTs). Yet little is known about practices for assessing and reporting blinding in chronic pain trials. This report examined rates and predictors of assessing blinding and its success in pharmacological RCTs. The results indicate that blinding is rarely assessed and often fails. Some study characteristics were associated with lower rates of assessing blinding and its success, such as pharmaceutical sponsorship and side effects. The authors recommend that all researchers conducting RCTs for chronic pain assess and report on the status of patient blinding when reporting the trial outcome.

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ON THE COVER

Paclitaxel-induced peripheral neuropathy (PIPN) and associated neuropathic pain are the most common and serious adverse effects experienced by cancer patients receiving paclitaxel treatment. These effects adversely impact daily activities and consequently the quality of life, sometimes forcing the suspension of treatment. The results of this study conclude that retigabine (a clinically available medicine) can be used to attenuate the development of paclitaxel-induced peripheral neuropathy, as shown by both morphologic and behavioral evidence. See Li, et al, page 528.

ORIGINAL REPORTS

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Cannabinoid Type 2 Receptor System Modulates Paclitaxel-Induced Microglial Dysregulation and Central Sensitization in Rats

Jiang Wu, Mark Hocevar, Bihua Bie, Joseph F. Foss, and Mohamed Naguib

Paclitaxel induces microglial activation and production of proinflammatory mediators in the dorsal horn, which contribute to the development and maintenance of central sensitization and pain behavior. The authors tested the hypothesis that activation of CB2 receptor by MDA7 modulates microglial dysregulation, suppresses the overexpression of brain-derived neurotrophic factor (BDNF) in microglia in the dorsal horn, and attenuates the central sensitization and pain behavior in rats. Findings show that paclitaxel induced microglia dysregulation and epigenetically upregulated the microglial expression of BDNF, which led to sensitization of dorsal horn neurons and mechanical allodynia. MDA7 represents an innovative therapeutic approach for treatment of chemotherapy-induced neuropathy, the report concludes.

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Monoclonal Antibody Targeting the Matrix Metalloproteinase 9 Prevents and Reverses Paclitaxel-Induced Peripheral Neuropathy in Mice

Raquel Tonello, Sang Hoon Lee, and Temugin Berta

Chemotherapy-induced peripheral neuropathy (CIPN) is a common adverse effect associated with anticancer drugs. Nearly 70 percent of treated cancer patients experience neuropathic pain symptoms. CIPN remains ineffectively managed in cancer patients, potentially leading to the discontinuation of treatment. This work demonstrates that a monoclonal antibody targeting the matrix metalloproteinase 9 (MMP9) alleviates neuropathic pain and several mechanisms linked to CIPN. This study is particularly relevant since a humanized MMP9 antibody is already in advanced clinical trials for the treatment of colitis and cancer, and it may be straightforwardly repurposed for the relief of CIPN.

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Activation of KCNQ Channels Prevents Paclitaxel-Induced Peripheral Neuropathy and Associated Neuropathic Pain

Lin Li, Jinxiu Li, Yan Zuo, Danny Dang, Jeffrey A. Frost, and Qing Yang

Paclitaxel-induced peripheral neuropathy (PIPN) and associated neuropathic pain are the most common and serious adverse effects experienced by cancer patients receiving paclitaxel treatment. These effects adversely impact daily activities and consequently the quality of life, sometimes forcing the suspension of treatment. The results of this study conclude that retigabine (a clinically available medicine) can be used to attenuate the development of paclitaxel-induced peripheral neuropathy, as shown by both morphologic and behavioral evidence. While retigabine has been approved by the Food and Drug Administration as an anticonvulsant, this study suggests that this drug can be repurposed to attenuate the development of PIPN.

- 540** **Preoperative Psychosocial and Psychophysical Phenotypes as Predictors of Acute Pain Outcomes After Breast Surgery**
Kristin L. Schreiber, Nantthasorn Zinboonyahgoon, Xinling Xu, Tara Spivey, Tari King, Laura Dominici, Ann Partridge, Mehra Golshan, Gary Strichartz, and Rob R. Edwards
- The severity and impact of acute pain after breast surgery varies markedly among individuals, underlining the importance of comprehensively identifying specific risk factors. In this prospective observational study involving 234 women, the authors measured differences in the psychosocial and psychophysical processing of pain among patients before breast surgery using simple validated questionnaires and brief quantitative sensory testing. Independent of younger age and procedural extent (axillary surgery and reconstruction), affect and greater temporal summation of pain predicted acute postoperative pain and opioid use.
- 557** **Pan-Canadian Estimates of Chronic Pain Prevalence From 2000 to 2014: A Repeated Cross-Sectional Survey Analysis**
Matthew S. Shupler, John K. Kramer, Jacquelyn J. Cragg, Catherine R. Jutzeler, and David G.T. Whitehurst
- Recent temporal trends of chronic pain in Canada on a national and provincial level are unknown. This report shows the prevalence of chronic pain among the general population increased significantly between 2010 and 2012. The sudden increase was observed across all provinces, in all age categories, and among Canadians with no other chronic health conditions. This increase is of major concern because chronic pain is associated with substantial costs to the individual and to society. This parallels changes reported in other western countries, including the United States, and emphasizes the importance of directing further research and resources to help mitigate this trend.
- 566** **Enlarged Areas of Pain and Pressure Hypersensitivity by Spatially Distributed Intramuscular Injections of Low-Dose Nerve Growth Factor**
Line B. Sørensen, Shellie A. Boudreau, Parisa Gazerani, and Thomas Graven-Nielsen
- Intramuscular injection of nerve growth factor (NGF) causes muscle hyperalgesia without immediate pain. This study assessed pain and muscle hypersensitivity after a single-site bolus NGF injection compared with five spatially distributed, low-dose NGF injections in 20 healthy subjects. Findings show that spatially distributed low-dose NGF injections induced prolonged pain, mechanical muscle hypersensitivity and enlarged contraction-evoked pain areas. These features mirror some clinical muscle pain conditions where diffuse pain areas and muscle hypersensitivity is present during daily activities. Low-dose NGF injections may be useful for further studies of prolonged pain conditions.

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Alleviation of Mechanical Allodynia by 14,15-Epoxyeicosatrienoic Acid in a Central Poststroke Pain Model: Possible Role of Allopregnanolone and δ -Subunit-Containing Gamma-Aminobutyric Acid A Receptors

Xuhui Chen, Zuofan Li, Bo Zhang, Rong Hu, Jiayan Li, Miaomiao Feng, Wenlong Yao, Chuanhan Zhang, Li Wan, and Yue Zhang

Central post-stroke pain (CPSP) is a neuropathic pain syndrome arising after lesion of the central nervous system (CNS) due to cerebrovascular insult. Impaired activities and reduced quality of life justify the need for improved treatment. The detailed mechanism of CPSP is not well understood but central disinhibition has been suggested. Recent reports indicated that epoxyeicosatrienoic acids (EETs), the cytochrome P450 metabolites of arachidonic acid, promoted neuronal survival after stroke, displayed antinociception in peripheral inflammatory pain, and reduced neuronal excitability in seizure model. The authors tested this hypothesis. Results show that agents targeting EETs may serve as a potential therapeutic option for stroke. Use, at the initial period, could not only block further nerve damage but also prevent the occurrence of CPSP.

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Trait Perceived Injustice Is Associated With Pain Intensity and Pain Behavior in Participants Undergoing an Experimental Pain Induction Procedure

Esther Yakobov, Carlos Suso-Ribera, Tudor Vrinceanu, Heather Adams, and Michael JL Sullivan

Studies have revealed associations between perceived injustice, pain, disability, and depressive symptoms in patients with chronic pain. Research has proceeded from the assumption that perceived injustice arises as a consequence of debilitating injury or illness. However, it is possible that perceived injustice might have trait-like characteristics, persisting in the absence of an injustice-related eliciting event. This study sought to develop and test a measure of trait perceived injustice (Trait Injustice Experiences Questionnaire; T-IEQ). The results suggest that perceived injustice might reflect an enduring tendency to experience negative life events as unjust, and that trait perceived injustice is associated with higher ratings of pain intensity, anger, and more pronounced displays of pain behavior.

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Tropomyosin Receptor Kinase B Receptor Activation in the Locus Coeruleus Restores Impairment of Endogenous Analgesia at a Late Stage Following Nerve Injury in Rats

Takashi Suto, Daiki Kato, Hideaki Obata, and Shigeru Saito

A rat model of neuropathic pain at 6 weeks after spinal nerve ligation (SNL6w) exhibits both mechanical hypersensitivity and impaired noxious stimuli-induced analgesia (NSIA). Repeated treatment with antidepressants can produce anti-hypersensitivity and restore NSIA. To examine the involvement of a brain-derived neurotrophic factor-mediated mechanism, a tropomyosin receptor kinase B (TrkB) agonist, 7,8-dihydroxyflavone (DHF), was administered to SNL6w rats. The findings reveal that repeated treatment with TrkB agonist, 7,8-dihydroxyflavone, restored endogenous analgesia. Repeated amitriptyline treatment showed similar effect via TrkB mediated mechanisms, and the effect may be independent from the effect of anti-hypersensitivity. This effect of TrkB activation is promising for chronic pain patients with impaired descending inhibition.

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