JOURNAL WATCH

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Our panel of experts highlight the most important research articles across the spectrum of topics relevant to the field of pain management

Expert panel: Michael Erdek, Johns Hopkins University, MD, USA; Nanna B Finnerup, Aarhus University, Denmark; John D Loeser, University of Washington, WA, USA

Rief W, Glombiewski JA. The hidden effects of blinded, placebo-controlled randomized trials: an experimental investigation. *Pain* 153, 2473–2477 (2012).

This is a very clever and important study of 144 healthy volunteers who were administered either inert placebo nasal spray or a spray with a mild prickling effect. They were given instructions that they were either receiving a new analgesic preparation or that they were in a randomized trial of a new analgesic and, therefore, had a 50% chance of receiving the active drug. Pain thresholds were assessed before and after the administration of the nasal spray. Those who believed that they had a 100% chance of receiving the active drug but, in fact, received the inert placebo, demonstrated a significant expectation effect with the greatest increase in pain thresholds. Those subjects who were in the 50% chance of getting the active drug (as in a blinded randomized clinical trial [RCT]) showed a significant difference between the active and inert placebo in threshold changes. This study indicates that blinded RCTs present violations of both internal and external validity. Clinical trials can result, therefore, in observations that do not accurately reflect the specific action of the drug under study. The authors prudently suggest that an open-label arm should accompany an RCT so as to provide better information about clinical usefulness. Judicious use of placebo mechanisms that are already understood, such as expectation or learning, can

enhance drug efficacy for our patients. The placebo response should be seen as the physician's friend, not enemy. Of course, this study does not address the issue of persistence of the placebo response, or the differences between a volunteer in a short-term study and a chronic pain sufferer. It does, however, offer important food for thought as we evaluate new treatments for pain.

– Written by John D Loeser

Eibl JK, Strasser BC, Ross GM. Structural, biological, and pharmacological strategies for the inhibition of nerve growth factor. *Neurochem. Int.* 61, 1266–1275 (2012).

The inhibition of NGF is a timely and frequently discussed topic with the potential for substantial therapeutic import. A review has been carried out elucidating the actions, structure, receptor binding and strategies for inhibition of NGF. NGF is a member of the neurotrophin family, a group of proteins responsible for maintenance of the central and peripheral nervous system, as well as transmission of nociceptive and neuropathic pain signals. NGF mediates its effect by binding to two separate receptors, p75NTR and TrkA. This binding has the beneficial effect of neuronal survival and differentiation, but also the deleterious effect of contributing to neuropathic pain. Several strategies for the inhibition of NGF are discussed. Human monoclonal anti-NGF antibodies, such as tanezumab, have shown promise in the treatment of conditions, such as

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osteoarthritis, due to their specificity and binding times with NGF. Unfortunately, the side effects of worsening osteoarthritis and osteonecrosis in study participants have led to the cessation of clinical trials of tanezumab, other than those expressly for cancer pain. Other therapies discussed include protein kinase inhibitors such as K252a, mimetic peptides that interact with the TrkA or p75NTR receptors, and small molecule neurotrophin antagonists that alter the molecular topology of NGF and inhibit its receptor binding. Further research is indicated to allow use of the considerable advantages of NGF inhibitors while minimizing their recently prohibitive adverse effects.

– Written by Michael Erdek

Cohen SP, Huang JHY, Brummett C. Facet joint pain – advances in patient selection and treatment. *Nat. Rev. Rheumatol.* 9(2), 101–116 (2013).

Zygoapophysial (facet) joint pain is a leading cause of mechanical axial pain in those patients presenting with chronic low back and neck pain, with an estimated prevalence of 10–15% in the low back and 45–55% in the neck. Careful patient selection with initial medical history and physical examination is essential in the diagnostic and treatment process. The authors note that traditional findings, such as ‘facet loading’, are not predictive of facet pain; the physical finding of paraspinal tenderness is much more strongly associated with this diagnosis. Single medial branch blocks are found to be more predictive of overall success with radiofrequency treatment when compared with double blocks or intra-articular injections. Excessive use of local anesthetic and sedation are associated with false-positive blocks, and inadequate doses or vascular uptake of local anesthetic are associated with false-negative blocks. The authors cite that short-term opioid therapy for facetogenic pain has been demonstrated, but that long-term evidence is lacking for its efficacy. Also cited is the superiority of conventional radiofrequency

medial branch ablation over pulsed radiofrequency therapy. Technical factors, such as using larger electrodes, placing the electrodes parallel to the nerve to be lesioned and using electrolyte solution prior to lesioning to increase lesion size, are all supported by moderate levels of evidence. The most common complication of neuritis occurs in <5% of procedures. There is a lack of evidence to support arthrodesis for treatment of facet joint pain.

– Written by Michael Erdek

Ostenfeld T, Krishen A, Lai RY et al. Analgesic efficacy and safety of the novel p38 MAP kinase inhibitor, losmapimod, in patients with neuropathic pain following peripheral nerve injury: a double-blind, placebo-controlled study. *Eur. J. Pain* doi:10.1002/j.1532-2149.2012.00256.x (2012) (Epub ahead of print).

The p38 MAPK pathway participates in an intracellular cascade controlling cellular responses to cytokines. p38 MAPK activation may mediate central sensitization following nerve injury, and preclinical studies have suggested that p38 MAPK inhibitors may reduce neuropathic pain. This double-blind placebo-controlled study evaluated the analgesic efficacy of losmapimod (GW856553), a novel p38 α/β inhibitor, in 168 patients with peripheral post-traumatic or post-surgical pain. Losmapimod was well tolerated; however, there were no statistically significant or clinically meaningful differences between the treatment groups over the 4-week dosing period for either the primary or secondary efficacy variables. In a previous trial, the p38 inhibitor diltapimod was associated with significant pain reduction in a small trial in mixed neuropathic pain, although a period-by-treatment interaction was present [1]. It is possible that the lack of response in this study was due to inadequate exposure at central sites, but further studies are needed to determine

whether p38 MAPK inhibitors will have a role in neuropathic pain treatment.

– Written by Nanna B Finnerup

■ Reference

- 1 Anand P, Shenoy R, Palmer JE et al. Clinical trial of the p38 MAP kinase inhibitor diltapimod in neuropathic pain following nerve injury. *Eur. J. Pain* 15, 1040–1048 (2011).

Moseley GL, Gallace A, Iannetti GD. Spatially defined modulation of skin temperature and hand ownership of both hands in patients with unilateral complex regional pain syndrome. *Brain* 135, 3676–3686 (2012).

Complex regional pain syndrome is characterized by disrupted thermoregulation as well as disrupted tactile processing. In this extensive study, experiments demonstrated that in patients with unilateral upper limb complex regional pain syndrome, the hand temperature depended on its location with respect to the body midline. Crossing the affected hand over the body midline also had small effects on both spontaneous pain and the sense of ownership over the hand. The authors concluded that impaired spatial perception and complex neurological dysfunction are involved in complex regional pain syndrome.

– Written by Nanna B Finnerup

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