

**EFIC5-1139**  
**Special Lecture and Plenary Session**

**PERSONALIZED TREATMENT IN NEUROPATHIC PAIN: VISION BECOMES REALITY**

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Neuropathic pain represents a major medical problem and treatment is still unsatisfactory.<sup>1</sup> Therefore, a new hypothetical concept was proposed in which pain is analyzed on the basis of underlying mechanisms and sensory abnormalities rather than on the basis of the causative etiology.<sup>2</sup> If a systematic clinical examination and a precise phenotypic characterization is combined with a selection of drugs acting at those particular mechanisms, it should ultimately be possible to design optimal treatments for the individual patient.

To achieve these goals several international consortia (German Research Network on Neuropathic Pain, IMI-Europain, Neuropain) established a large data-base that includes epidemiological and clinical data as well as standardized symptom questionnaires and quantitative sensory testing. More than 2000 patients with different neuropathic pain states have been examined.<sup>5</sup> Furthermore, epidemiological and clinical data on the symptomatology of 4200 patients from a cross sectional survey (painDETECT) are available.<sup>3</sup>

Using a subgroup analysis three different somatosensory profiles could be identified in all neuropathic etiologies. Thus, clear phenotypic subgroups exist in neuropathic pain which might indicate specific mechanisms and thus be specifically treated.

Several recent clinical trials using QST-based classification techniques could already identify a differential treatment effect in subgroups of patients. Patients with peripheral neuropathic pain were treated with topical 8% capsaicin patches.<sup>6</sup> Capsaicin responders had more severe cold- and pin-prick hyperalgesia. The sodium channel blocker oxcarbazepine was evaluated in a cohort of patients with peripheral neuropathic pain who were prospectively stratified into two groups by QST.<sup>4</sup> Patients in the first group (irritable nociceptor phenotype) had hypersensitivity and preserved small nerve fiber function, patients in the second group signs of cutaneous deafferentation (non-irritable nociceptor). The number needed to treat was 6.9 in the total sample, 3.9 in the irritable, and 13 in the non-irritable nociceptor phenotype.

In summary, patients with different sensory profiles respond differently to treatment. Consequently, cohorts in clinical trials should be stratified and potentially enriched with patients who likely respond to the study drug based on the sensory profile rather than on the underlying etiology. This approach has the potential to minimize pathophysiological heterogeneity within the groups under study and to increase the power to detect a positive treatment result. In clinical proof-of-concept trials the study population can be enriched prospectively on the basis of "a priori" defined entry criteria. In clinical practice it will be possible to establish an individualized therapy, i.e. to identify the right patients who require a specific treatment option.

**References**

1. Baron R, Binder A, Wasner G. Neuropathic pain – diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol.* 2010, 9:807-19
2. Baron R, Förster M, Binder A. Subgrouping of patients with neuropathic pain according to pain-related sensory abnormalities: a first step to a stratified treatment approach. *Lancet Neurol* 2012;11:999-1005

3. Baron R, Tölle, T.R., Gockel, U., Brosz, M., Freynhagen, R. A cross sectional cohort survey in 2100 patients with painful diabetic neuropathy and postherpetic neuralgia: Differences in demographic data and sensory symptoms. *Pain* 2009;146:34-40
4. Demant DT, Lund K, Vollert J, Maier C, Segerdahl M, Finnerup NB, Jensen TS, Sindrup SH. The effect of oxcarbazepine in peripheral neuropathic pain depends on pain phenotype: A randomised, double-blind, placebo-controlled phenotype-stratified study. *Pain*. 2014 Nov;155(11):2263-73
5. Maier C, Baron R et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. *Pain* 2010, 150:439-50
6. Mainka T, Malewicz NM, Baron R, Enax-Krumova EK, Treede RD, Maier C. Presence of hyperalgesia predicts analgesic efficacy of topically applied capsaicin 8% in patients with peripheral neuropathic pain. *Eur J Pain*. 2015 Apr 8. doi: 10.1002/ejp.703.

**EFIC5-1205**  
**Plenary Session**

**TOWARD A SCIENCE AND PRACTICE OF RESILIENCE IN THE FACE OF PAIN**

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In the past few decades, numerous studies have identified neurobiological and psychosocial risk factors for developing chronic pain and pain-related disability. Recent research has for instance suggested reduced reward responsiveness as a neurobiological marker of chronic pain vulnerability. With regard to psychosocial risk factors, the Fear-Avoidance Model has proliferated our knowledge on the development and treatment of pain-related disability and distress in adult and pediatric populations. Moreover, also social-contextual factors have been found to increase the risk for adverse outcomes. An increased understanding of those risk factors over the years has informed and improved the multidisciplinary treatment of chronic pain.

However, evidence is available that a substantial number of individuals reporting high-intensity chronic pain keep on functioning well despite pain. This indicates that many individuals show resilience, which has been defined as a construct reflecting overall individual well-being despite the presence of a significant stressor (such as chronic pain). In this presentation, it will be argued that considering both risk and resilience mechanisms may be crucial in the prevention and treatment of pain-related disability and reduced quality of life.

Different theoretical perspectives on resilience will be discussed and illustrated with empirical evidence within the context of pain. These include positive psychology accounts of resilience (e.g., Broaden-and-Build Theory of positive emotions) and the psychological flexibility model. I will also highlight the powerful role of the social environment in bolstering patient resilience. Furthermore, an agenda for future research on resilience in the context of pain will be outlined. Finally, implications of the different perspectives on resilience for clinical practice will be illuminated.

**EFIC5-1245**  
**Plenary Session**

**EXERCISE FOR CHRONIC MUSCULOSKELETAL PAIN: UPDATE AND FUTURE CHALLENGES**

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Clinical practice guidelines for the management of musculoskeletal pain commonly recommend exercise and/or activity as a mainstay of treatment. Whilst exercise may be superior to rest in the management of musculoskeletal pain conditions, recent clinical trials indicate that the effects are modest at best (1, 2). Various exercise approaches have been advocated including specific regional exercises to improve movement control, more general functional exercise, strengthening and aerobic exercise but there is currently no evidence that one is superior to another. It may be that certain sub-groups of patients respond to exercise but at present it is not clear if such sub-groups exist and what their characteristics are. A preliminary study in chronic whiplash suggested that clinical sensory signs of central sensitisation may moderate the effects of exercise (3) but this was not verified in a more recent and larger trial with a priori aims to identify treatment effect moderators (1). In other studies, some psychosocial factors may be effect modifiers (4). The reasons for the lack of effect of exercise interventions in people with chronic pain is intriguing. In healthy asymptomatic individuals various exercise types have been shown to induce hypoalgesic effects, but in patients with chronic pain the opposite has been demonstrated, ie sensitivity to pain increases. This indicates that impaired pain inhibitory processes of chronic musculoskeletal pain conditions may be one reason for poor response to exercise interventions. We recently sought to follow-up patients from a previous trial that showed little additional benefit of an exercise rehabilitation program to explore their perceptions of the exercise and its lack of effect. The results of this study will be discussed. It is important that patients with chronic musculoskeletal exercise undertake exercise in order to prevent diseases related to inactivity. Future directions for the incorporation of exercise in the management of chronic musculoskeletal pain will be explored.

1. Michaleff Z, Maher C, Lin C, Rebeck T, Connelly L, Jull G, et al. Comprehensive physiotherapy exercise program or advice alone for chronic whiplash (PROMISE): a pragmatic randomised controlled trial (ACTRN12609000825257). *The Lancet*. 2014;384(9938):133-41.
2. van Middelkoop M, Rubinstein SM, Verhagen AP, Ostelo RW, Koes BW, van Tulder MW. Exercise therapy for chronic nonspecific low-back pain. *Best Pract Res Clin Rheumatol*. 2010;24(2):193-204.
3. Jull G, Sterling M, Kenardy J, Beller E. Does the presence of sensory hypersensitivity influence outcomes of physical rehabilitation for chronic whiplash? - A preliminary RCT. *Pain*. 2007;129(2):28-34.
4. Hill JC, Fritz JM. Psychosocial Influences on Low Back Pain, Disability, and Response to Treatment. *Physical Therapy*. 2011;91(5):712-21.

**EFIC5-1155**  
**Special Lecture and Plenary Session**

**PLACEBO AND PAIN: AN EXPLORATION OF RESEARCH AND CLINICAL FINDINGS**

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Placebo analgesia produces pain relief in individuals by virtue of expectations and anticipations of a benefit. Placebo analgesia can also occur when placebos are used following the administration of active and effective painkillers. Pharmacological studies indicate that placebos might mimic the action of active treatments and promote the endogenous release of opioids in both humans and animals. Social observational learning can also lead to expectancy-driven analgesic effects. Here I present recent behavioral and neurobiological advances on the placebo effect. Based on a well-established proposed conceptual framework, the placebo effect is presented as the product of expectancy mechanisms in which conditioned verbal, observational, and social cues are centrally integrated to change behaviors and outcomes.

Recent scientific investigation in the field of brain imaging is advancing the understanding of cognitive mechanisms and neurobiological substrates of placebo analgesia and associated pain modulation. Neuroimaging studies that have capitalized on well-established behavioral paradigms within this framework, such as placebo analgesia, implicate the anterior cingulate cortex, insula, thalamus, amygdala, and dorsolateral prefrontal cortex as key regions in producing these placebo analgesic effects. Expectations of analgesia facilitate the activation of the systems for pain control along with the release of endogenous mediators crucially involved in placebo-induced benefits. Indeed, neurobiological studies have identified dopaminergic, opioidergic, serotonergic, and endocannabinoidergic pathways as promising systems contributing to pain modulation. Furthermore, candidate variants in genes linked for such pathways are opening new avenues to identifying potential individual placebo responses.

It is becoming clear that every analgesic treatment is significantly modulated by placebo effects and drug specific actions and placebo effects interact additively or synergistically depending on the condition. In clinical settings, learned placebo analgesic effects can be elicited in patients suffering from pain disorders even when pain appears to be refractory to conventional pharmacological interventions. Since placebo effects act as reinforcers of clinical outcomes, gaining deeper understanding of the top-down mechanisms of pain modulation has enormous implications for personalizing and optimizing pain management.

**References:**

**Colloca L.** Placebo, nocebo and learning. **HandbExpPharmacol** 2014;225:17-35

**Colloca L.** Flaten M., Meissner K. Editors. Placebo and Pain: From bench to bedside. **Elsevier**, Oxford, UK – 2013 – ISBN: 978-0-12-397928-5

Simmons K, Ortiz R, Kosswsky J, Krummenacher P, Grillon C, Pine D, **Colloca L.** Pain and Placebo in Pediatrics: A comprehensive review of laboratory and clinical findings. **Pain** 2014;155(11):2229-35