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Guest editorial

Opioids for chronic nonmalignant and neuropathic pain

It is now two hundred years ago that the German pharmacist F.W. Sertürner isolated the first pure opium alkaloid (Sertürner, 1805, 1806, 1817) that he named "morphine". Up-to-now the later so-called opioids are still the mainstay in modern pharmacological treatment of acute and chronic pain. Driven by the growing awareness of an unacceptably widespread undertreatment of pain together with the development of new semisynthetic and synthetic drugs with opioid receptor-mediated actions, the medical use of opioids has now progressively increased throughout the world not only for the relief of acute surgical, posttraumatic and cancer-related pain, but also for the challenging group of nonmalignant chronic pain syndromes. Moreover, opioids provide an expanding field for clinical and basic sciences research, and consequently the last few years have witnessed an unmatched progress in understanding opioid drug action, the physiological role of endogenous opioids and their receptors. Much of this recent progress is reviewed in this special issue of the *European Journal of Pain.*

Bringing together experts in basic neurosciences, pharmacology, psychology and clinical pain medicine from all parts of Europe, the fine collection of review articles in this issue of the journal provides a timely and state-of-the-art overview on current developments and breakthroughs in the field. On the basis of current knowledge and clinical experience, the present mini-reviews draw together experimental observations pertaining to opioid pharmacology, analgesic efficacy, tolerance, addiction and other aspects without loosing sight on the clinically relevant possibility of serious morbidity associated with opioids in special indications or patient populations.

The impact of the patient's genetic background on drug action is currently being unravelled. For example, variations in the expression of drug metabolizing enzymes such as the polymorphic cytochrome P450 enzyme directly influences blood levels of the respective drug, including opioids (see Stamer, Bayerer and Stüber, this issue). To study the classical analgesic actions of opioids new technologies have been applied, including ligand-PET studies illuminating receptor distribution in health and disease (Sprenger et al.). In patients suffering from rheumatoid arthritis, central poststroke pain or trigeminal neuralgia, decreased availability of opioid receptors was found. This likely affects efficacy of exogenous opioids.

In inflamed tissue not only hyperalgesic, but also analgesic mediators are produced, including opioid peptides, somatostatin, endocannabionoids and anti-inflammatory cytokines (Rittner and Stein). Evidence has been provided that acute and pathological pain involves, at least in part, different populations of spinal dorsal horn neurons at the origin of parallel ascending pain pathways. Neurons which mediate hyperalgesia but not normal pain are located in lamina I of spinal dorsal horn, express the NK1 receptor for substance P and activity-dependent synaptic long-term potentiation (Sandkühler and Ruscheweyh). Activation of these separate ascending pain pathways leads to differential activity patterns in the brain. One consequence of which is the distinct aversive character of inflammatory pain (Lorenz and Casey). The new vistas on peripheral and central forms of sensitisation now allow more concise views on opioid drug action for (pre-emptive) analgesia.

Better understanding of pain mechanisms and opioid drug action has widened the indications for opioids in pain therapy to noncancer pain including neuropathic pain (Dickenson and Suzuki). There might be also a role for perioperative opioids in primary and secondary prevention of chronic postoperative pain, particularly in combination with other preventive approaches (Stubhaug). Only recently opioid sensitivity in infancy and developmental regulation of opioid receptor binding have been studied in experimental animals (Nandi and Fitzgerald). Clearly, age affects not only pain sensitivity, but also opioid pharmacology and opioid analgesia and this requires careful opioid titration to effect, both in the very young and in the very old (Wilder–Smith).

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In chronic pain conditions, the therapeutic appropriateness of any measures has to be assessed in terms of enhanced patient's comfort and functional restoration, but also with respect to potential harmful and contrary effects (Breivik; Kress and Kraft). Whereas long-term systemic opioid therapy is now generally accepted as an effective and beneficial approach for all kinds of cancer-related pain, the appropriate use, the potential risks and adverse effects of opioids in the management of chronic nonmalignant pain are still under investigation and remain a matter of controversy. What is the evidence-base for opioid treatment of chronic noncancer pain (Breivik)? May intravenous opoid testing actually help to identify opioid responders or even pain generating mechanisms (Gustorff)? How does chronic opioid therapy affect the driving ability of pain patients, and on which conditions may patients under continuous opioid medication be considered fit to drive (Kress and Kraft)?

In Denmark, where the use of opioids for chronic noncancer pain has started more than 15 years ago, iatrogenic opioid abuse has now become a problem. Controlled long-term trials of opioid therapy in chronic noncancer pain are still missing. As outlined by various contributions to this issue, there are compelling questions that indeed do justify the present thorough examination of the clinical effects of opioids in the treatment of chronic nonmalignant pain, in particular in terms of the fundamental medical issues of safety and efficacy. Guidelines for appropriate and responsible prescription and follow up of patients do exist (Breivik; Kalso), but the potential development of tolerance, physical dependence, addiction (Jage) or even opioid-induced hyperalgesia (Ruscheweyh and Sandkühler) are crucial aspect of the clinical considerations inherent to this approach, as they could compromise the long-term benefits and limit the utility of this pharmacological option in patients with chronic pain.

Changing the route of administration, switching, rotating and combining opioids with other analgesic and adjuvant drugs, such as pregabalin or NMDA antagonists, may improve the effectiveness of opioids and reduce tolerance and side effects as well (Kalso).

The editors are convinced that this interdisciplinary, multifaceted, short but comprehensive overview on current basic and clinical research on opioids not only provides valuable insights into current aspects and future perspectives of opioid research and clinical practice, but is also equally helpful to the individual researcher and to the medical practitioner. Last but not least, the generous support of the *European Journal of Pain* and its Editor making this special issue possible is very much appreciated.

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