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Editorial – Musculoskeletal pain: which role for tapentadol?

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Chronic pain is defined as pain persisting after healing of an underlying pathology or as persisting pain in the absence of tissue damage. In the last decade, the understanding of mechanisms involved in chronic pain led to an improved approach to patient management, with the aim to reduce discomfort, improve quality of life (QoL) and enhance functional recovery.

Chronic musculoskeletal pain, which is frequently encountered in clinical practice, can affect patients of all ages and is particularly common in older patients. Indeed, low back pain is the most frequent chronic pain condition worldwide, with a lifetime prevalence of >70% in western countries[1,2]. Neck pain is also a common disabling disease, with a prevalence of 23%, and is associated with high costs for medical visits and physiotherapy[3]. Both low back pain and neck pain involve nociceptive and neuropathic pain mechanisms[4,5].

Another major cause of chronic pain is osteoarthritis (OA), the most prevalent joint disease in the elderly[6,7]. Pain is usually induced by activity in the early stages of OA, and becomes more and more frequent in the following stages, to become constant, with increasing impairment of daily living[8]. OA pain has long been considered as nociceptive, but mounting evidence suggests that neuropathic pain, with both peripheral and central sensitization, also plays a major role, thus making innocuous stimuli, such as normal joint movements, painful (allodynia) and the response to become exaggerated (hyperalgesia)[8].

Different peripheral events underly neuropathic, nociceptive and inflammatory pains, and, in addition, the final pain experience is a combination of peripheral and of central events. Descending modulatory systems link the brain back to the spinal cord, where noradrenaline is a key inhibitory transmitter in pain control. Excitation and inhibition systems imbalance is the basis of persistent pain states, when pain transmission is persistently reinforced[9]. The ability of a drug to restore normal modulation in the central nervous system (CNS) restores normal transmission, although it does not remove the cause of the pain.

Although chronic pain can be managed with a variety of pharmacological and nonpharmacological interventions, most currently used treatments have not been evaluated in long-term studies, and there is great heterogeneity in patient presentation, course of illness and response to treatment in chronic pain[10]. The risk/benefit ratio for most pharmacologic options is not clear[11-13].

Two of the most commonly used medications for chronic pain are non-steroidal anti-inflammatory drugs (NSAIDs) and opioid pain medications. NSAIDs are widely taken and prescribed for the treatment of pain and inflammation in patients with various musculoskeletal conditions, with over 17% of the population in the USA who reported the use of at least one NSAID in the past week[14]. Prescription opioids are also commonly prescribed for pain. In 2012, healthcare practitioners in the USA wrote more than 200 million prescriptions for opioids[15]. Unfortunately, these drugs are not so free of adverse events as otherwise it would be desirable for long-term use. Both cyclo-oxygenase-2 selective inhibitors and traditional NSAIDs have been associated with a cardiovascular risk and an array of potentially serious side effects[16], and, on the other end, prescription opioids have been associated with tolerability issues[17]. Besides morphine, other μ-opioid receptor (MOR) agonists, such as fentanyl and buprenorphine, hydromorphone and oxycodone, have been developed for improved efficacy and safety. However, true innovative analgesics that utilize combined mechanisms of action are required for generating better response rates, fewer side effects, and improved tolerability, particularly in elderly patients.

Tapentadol is an innovative pharmacological tool, acting centrally on the as cending and on the descending modulatory systems. It has a dual mechanism of action, providing the efficacy of a strong

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opioid (but with a reduced opioid load) and an improved safety. It represents the first, and so far unique, member of a new class of analgesic agents, acting on the MOR, although much less than morphine, and simultaneously inhibiting the reuptake of noradrenaline (NRI), a key inhibitory transmitter in pain control[18,19]. Tapentadol analgesic activity takes advantage from the synergy between the MOR activity and the efficacy of the serotonin-noradrenalin reuptake inibitors (SNRIs), which is considered a favorable option for the treatment of neuropathic pain[11].

The extensive preclinical data on tapentadol reveal an efficacy equal to that of morphine but with a major noradrenergic component in behavioral and neuronal measures in models of nerve injury, arthritis, and cancer-induced bone pain[20,21].

There is evident synergy between the MOR and NRI actions, and the ability to control central sensitization. The MOR action inhibits pain messages at the spinal cord level and in the brain, and the NRI provides a powerful inhibitory action on spinal events. Data from experimental studies has shown great efficacy on pain from tissue and nerve damage, and on mixed pain. Such evidence was consistent with clinical efficacy in patients with chronic pain[22].

Indeed, in rats and humans, tapentadol restores the failed noradrenaline inhibitions as measured directly in patients through conditioned pain modulation[23].

Experimental evidence showing that NRI is a key mechanism that can be predominant in chronic/neuropathic pain reinforces the concept that tapentadol is different to classical opioids and may, therefore, be an *a priori* choice for the treatment of chronic, neuropathic and mixed pain[22].

It may be here remembered that noradrenaline functions in the CNS include restricting the development of neuroinflammatory activation, providing neurotrophic support to neurons, and providing neuroprotection against oxidative stress. In recent years, it has become evident that disruption of physiological NA levels or signaling is a contributing factor to a variety of neurological diseases and conditions[24].

Pivotal studies, assessing thousands of patients, have shown that tapentadol is effective and well tolerated for the management of moderate-to-severe chronic non-cancer pain with comparable efficacy, but with a significantly superior gastrointestinal tolerability to oxycodone controlled release (CR)[25]. Two clinical trials in patients with painful diabetic polyneuropathy have proven the efficacy of tapentadol prolonged release (PR) even in typical neuropathic pain conditions, and preliminary evidence also exists for its effectiveness in chronic low back pain and other mixed pain conditions characterized by a concomitant neuropathic pain component[25].

The efficacy of tapentadol is linked to a good tolerability and safety profile due to several characteristics. Tapentadol shows a minimal serotoninergic activity, with long-term safety advantages (e.g., reduced emesis) in comparison with opioids[26]. It is characterized by a predictable and reliable pharmacokinetic profile that makes drug-drug interactions unlikely to occur. No pharmacologically active metabolites are generated, and no potential inhibition or induction on cytochrome P450 enzymes have been demonstrated. Explicitly, there was a lack of clinically undesired interactions with paracetamol, acetylsalicylic acid, naproxen, probenecid, omeprazole or metoclopramide.

Tapentadol produces its strong analgesic effect via two separate and complementary analgesic mechanisms, only one of which is μ-opioid. The percentage contribution of each component of the mechanism of action to analgesia and to adverse effects was estimated applying the standard drug-receptor theory and novel techniques to *in vitro* and *in vivo* data. It was found that the percentage contribution of the opioid component to the adverse effect magnitude relative to a pure/classical μ-opioid at equianalgesia (termed the μ-load of tapentadol) was ≤40%, relative to pure MOR agonists, which have, by definition, a μ-load of 100%, having a single mechanism of action. This reduced μ-load likely translates into a more favorable tolerability profile of tapentadol compared with strong classical opioids[25].

According to the above, the MOR-NRI-based mechanism, together with the reduced μ-load makes tapentadol an innovative strong analgesic, characterized by a good tolerability profile. Beyond these immediate outcomes on pain control, several studies showed that tapentadol attains further goals, which may be considered the ultimate aims of analgesia in chronic pain: the improvement of QoL and functional recovery[27-30].

Indeed, reduced pain is associated with improved QoL and more rapid recovery of functionality. These improvements, in turn, lead to increased productivity of the patient – and this further contributes to ameliorate QoL, in a vicious circle. At the same time, the patient has a reduced need for medical therapies, with a potential cost saving[31].

The impact of tapentadol PR on QoL and functional recovery was evaluated by a pooled analysis of randomized trials in patients with non-oncological pain, using oxycodone CR as a comparator. Overall, therapy with tapentadol PR improved all dimensions of QoL, often showing an advantage over oxycodone. Improved QoL was associated with more rapid functional recovery and better quality of sleep. This action of tapentadol PR can likely be due to its peculiar pharmacological profile, which is endowed with a pronounced noradrenergic activity[27-30].

Moreover, an analysis using a Bayesian Markov chain Monte Carlo method showed that tapentadol is associated with reduced time missed from work, less impairment during work, and a diminished loss in work productivity, as compared with oxycodone CR[31]. In a pharmacoeconomy analysis, tapentadol PR showed more favorable outcomes than oxycodone/naloxone: in 65% of cases, it was less costly and led to a marked quality-adjusted life-years gain[32]. The cost-effectiveness of tapentadol PR can be attributed to its price, the lower incidence of adverse events and the lower rate of discontinuation, leading to a further economic advantage. As a whole, evidence specifically collected on tapentadol PR unequivocally shows its beneficial and profound effect on QoL and functionality. This contributes to a comprehensive recovery of the patient, not limited to pain reduction.

To support a correct and beneficial use of this innovative centrally acting analgesic, experience in a real-life setting is being compared with evidence from clinical trials and is providing additional information that may help the clinical practice. This supplement reports recent studies collected in a real-life setting, where chronic musculoskeletal pain was treated with tapentadol.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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