

# Pain Management Review Part 4

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## Objectives

- Discuss important considerations in ketamine administration for analgesia.
- Discuss mechanisms contributing to a state of calm alertness in the yoga system.
- Review current understanding of the mechanism of and treatments for fibromyalgia syndrome.
- Evaluate outcomes associated with the use of controlled-release oxycodone for up to 3 years in the treatment of noncancer pain.
- Describe the association of active trigger points with lumbar disc lesions.
- Consider factors that can influence the two-way pain-cognition interactions when designing neuroimaging experiments.
- State the most important factor in the stability of a cluster solution.
- Review adverse effects of opioids on the central nervous systems of palliative care patients.
- State three effects produced by glutamate activation of NMDA and non-NMDA receptors.
- State the early ratios used to convert from oral morphine equivalents to oral hydromorphone.

## Chronic administration of ketamine for analgesia.

*Ben-Ari A et al*

**Journal:** J Pain Palliat Care Pharmacother 21(1):7-14, 2007. 62 References

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**Faculty Disclosure:** Abstracted by J. Joyce, who has nothing to disclose.

Ketamine has been available in clinical practice for over 40 years. It has been recommended as an anesthetic agent, especially in pediatrics, for trauma, hypovolemic patients, those with septic shock, and patients with pulmonary diseases and for skin grafts and dressing changes associated with burn trauma. When ketamine is administered in subanesthetic doses it has a significant analgesic action and therefore could have a role in pain medicine. Current practice is to reserve ketamine as a last resort after first and

second line drugs have failed.

There has been a renewed interest in the use of ketamine for the treatment of acute and chronic pain. Ketamine is a non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptors for glutamate, although its effects are mediated by interaction at other sites as well, including opioid receptors, voltage-gated Ca<sup>++</sup> channels, and monoamine receptors.

There is evidence to suggest that the site of action of ketamine administered neuraxially in the lumbar intrathecal or epidural space is in the spinal cord. Even so, the major site of action is not clear. It is possible that ketamine analgesia is not mediated by opioid receptors in the supraspinal CNS.

It would seem fair to conclude that the prevailing data suggest that ketamine should have a place, although a cautious one, in the pain clinician's armamentarium for selected patients. Tolerance and dependence are important in light of the fact that ketamine is similar to phencyclidine (PCP), a known recreational or "club drug." The danger from ketamine use lies in the interaction of the patient using the drug and the setting where it is used. Ketamine can leave the patient confused, possibly causing risk for road traffic accidents, falls, polypharmacy adverse interactions, etc.

Further work is needed to characterize the profile of the patient who might be prone to substance abuse behavior with this drug, compared with opioids and other psychoactive compounds. Another issue that is unclear relates to prolonged administration of ketamine, which has been associated with cognitive impairment. Neurological changes following chronic administration of neuraxial ketamine are unclear.

### **Effectiveness of yoga therapy in the treatment of migraine without aura: a randomized controlled trial.**

*John PJ et al*

**Journal:** Headache 47(5):654-661, 2007. 31 References

**Reprint:** Department of Zoology, University of Rajasthan, Jaipur, Rajasthan, India (PJ John, PhD)

**Faculty Disclosure:** Abstracted by J. Joyce, who has nothing to disclose.

In recent years, it has become common practice to use complementary and alternative medicine (CAM) in the treatment of headache, alone and in combination with drugs. Alternative health care may be more congruent with values, belief, and philosophical orientation toward health and life. Interestingly, most patients do not report the use of CAMs to their doctors. Massage, exercise, acupuncture, chiropractic, and herbs are the most used CAM therapies for headaches. The most common reason for deciding to try a CAM therapy was that it offered a potential improvement of headache. Yoga, coupling physical exercise with breathing and relaxation, is a popular alternative form of mind-body therapy. Generally, positive results in

stress, anxiety, depression, epilepsy, multiple sclerosis, carpal tunnel syndrome, musculoskeletal and cardiopulmonary disease, back pain, arthritis, and even cancer suggest that yoga has potential as a therapeutic intervention in a variety of disorders.

The authors designed a clinical trial to evaluate the effectiveness of yoga for migraine. This randomized controlled trial evaluated the effectiveness of yoga-based intervention on migraine headache. As a result, yoga was found to have a beneficial effect on various parameters (frequency, intensity, duration of attack, medication score) psychological parameters (anxiety and depression), and the nature of pain. Yogic breathing is a unique method for balancing the autonomic nervous system and influencing psychological and stress-related disorders. Mechanisms contributing to a state of calm alertness include increased parasympathetic drive calming of stress response systems, neuroendocrine release of hormones, and thalamic generators. Through active yoga postures and deep relaxation techniques, the parasympathetic system may induce a more balanced physiological and psychological state.

In this study the authors developed a series of simple, relaxation-focused postures which excluded vigorous bending. Obviously unclear from this study was whether a different yoga regimen would have yielded similar benefit. The study's most evident limitation lies in the absence of a placebo group. Consequently, patient expectation well might have confounded the reported results. The yoga group received special attention during sessions, perhaps evoking the so-called Hawthorne effect. The outcome measures were questioner-based and subjective, and yoga therapy ideally should be tested with an objective derived outcome measure as well. Finally, the authors obtained no long-term follow-up data which would allow them to comment upon the durability of the treatment effect.

### **Fibromyalgia syndrome's new paradigm: neural sensitization and its implications for treatment.**

*Podell RN*

**Journal:** J Musculoskel Pain 15(2):45-54, 2007. 60 References

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**Faculty Disclosure:** Abstracted by J. Joyce, who has nothing to disclose.

When first defined by the American College of Rheumatology (ACR), fibromyalgia syndrome (FMS) was viewed as a rheumatological illness—a matter of sore muscles. The current "neural sensitization" model focuses on abnormal sensitivity within the central nervous system's pain signaling pathways. Current thinking emphasizes the likelihood that there are several subtypes of FMS with over-lapping but not identical clinical presentations, mechanisms, and treatments. The ACR's criteria for FMS require: 1) a history of widespread chronic pain, and 2) abnormal tenderness at 11 of 18 designated pain-sensitive anatomic sites, called tender points (TePs).

Several lines of research now provide objective evidence of physical abnormalities in the FMS patient's pain signaling pathways. Fibromyalgia syndrome patients had increased regional blood flow in multiple areas of the brain at relatively low intensities of pressure. Changes in blood flow coincided with the patient's report of pain. Others have described regional cerebral blood flow and cerebrospinal fluid (CSF) neurochemical abnormalities in FMS, including increased CSF levels of Substance P and decreased CSF levels of serotonin. For mild cases, medication for pain together with lifestyle advice may be all that is needed. When pain is severe or accompanied by other symptoms, the treatment plan should cover at least the following main problem areas: pain, sleep quality, how patient and family are coping with the distress of chronic illness, exercise, and whether depression and/or anxiety have developed.

Additional problems that may have to be addressed include: low blood pressure, tachycardia, neurocognitive problems such as concentration or memory problems, fatigue and poor stamina, local or regional peripheral sources of musculoskeletal pain, irritable bowel syndrome, or post-prandial syndrome. For each area, patient education and support are important in addition to physical, psychological, and pharmacological attention.

Clinical experience suggests that FMS patients may be atypically more "sensitive" to medicine side effects, particularly those who display chronic fatigue, neurocognitive difficulties, irritable bowel syndrome, etc. A substantial proportion of patients are unable to tolerate any given medicine, especially at higher doses.

### **Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study.**

*Portenoy RK et al*

**Journal:** Clin J Pain 23(4):287-299, 2007. 44 References

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The use of opioid therapy for chronic noncancer pain has steadily increased during the past two decades. With increasing use, there is a new recognition of the need to carefully select patients for therapy and to regularly monitor outcomes related to effectiveness, safety, and the potential for problematic drug-related behaviors. Empirical data are needed to document long-term outcomes associated with opioid therapy.

The present study was designed to assess long-term outcomes associated with controlled-release oxycodone therapy, administered for up to 3 years to a population of patients with chronic pain from osteoarthritis, diabetic neuropathy, or low back pain. The increasing medical use of controlled-release (CR) oxycodone and other long-acting opioids when pain is continuous or frequently recurrent has resulted from several

factors, including the evolving consensus of pain specialists, professional education, professional and public outcry about undertreatment of pain, reassurance about the legitimate medical role of opioid medications by regulatory and law enforcement communities, and new research that has provided evidence of favorable outcomes associated with opioid therapy of varying durations in many conditions.

One of the most important concerns during long-term opioid therapy relates to the potential need for repeated, and ultimately unsustainable, dose increases to maintain benefits. This study provides evidence that the greatest need for opioid titration occurs during the first 3 months for most patients, after which further dose escalation may be gradual and minimal.

Opioids are potentially abusable drugs and the possibility of misuse, abuse, and even addiction or diversion exists whenever a patient is treated. The risk of these types of adverse outcomes is likely to be higher in varied subgroups of patients, most notably those with a history of drug abuse or addiction.

The data support the conclusion that there is a subgroup of patients with chronic pain who can receive long-term opioid therapy and experience pain relief. The risk of problematic drug-related behaviors is low, but not zero and when these behaviors occur, they mandate a careful assessment and appropriate diagnosis.

#### **The association of active trigger points with lumbar disc lesions.**

*Samuel AS et al*

**Journal:** J Musculoskel Pain 15(2):11-18, 2007. 43 References

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**Faculty Disclosure:** Abstracted by J. Joyce, who has nothing to disclose.

An important component of the low back pain syndrome (LBP) is pain radiating out to the legs, known as sciatica. There can be causes of sciatica pain that do not originate in the lumbar spine. The myofascial pain syndrome (MPS) involving trigger points (TrPs) in the piriformis muscle and gluteus medius can refer pain in the distribution of the sciatic nerve. Pain and muscular dysfunction often leads to the formation of secondary and associated TrPs with their own referred pain zones. TrPs are the immediate cause of pain in many patients with musculoskeletal conditions. After TrP inactivation, pain disappears for a long period of time or permanently, demonstrating the myofascial factor as the immediate cause of pain. These authors hypothesize that there should be a direct association between presence of active TrPs in patients who have lumbar disc prolapse and this should also correspond with the level of disc lesion.

The results from this study suggest that there is a MPS component in the subjects with lumbar disc prolapse and it corresponds with the myotome of the disc lesion. This could be due to segmental sensitization and irritation. The etiology of sensitization of nerves usually results from an area of damaged tissue that generates continuous nociceptive impulses and is most properly described as "irritative focus." Segmental sensitization is the response of nerves and the spinal cord to the irritative focus, which spreads proximally and distally if the irritative foci are not treated and becomes a TrP. Segmental sensitization induces spasms, tightness, and TrPs in the myotome corresponding to the involved spinal segment.

If the clinical situation allows a choice between conservative and surgical treatment, the patient should be informed that the benefit expected from the operation is immediate relief of sciatic pain and not improvement of the long-term prognosis. The overuse of surgery has been perhaps the single most damaging medical intervention for back pain sufferers. Strong association between the disc disease and TrPs indicated that an MPS component may be the main causative factor in the low back and leg pain.

One interesting finding is that the subjects whose MRI confirmed the location of lesion had TrPs in the corresponding myotome level in the tibialis anterior, extensor hallucis longus, gluteus maximus, quadriceps, and gastrocnemius. Trigger points were not found or found less in the tibialis posterior, extensor digitorum longus, gluteus minimus, and hamstrings.

The authors hypothesize that the variability of TrPs may be attributed to disturbed body statics, equilibrium, and altered motor patterns provoked by pain leading to muscle imbalances.

#### **A re-examination of pain-cognition interactions: implications for neuroimaging.**

*Seminowicz DA, Davis KD*

**Journal:** Pain 130(1-2):8-13, 2007. 77 References

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**Faculty Disclosure:** Abstracted by J. Joyce, who has nothing to disclose.

The interaction between pain and cognition has become a hot area of research. Several studies have shown that cognitive engagement can reduce pain-related brain activity, especially in primary and secondary somatosensory, insula, and cingulate cortices. The relationship between pain and attention appears to be complex. There is evidence that pain can affect large cortical networks involved in allocating attentional resources. Several factors that can influence the two-way pain-cognition interactions must be considered when designing neuroimaging experiments. Divided attention pertains to the ability to attend to multiple stimuli at once. Focused attention allows for background information to be ignored.

When we focus attention on something in particular, we suppress attention to and sometimes awareness of other information. During focused attention, stimulus-evoked activity in some neurons is enhanced. There is substantial evidence that chronic pain can impair cognitive abilities. One possible mechanism for this effect is based on cortical plasticity and involves impairment of brain function. Another possible mechanism is based on the concept of limited processing capacity, whereby ongoing pain demands attention and limits the amount of resources available for task performance.

The assumption that distraction disrupts pain is a contentious issue. Electrophysiological and behavioral studies in animals have also shown that attentional state can modulate nociception. More recent studies have questioned the capacity of cognitive engagement to significantly affect both acute and chronic pain. It is nearly impossible to quantify the unique effect of cognitive distraction on pain because of a paradox inherent in studies of divided attention: one cannot simultaneously attend to pain in order to give a rating while being distracted. Any effect of distraction is lost the moment the subject is asked to rate the pain. One should therefore distinguish between pain *evaluation* and pain *perception*. Once the subject begins to describe the perception, the evaluation begins, which may in turn affect the perception. This problem complicates the interpretation of neuroimaging studies that reported decreased pain ratings during cognitive task performance.

Two additional factors affect the outcome of pain cognition interaction studies. One is the instruction set given to subjects. The second factor is the delay between the effect of interest and the acquisition of pain ratings. Pain ratings have been reported as not being affected by cognitive task performance when obtained immediately following stimulation, but were significantly lower when subjects were asked to rate the pain 10 minutes following removal of the stimulus.

The findings on the effects of cognitive engagement on pain ratings are inconsistent and can differ for experimental versus clinical pains. While there is evidence that cognitive engagement can affect pain ratings, the interpretation of such findings should include whether the cognitive engagement is active or passive, as well as the instructions given to subjects and their potential for influencing the type of engagement.

#### **A revised taxonomy of patients with chronic pain.**

*Sheffer CE et al*

**Journal:** Pain Med 8(4):312-325, 2007. 47 References

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**Faculty Disclosure:** Abstracted by J. Joyce, who has nothing to disclose.

The classification of patients into meaningful groups is fundamental to medicine and psychology. Classifying patients with chronic pain is an ongoing challenge. Although progress is being made, there is still much to be accomplished in the process of defining and refining a useful, reliable, and valid taxonomic system. Some of the concerns about the Multidimensional Pain Inventory (MPI)/Multiaxial Assessment of Pain (MAP), MPI/MAP, system are related to its psychometric development. Because the MAP/MPI system was derived from a cluster analysis of the scales from the West Haven-Yale MPI (WHYMPI), the stability of the system is linked to the original factor analysis of the WHYMPI.

This study will derive and evaluate a taxonomic classification system generated from the revised scales of the MPI using recommended methods in a step-by-step manner. The results are derived from replicable, cross-validated, revised scaling structure of the MPI, an improvement over the scaling structure used in the MPI/MAP system. The stability of a cluster solution is assumed to be directly related to the replicability of the cluster solution across methods and data sets.

The clusters were also validated with measures not used to generate the solution. Significant differences were found between at least two clusters for each tested variable, indicating that the clusters consist of groups with distinct features that can be assessed by other instruments and are not simply an artifact of the analysis. Although there is value in comparing the differences in the original and the revised patient categories, note that these two sets of categories are inherently qualitatively different.

Reporting the mean scale scores allows clinicians who use the revised scoring/scaling structure to directly compare their patients' scores with these results in their offices. A clinician can then score a patient's MPI responses according to the Deisinger et al. revision, plot the scale scores and directly compare the results to the profiles. Results from this study have potential usefulness for clinicians in case conceptualization. The large heterogeneous sample and use of mean scaled scores are strengths of this investigation. Limitations of this study lie in the exclusion of participants representing certain populations.

#### **Adverse effects of opioids on the central nervous systems of palliative care patients.**

*Vella-Brincat J, Macleod AD*

**Journal:** J Pain Palliat Care Pharmacother 21(1):15-25, 2007. 49 References

**Reprint:** Nurse Maude Hospice, Mansfield Avenue, Merivale, Christchurch, New Zealand (J Vella-Brincat, BSc Pharm, Clinical Pharmacist)

**Faculty Disclosure:** Abstracted by J. Joyce, who has nothing to disclose.

Each year cancer-related pain affects around nine million people world-wide. The prevalence of pain in



patients with malignancies is around 50% at some stage of the disease and 80% or greater in the advanced or terminal stages. Opioids, to varying degrees, antagonize N-methyl-D-aspartate (NMDA) receptors and activate the descending serotonin and noradrenalin pain pathways from the brain stem, all of which inhibit nociceptive transmission and result in analgesia. The extent to which each mechanism contributes to analgesia varies between individual opioids. Conversely, agonism of NMDA receptors may result in chronic, neuropathic or paradoxical pain and the development of tolerance.

The adverse effects of opioids on the central nervous system (CNS) are complex, but divided into three groups: 1) those that result in a decrease in the level of consciousness, 2) those that affect the thinking process and ability to react, 3) direct toxic effects of opioids on neurons.

The development of tolerance to opioid analgesia is a common physiological effect of opioids but its existence remains controversial. Tolerance can in fact develop to any opioid effect, including analgesia, sedation, cognitive changes, respiratory depression, and nausea. There are two different types of tolerance—innate tolerance (which is genetically determined and will be present from the initial dose of drug) and acquired tolerance. Acquired tolerance can be further divided into pharmacokinetic (or dispositional), pharmacodynamic, and learned tolerance. Pharmacokinetic tolerance results from changes in disposition or metabolism of a drug. Pharmacodynamic tolerance results from drug-induced changes to body systems on prolonged drug use. Learned tolerance results in a decrease in efficacy as a result of compensatory mechanisms that are learned.

The exact mechanism by which tolerance to opioid analgesia develops is unclear but is thought to be multifactorial and include changes in opioid receptors, activation of NMDA receptors, and movement of calcium and magnesium ions. The diminished response to opioids may also be due to compensatory responses that counteract the analgesic opioid effects leading to enhanced nociceptive signaling, probably via NMDA receptor agonism. The enhanced NMDA receptor excitability and increased synaptic glutamate may lead to the activation of NMDA receptors even in the presence of overwhelming inhibitory opioid effect.

The treatment or prevention of opioid tolerance revolves around NMDA receptor antagonism and nitric oxide synthetase inhibition. NMDA antagonists affect central hyperexcitability and inhibit "windup" in dorsal horn neurons by inhibition of an increase in neural responses to successive stimuli. NMDA receptor antagonists such as ketamine have the ability to prevent and reverse tolerance and abolish hyperalgesia. Knowledge of the cerebral side effects of opioids is essential in the care of palliative patients.

#### **Glutamate levels in cerebrospinal fluid and triptans overuse in chronic migraine.**

*Vieira DS et al*

**Journal:** Headache 47(6):842-847, 2007. 36 References

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**Faculty Disclosure:** Abstracted by J. Joyce, who has nothing to disclose.

Chronic migraine (CM) is a common disorder, affecting 2-3% of the general population, being one of the most debilitating and difficult-to-treat headache disorders. The vascular hypothesis of migraine has now been superseded by a more integrated theory involving vascular and neuronal components. Glutamate, the major excitatory neurotransmitter in the central nervous system, has been shown to be involved in migraine mechanisms. Since glutamate is linked to central sensitization, the authors hypothesize that it might be related to triptan response mechanisms.

Accordingly, in this study the authors investigated glutamate levels in the CSF in CM patients treated with different acute medications, such as analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and triptans in order to test their hypothesis. The study included 19 patients (13 women), mean age 42.89 yrs, mean frequency of headache 28.94 days/month. Patients were divided into those overusing analgesics (such as NSAIDs), those without overuse, and those overusing triptans.

The results from this study showed low CSF glutamate levels in CM patients overusing triptans when compared to nonoveruser CM patients. Glutamate is one of the putative candidates in the development and maintenance of chronic headache via its action on ionotropic and metabotropic receptors. Several lines of investigation have shown that glutamate levels are altered in plasma, platelets, and CSF of patients with migraine when compared with control subjects what has been considered to indicate a systemic dysfunction of the glutamatergic system in this syndrome. Previous data from these authors have indicated that CSF glutamate levels in CM patients with and without fibromyalgia were increased in those CM patients with widespread pain.

The N-methyl-D-aspartate (NMDA) and non-NMDA receptor activation by glutamate released by central nociceptor terminals induces calcium entry into the dorsal horn neurons, in neurons of the trigeminal nucleus caudalis, and also in supraspinal structures, structures that have been considered to participate in the processing of head pain. Activation of NMDA receptors makes the spinal cord neurons more responsive to all nociceptive and nonnociceptive inputs, resulting in central sensitization.

One proposed site for triptan action is within the trigeminocervical complex. It has been assumed, based on observations of inhibition of plasma protein extravasations, and due to the localization of 5-HT<sub>1D</sub> mRNA in the trigeminal ganglion, that triptans block trigeminal transmission by a prejunctional mechanism. It has been shown that some component of transmission across the trigeminal nucleus involves glutamatergic

mechanisms.

From these data, it cannot be suggested that triptans are more indicated than other antimigraine drugs for CM treatment, but further clinical studies are necessary to clarify if triptans could prevent migraine chronification, reduced headache frequency, or be used as a transitional treatment in CM. Triptans may affect glutamate neurotransmission by several hypothetical ways such as inhibiting the glutamate release, affecting the glutamate receptors binding site, increasing the glutamate uptake by glial cells and/or by neuronal transporters, decreasing the neuronal firing in the trigeminal nucleus.

#### **Clinical trial results with OROS® hydromorphone.**

*Wallace MS, Thipphawong J*

**Journal:** J Pain Symptom Manage, 33(2S):S25-S32, 2007. 15 References

**Reprint:** Center for Pain and Palliative Medicine, Department of Anesthesiology, University of California, San Diego Medical Center, 9500 Gilman Drive, #0924, La Jolla, CA 92093 (MS Wallace, MD)

**Faculty Disclosure:** Abstracted by J. Joyce, who has nothing to disclose.

OROS® hydromorphone is an osmotically controlled delivery system that was designed to provide sustained relief from chronic pain with once-daily oral administration. The authors reviewed recently released data from several short-term studies, including dose conversion studies and comparison studies with other commonly prescribed long-acting opioids. Hydromorphone was introduced clinically for the treatment of pain in 1926. Initial doses for patients switching from other oral opioids to oral hydromorphone typically are calculated using ratios of 5:1 to 7.5:1 morphine equivalents to oral hydromorphone. Results of early nonrandomized, open-label, dose conversion studies support a 5:1 ratio to convert oral morphine equivalents to OROS hydromorphone. Results of a randomized, double-blind study conducted in Europe and Canada showed that once-daily OROS is at least as effective as twice-daily, sustained-release morphine for the management of severe chronic cancer pain. The primary efficacy outcome measure was the Brief Pain Inventory (BPI) worst pain in the past 24 hours item, on a 0 to 10 scale, with higher scores indicative of greater pain. Patients in the hydromorphone group used significantly less breakthrough pain medication during the immediate-release phase, but not during the sustained-release phase. The adverse events profiles for OROS and controlled-release morphine were similar and typical of opioids.

OROS has also demonstrated efficacy in patients with chronic low back pain. The primary efficacy outcome was the change in patient-evaluated pain relief over time. The efficacy of OROS has also been demonstrated in opioid-naïve patients with chronic moderate to severe osteoarthritis pain despite therapy with nonsteroidal anti-inflammatory drugs or cyclooxygenase-2 inhibitors. The mean change from baseline pain relief scores was similar in both groups.

