

# Medication Approaches to Pain Management

Rahimzadeh P\*

Department of Anesthesiology and Pain Medicine, Iran University of Medical Sciences, Iran

## Abstract

Acetaminophen can be effective for mild to moderate pain. Risks of acetaminophen include dose-dependent liver toxicity, especially when the drug is taken at high doses, with alcohol, or by those with liver disease. This risk further illustrates why patients should be aware of the presence of acetaminophen in both over-the-counter and prescribed combination medications. NSAIDs such as aspirin, ibuprofen, and naproxen can provide significant pain relief for inflammation, such as from arthritis, bone fractures or tumors, muscle pains, headache, and acute pain caused by injury or surgery.

**Keywords:** Cardiac-related events; Liver toxicity; Pain syndromes; Ibuprofen; Inflammation; Acute pain

## Introduction

Non-selective NSAIDs can be associated with gastritis, gastric ulcers, and gastrointestinal bleeding. Conversely, COX-2 inhibitors have fewer GI adverse effects. The use of NSAIDs may be associated with renal insufficiency, hypertension, and cardiac-related events. Anticonvulsants are medications originally developed to treat seizures, but they are also commonly used to treat different pain syndromes, including post therapeutic neuralgia, peripheral neuropathy, and migraine. They are often used as part of a multimodal approach to the treatment of perioperative pain. Some of these agents can effectively treat the neuropathic components of pain syndromes. Anticonvulsants, which include gabapentinoids such as gabapentin and pre-gabalin, may cause significant sedation and have recently been associated with a possible risk of misuse. Antidepressants are commonly used in various chronic pain conditions. TCAs are effective in a variety of chronic pain conditions, including neuropathic pain [1]. As with other medications, they have risks and adverse effects, including dry mouth, dizziness, sedation, memory impairment, orthostatic hypotension, urinary retention, and cardiac conduction abnormalities. Trials with different TCAs should be initiated at a low dose and gradually titrated to optimal effect. SNRIs, such as venlafaxine and duloxetine, are effective for a variety of chronic pain conditions, including musculoskeletal pain, fibromyalgia, and neuropathic pain conditions, but have markedly fewer adverse effects than TCAs. There have been some reports of withdrawal reactions when these medications are suddenly stopped. Although selective serotonin reuptake inhibitors, such as fluoxetine, sertraline, citalopram, and paroxetine, are effective antidepressants; they have less analgesic effect compared with other anti-depressant classes [2]. Overall, the analgesic actions of antidepressants occur even in patients who are not clinically depressed, and their analgesic effect typically occurs sooner and at lower doses than those required for the treatment of depression. Musculoskeletal agents commonly used for pain treatment include baclofen, tizanidine, and cyclobenzaprine. Carisoprodol is metabolized to meprobamate, which is both sedating and possibly addictive, so the use of carisoprodol is not recommended; particularly because alternatives are available. Antianxiety medications are often prescribed to treat the anxiety that accompanies acute pain as well as anxiety resulting from fluctuations in chronic pain. They may also be prescribed for co-morbid anxiety disorders such as generalized anxiety disorder, panic disorder, post-traumatic stress disorder, and agoraphobia, which as a group have a prevalence estimated in the range of 30% in patients with chronic pain [3]. SSRIs and SNRIs may also help manage the anxiety associated with co-morbid depression. It is

important to recognize and treat anxiety effectively because it can worsen the severity of pain as well as interfere with a patient's coping skills for managing his or her pain. Several classes of medications can be used to treat anxiety. Benzodiazepines do not have independent analgesic effects but may have indirect pain-relieving effects. Thus, they can be helpful when used briefly for the anxiety associated with pain in an acute medical setting, but benzodiazepines should generally be avoided for regular or long-term use for three reasons [4]. First, benzodiazepines increase the risk of substance use disorder. Second, co-prescription of benzodiazepines and opioids is associated with enhanced risks of overdose, respiratory depression, and death. Third, the cognitive effects of benzodiazepines, when used chronically, may interfere with a patient's development of new coping skills needed to manage a chronic pain condition [5]. For chronic anxiety disorders, usually a combination of medications indicated for that specific condition plus evidence-based psychotherapy, such as cognitive-behavioural therapy, works best. SSRIs and SNRIs are the medications most frequently used for the generalized anxiety that often accompanies chronic pain conditions. Buspirone is another choice. SSRIs, because of their lower side effect profile, are generally the first choice for panic disorder, but TCAs can also be used. Venlafaxine ER and prazosin are used for PTSD. For more severe cases of co-morbid anxiety disorders, psychiatric consultation for medication regimens is advised. It should be noted that gabapentinoids have been useful in treating anxiety in patients with pain. The following paragraphs briefly describe opioid medications [6]. Opioids are a controlled substance group of broad-spectrum analgesics that provide pain relief for a variety of conditions. Administration of opioid medication can include short-or long-acting formulations and different delivery modalities, such as oral, buccal, sublingual, spray, intravenous, intramuscular, intrathecal, suppository, transdermal patches, and lozenge formulation. Opioids bind to opioid receptors in the brain, spinal cord, and other sites, activating analgesic and reward pathways. It is important to point out that opioid

**\*Corresponding author:** Rahimzadeh, Department of Anesthesiology and Pain Medicine, Iran University of Medical Sciences, Iran, Tel: 0982166509059, Email: p-rahimzadeh@tums.ac.ir

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medications vary in the ratio of their analgesic potency and their potential for respiratory depression, the major cause of opioid overdose death.<sup>107</sup> For example, synthetic fentanyl and fentanyl analogues are particularly potent for respiratory depression. Illicit fentanyl-related overdoses are now a leading cause of deaths from overdose in the United States, often because of its use in combination with alcohol or illicitly obtained heroin, cocaine, diverted prescription opioids, and other drugs such as benzodiazepines [7]. Common prescription opioid medications that can be considered for management of acute and chronic pain include hydro-morphone, hydrocodone, codeine, oxycodone, methadone, and morphine. Although effective for moderate to severe acute pain, the effectiveness of opioids beyond three months requires more evidence. A recent study demonstrated that treatment with opioids alone was not superior to treatment with trials of various combinations of non-opioid medications for improving pain-related function over 12 months; the authors concluded that the results do not support initiation of opioid therapy alone for moderate to severe chronic back pain or hip or knee osteoarthritis pain. There are challenges to completing long-term studies of any therapy for moderate to severe pain, particularly patient drop-out from intolerable pain. Opioid medications can be associated with significant side effects, including constipation, sedation, nausea, vomiting, irritability, pruritis, and respiratory depression. Opioid medications can be associated with OUD and can be diverted [8]. Buprenorphine, an opioid medication that the FDA has approved for clinical use, is a partial agonist at the mu opioid receptor and therefore has a reduced potential for respiratory depression; it is thus safer than full agonists such as morphine, hydrocodone, and oxycodone. Buprenorphine also acts as an antagonist at the kappa receptor, an effect shown in experimental studies to reduce anxiety, depression, and the unpleasantness of opioid withdrawal. Buprenorphine is widely used and encouraged for treating patients with OUD and is approved for the treatment of pain. In some states, there is a significant challenge, however, for prescribing clinicians to get authorization for using buprenorphine for chronic pain management [9]. Tapentadol is structurally similar to tramadol, and both have a dual mode of action as an agonist at the mu opioid receptor and as a serotonin and norepinephrine reuptake inhibitor. Tapentadol is at least equivalent to oxycodone in terms of analgesia, with better GI tolerability. As outlined in recent guidelines, including the VA/DoD Clinical Practice Guidelines for Opioid Therapy for Chronic Pain, the CDC Guideline, and the American Society of Interventional Pain Physicians guidelines, risk assessment, close follow-up, and pain re-evaluation are important aspects of the treatment plan prior to and throughout the duration of opioid therapy for pain management. Initiation of opioid therapy, when the patient and the clinician deem the benefits to outweigh the risks, should be at a low dose and titrated upward to find the lowest dose required to optimally control the pain or improve function and QOL. Opioid treatment should be maintained for a period no longer than necessary for adequate pain control. Similarly, assessing for tolerance and consideration of adjunctive therapies, opioid rotation, tapering, and discontinuation should be considered. Safe opioid stewardship involves a proper history and examination, periodic re-evaluation, and risk assessment, with a focus on measurable outcomes, including function, QOL and ADLs. Accurate dose adjustment is critical because patients vary widely in the dose required for analgesic efficacy. The idea of a ceiling dose of opioids has been recommended, but establishing such a ceiling is difficult, and the precise level for such

a ceiling has not been established. The risk of overdose increases with the dose, but the therapeutic window varies considerably from patient to patient. For example, the CDC Guideline identified a dose limit of 90 morphine milligram equivalents per day. A more recent study evaluated the risk of death related to opioid dose in 2.2 million North Carolinians and found that the overall death rate was 0.022% per year. The researchers noted that: Dose-dependent opioid overdose risk among patients increased gradually and did not show evidence of a distinct risk threshold. Much of the risk at higher doses appears to be associated with co-prescribed benzodiazepines. It is critical to account for overlapping prescriptions, and justifies taking a person-time approach to MME calculation with intent-to-treat principles [10].

## Conclusion

DEA has classified medications according to categories, or schedules, based on the perceived risk of addiction. These scheduled medications require prescribers to register with DEA. Opioids are mainly category CIII or CII. CIII medications include acetaminophen with codeine and buprenorphine, while CII medications include hydrocodone, oxycodone, morphine, fentanyl, and methadone. CIV drugs are defined as drugs with a low potential for abuse and low risk of dependence, such as Tramadol. CI medications are those that are considered not to have medicinal value, including heroin, methamphetamine, and cannabis..

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## Conflict of Interest

None

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