Postoperative Analgesia in the Chronic Pain Patient

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KEYWORDS

• Chronic pain • Opioid management • Postoperative pain • Opioids

KEY POINTS

- An increasing number of chronic pain patients are on long-term opioid therapy.
- Chronic opioid users may have increased analgesic requirements postoperatively due to tolerance, dependence, and opioid-induced hyperalgesia.
- Chronic pain patients are at risk of inadequate pain management in the perioperative setting.
- Undertreated acute pain may lead to the development of chronic pain syndromes in several patients.
- The use of multimodal analgesia is essential to reducing opioid consumption.

INTRODUCTION

The chronic pain patient poses a variety of challenges to the clinician. These often are attributed to psychosocial implications and physiologic changes that occur as a result of long-term opioid use. It is important to be aware of several pharmacologic phenomena that are typical of chronic opioid users.

Tolerance refers to the decreased responsiveness to the effect of opioids as a result of chronic use. Closely related to tolerance is physical *dependence*, which is characterized by withdrawal symptoms precipitated by the abrupt cessation or drastic dose reduction of opioids.[1]

Addiction, on the other hand, is a chronic disease that is characterized by craving, impaired control, and compulsive substance use, which is continued despite negative consequences. In contrast, the term, *pseudoaddiction*, refers to behaviors engaged by those whose pain conditions are undertreated.[1]

Chronic pain syndromes and addiction are not mutually exclusive. A majority of patients taking opioids for chronic pain, however, do not demonstrate the behaviors associated with addiction, such as craving, compulsive use, and loss of control.

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Opioid-induced hyperalgesia (OIH) occurs when opioid exposure results in nociceptive sensitization, rendering patients more responsive to painful stimuli. The exact mechanism of the development of OIH is not yet understood. In addition to genetic factors, proposed mechanisms involve enhanced nociceptive response as a result of sensitization of spinal neurons as well as the decreased reuptake of neurotransmitters from primary afferent nociceptive fibers. OIH is thought to explain the loss of efficacy of opioid medications in some patients, especially in the absence of known pathology or existing disease progression.[1]

FROM ACUTE TO CHRONIC PAIN: THE WIND-UP PHENOMENON AND SENSITIZATION

Several patients recovering from surgery develop chronic pain syndromes beyond what is expected in the immediate postoperative setting. The *wind-up phenomenon* refers to peripheral and central nociceptive sensitization that is a result of neurochemical changes after repeated noxious stimuli. Initial *primary sensitization* refers to a hyperexcitable neuronal state following neurogenic inflammation.[2] *Secondary sensitization* occurs in the central nervous system (CNS) and leads to increased sensitivity to noxious stimuli of the area surrounding injured tissue. This occurs as a result of the conversion of nociceptive-specific neurons to nonspecific wide dynamic range neurons, which respond to both noxious and non-noxious stimuli.[2] Central sensitization is thought to be responsible for the development of hyperalgesia and allodynia. *Allodynia* refers to the perceived sensation of pain in response to a non-noxious stimulus, such as light touch.[3]

Risk factors for the development of chronic pain after surgery include type and location of surgery (mastectomy, thoracotomy, and inguinal hernia repair being the most common), duration of procedure greater than 3 hours, intraoperative nerve damage, surgical techniques, and preoperative pain levels.[2] In addition, genetic and psychosocial factors—such as fear of pain, posttraumatic stress disorder, and catastrophizing—are important predisposing factors.

There are several important strategies clinicians may employ for the prevention of chronic pain developing after surgical intervention. These include the early identification of high-risk patients, multimodal analgesic techniques, communication between members of the care team, and setting realistic patient expectations.

To develop an effective perioperative pain management plan, a thorough pain assessment is necessary starting in the preoperative period. This includes determining previous exposure to opioid medications. It is useful to categorize the proposed procedure as minor, intermediate, or major. In general, the pain related to minor interventions may be managed with local anesthetic infiltration and oral analgesic medications postoperatively. Where applicable, regional anesthetic techniques should be employed to decrease opioid requirements. Intermediate and major surgical procedures may require intravenous analgesics postoperatively as well as consultation of the pain management service.

Opioid Management

The risk of the undertreatment of postoperative pain in chronic opioid users is high due to common prejudices and misconceptions regarding patients receiving opioids for chronic pain syndrome and those with addiction. Adequate postoperative analgesia is important for reducing patient anxiety and decreasing pulmonary and vascular complications related to undertreated pain.[4] Preoperatively, the surgeon should obtain a medication history that includes any opioid medications and doses. Generally,

patients should continue their usual oral opioid dose on the day of surgery, with additional administration prior to induction of anesthesia. It is important to maintain baseline opioid requirements to reduce the risk of withdrawal. Postoperatively, the patient requires at least the preoperative opioid requirement (for surgeries causing little to no postoperative pain) and possibly supplemental opioids (for surgeries causing moderate–severe pain). If high-dose opioid needs are anticipated, it is reasonable to use a patient-controlled analgesia system to provide patients with adequate analgesia according to their needs. Multimodal analgesia, including regional anesthesia and nonopioid medications (**Table 1**), is essential to reduce opioid consumption. Close coordination with a patient's outpatient provider is helpful prior to discharge.

Nonopioid Adjuvants

Since the recognition of current opioid epidemic, there has been growing emphasis on nonopioid adjuvants in chronic pain management.[5] The most commonly utilized nonopioid medications are nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, anticonvulsants, antidepressants, anxiolytics, musculoskeletal agents, and topical anesthetics.[6] Employing these medications with differing target receptors provides multimodal analgesia that leads to reduction in opioid consumption in chronic pain patients.[1] Because these medications have mutually exclusive mechanisms of action, they often complement one another in efficacy.

Nonsteroidal anti-inflammatory drugs

Readily available as over-the-counter medications, NSAIDs are best used for treating inflammatory pain. Nonselective NSAIDs, notably aspirin, ibuprofen, and naproxen, inhibit both cyclooxygenase (COX)-1 and COX-2 enzymes, which are involved in synthesis of biological substrates responsible for inflammation and blood clotting. Therefore, nonselective NSAIDs can put patients at increased risk for gastrointestinal (GI) ulcers or bleeds. More selective NSAIDs, notably celecoxib, inhibit COX-2 selectively, resulting in fewer GI adverse effects. All NSAIDs are associated with decreased kidney function and increased risk of adverse cardiac events, including myocardial infarction; thus, caution is recommended in patients with chronic cardiac or renal disease.[7]

Acetaminophen

Readily available over the counter, acetaminophen is best for treating generalized, nonspecific mild to moderate pain. The mechanism of action for acetaminophen is not understood completely but it appears to inhibit the reuptake of endogenous cannabinoids resulting in generalized analgesia. The most common and serious adverse effect is hepatic injury, because large intake of acetaminophen can lead to accumulation of hepatotoxic metabolites. Due to wide availability of acetaminophen, patients with acute or chronic liver disease, history of alcohol use disorder, or concomitant use of other hepatotoxic medications must be educated in avoiding acetaminophen. Historically and by current Food and Drug Administration standards, the maximum recommended daily dose for acetaminophen in adult is 4 g.[8] In 2011, however, McNeil Consumer Healthcare, a major manufacturer of acetaminophen, lowered the recommended maximum daily dose to 3 g, in advocate of lowering the risk for liver toxicity.[9]

Anticonvulsants

Although most anticonvulsants are used primarily as antiepileptic medications, some anticonvulsants, such as gabapentin and pregabalin, also are effective in treating neuropathic pain. Their main mechanism of action involves blocking $\alpha_2\delta$ subunit of voltage-dependent calcium channels, resulting in decreased neuronal firing. Clinically, this is exhibited as decrease in neuropathic pain and anxiety. In chronic pain medicine,

Table 1
An overview of the most common nonopioid adjuvants used in chronic pain practice

Drug	Mechanism of Action	Uses	Adverse Effects	Special Consideration
NSAIDs (nonselective: aspirin, ibuprofen, naproxen; selective: celecoxib)	Inhibits COX-1 and COX-2 (nonselective) or COX-2 only (selective) = decreased inflammatory mediators	Best for inflammatory pain	GI bleeds/ulcers (nonselective), thrombosis, worsening kidney function (all), increased risk of cardiac events (all)	Avoid in patients with cardiac history, acute or chronic kidney disease, history of stroke, peptic ulcer disease, or active bleeding
Acetaminophen	Modulation of endogenous cannabinoid system = increased analgesia	Best used for generalized mild to moderate pain	Liver damage/toxicity	Avoid in patients with acute or chronic liver disease, history of alcohol use disorder or concomitant use of other hepatotoxic medications. Maximum recommended daily dose: 3 g/d, or 2 g/d for patients with stable liver disease
Anticonvulsants (gabapentin, pregabalin)	Blocks $\alpha_2\delta$ subunit of voltage-dependent calcium channel (gabapentin, pregabalin) = anticonvulsant, analgesic, and anxiolytic effects	Best used for neuropathic pain, migraine	Sedation, increased suicidal ideation, lower extremity edema	Must be dosed 2–3 times a day to maintain therapeutic level; decreased dosage in patients with kidney disease
Antidepressants (SSRI: fluoxetine, sertraline. SNRI: duloxetine, venlafaxine. TCA: nortriptyline, amitriptyline)	Inhibits reuptake of serotonin (SSRI), inhibits reuptake of serotonin and norepinephrine (SNRI, TCA) = endogenous opioid modulation	Best used for neuropathic pain, fibromyalgia (SNRI, TCA), musculoskeletal pain (SNRI), and associated depression (SSRI)	Convulsion, cardiac arrhythmia, urinary retention, dry mouth, postural hypotension (TCA), sedation (TCA, SNRI), GI distress, sexual dysfunction (SSRI)	Careful risk-benefit analysis is warranted, especially when prescribing TCA due to serious side-effect profile. Effective in treating depression associated with chronic pain

Anxiolytics (benzodiazepines, buspirone)	Increases effectiveness of GABA at $GABA_A$ receptors = decreases neuronal excitability (benzodiazepines); serotonin agonist (buspirone)	Best used for muscle spasms (benzodiazepine), associated anxiety (benzodiazepine, buspirone)	Sedation, respiratory depression, anterograde amnesia, sexual dysfunction (benzodiazepine), dizziness, headache (buspirone)	Potential for addiction and overdose (benzodiazepine). Avoid taking with other serotoninergic medications (buspirone)
Musculoskeletal agents (baclofen, tizanidine, cyclobenzaprine)	Activates $GABA_B$ receptors (baclofen), α2-receptors (tizanidine), serotonin receptor antagonist (cyclobenzaprine)	Best used for muscle spasms	Drowsiness, dizziness, dry mouth	Avoid taking with alcohol/ benzodiazepines (all). Must be aware of numerous drug-drug interactions. Avoid taking with serotonergic drugs (cyclobenzaprine).
Topical anesthetics (lidocaine patch, capsaicin)	Blocks voltage-gated sodium channels in sensory neurons (lidocaine). Activates TRPV 1 = depletion of substance P (capsaicin)	Best used for peripheral neuropathy (all), musculoskeletal pain (capsaicin)	Burning, redness, skin discomfort	No more than 3 lidocaine patches at a time, because local anesthetic toxicity is possible

these medications are used most commonly in treating postherpetic neuralgia, central and peripheral neuoropathy, and migraine.[10] Gabapentin and pregabalin both have a short elimination half-life (approximately 6 hours), thus require redosing 2 times to 3 times a day to remain therapeutic. Because these medications are excreted renally, patients with acute or chronic kidney disease are prone to increased adverse effects, most commonly sedation.[11] Caution should be used in patients with renal disease and the medication dose should be adjusted.

Antidepressants

Two classes of antidepressants, tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), commonly are used to treat pain. Numerous studies have shown that TCAs, such as amitriptyline and nortriptyline, and SNRIs, including duloxetine and venlafaxine, are effective in treating different types of chronic pain, notably neuropathic pain and fibromyalgia.[10] Although the direct mechanism of action in which these medications provide analgesia is unknown, it is thought that their inhibition against serotonin and norepinephrine reuptake leads to endogenous opioid modulation resulting in analgesia.[12,13] TCAs must be prescribed with caution, because they have deleterious effects, notably cardiac arrhythmias, orthostatic hypotension, and convulsions. The most common side effects include sedation, dry mouth, urinary retention, and tachycardia. TCAs often are started at a low dose and titrated until maximum efficacy can be seen with minimal side effects. SNRIs have less notable side-effect profile, the most common being sedation.

Anxiolytics

Among the most common comorbidities that many chronic pain patients suffer are depression and anxiety.[14] Although anxiolytics, such as benzodiazepines and buspirone, do not have direct analgesic effects, these medications provide benefits to patients' perception of pain by alleviating their anxiety. Benzodiazepines also provide muscle relaxation, which can indirectly alleviate pain secondary to muscle spasms.[15,16] The main mechanism of action of benzodiazepines is allosteric binding to γ-aminobutyric acid (GABA) receptor, resulting in increased effectiveness of endogenous GABA. This leads to depression in neuronal activity. Along with anxiolysis, patients also may experience sedation, respiratory depression, anterograde amnesia, and sexual dysfunction. Some experience euphoria with benzodiazepine use, which puts patients at risk for addiction, abuse, and possible overdose. Because of their relatively safer side effect profiles and low potential for abuse compared with benzodiazepines, SSRIs and SNRIs are often considered more favorable adjuvants. Caution must be exercised when prescribing benzodiazepines, as concurrent use with opioids increase risk of respiratory depression and death.

Musculoskeletal agents

Among musculoskeletal agents, the most commonly used are baclofen, tizanidine, and cyclobenzaprine. They are most effective in treating painful muscle spasms accompanied by spastic movement disorders, such as cerebral palsy and multiple sclerosis. Each medication has different mechanism of action but all 3 medications achieve the goal of CNS depression, leading to the relaxation of skeletal muscles. Although these medications have relatively safe side-effect profiles, they have many drug-drug interactions that physicians must be aware of. All musculoskeletal agents must be prescribed with caution in patients who use alcohol, benzodiazepine, or any other CNS depressants due to synergistic CNS depression.[17] Tizanidine and concomitant use of cytochrome P450 1A2 inhibitors should be avoided because this combination may impair the metabolism of tizanidine.[18] Cyclobenzaprine should

be avoided in patients taking serotonergic medications because it could put patients at risk for serotonin syndrome.[19]

Topical anesthetics

Topical agents can be useful to target specific painful areas with decreased systemic effects compared with oral medications. Some of the most commonly used topical analgesics are lidocaine and capsaicin. Lidocaine targets voltage-gated sodium channels of sensory neurons. By blocking these channels, lidocaine inhibits neural conduction along the sensory neurons. Capsaicin works by activating transient receptor potential vanilloid (TRPV 1), which ultimately results in depletion of substance P, one of the major pain transmission neuropeptides. Capsaicin is effective in treating both peripheral neuropathy and musculoskeletal pain, such as osteoarthritis.[20] Outside of skin irritation and burning sensation, patients rarely experience adverse effects from these medications. Although local anesthetic toxicity is still a possibility with the use of lidocaine patches, it is rare even when applied above the recommended maximum dose of 3 patches daily.[21] If a patient's insurance does not cover prescription 5% lidocaine patches, over-the-counter 4% lidocaine patches or lidocaine cream may be offered to the patient as an alternative.

RECOMMENDATIONS FOR PATIENTS ON MAINTENANCE THERAPY

Patients on maintenance opioid therapy are a unique subset of patients who require particular attention in the postoperative period. Specific recommendations for patients on methadone, suboxone, or naloxone maintenance therapy are described.

Methadone

Methadone is a long-acting opioid that is used to treat chronic pain as well as opioid dependence. The drug binds and occupies μ-opioid receptors and effectively reduces pain, decreases opioid craving, and reduces the euphoric effects of subsequent illicit opioid use.

Patients on methadone maintenance therapy (MMT) should continue to receive their daily methadone maintenance dose in the perioperative period.[22] In the event that a patient is not receiving oral intake, the methadone may be dosed parenterally at half the oral dose, as noted in the manufacturer's labeling (ie, a patient receiving methadone, 10 mg orally, daily may receive methadone, 5 mg intravenously, daily). It is important to recognize that patients receiving methadone for maintenance therapy do not receive adequate analgesia from their maintenance dose. Although the duration of action of methadone for prevention of withdrawal is 24 hours to 48 hours, the duration of action for analgesia is only 4 hours to 8 hours. Thus, patients on MMT likely require additional opioid for treatment of acute postsurgical pain. The total methadone dose may be split into 3 doses, 8 hours apart, to improve analgesia. For example, a patient on methadone, 30 mg daily, may be given methadone, 10 mg every 8 hours, only while the patient is inpatient. The total daily dose of methadone should not be adjusted without consultation of the patient's MMT provider.

In the postoperative period, it is recommended that patients on MMT be treated aggressively with nonopioid analgesics. If patients require opioids, it is recommended to start short-acting opioids in addition to the methadone dosing. Long-term opioid use causes opioid tolerance and OIH. Thus, patients on MMT often have an increased short-acting opioid dose requirement in comparison to patients not on opioid maintenance therapy and often need higher and more frequent doses of opioid analgesics to achieve adequate pain control. If a patient requires ongoing short-acting opioids on discharge, the dose and duration of therapy should be communicated to the patient's

methadone clinic. If the patient is discharged home postoperatively, a methadone prescription should not be provided, because the patient should instead return to the methadone clinic.

Suboxone is a combination of 2 opioid medications: buprenorphine and naloxone. Buprenorphine is a partial μ-opioid agonist that has high affinity and low intrinsic activity at the μ-receptor. The drug's partial agonist properties make it effective in treating opioid dependence while its high affinity for the μ-opioid receptor blocks the effects of illicit opioids.[23–26] In suboxone, naloxone is only present to discourage misuse because it has low bioavailability when administered sublingually. Similar to methadone, suboxone has a duration of action for analgesia that is substantially shorter than its duration of action for suppression of opioid withdrawal.

The decision of whether to continue or discontinue suboxone prior to surgery is based on many factors. The type and urgency of the surgery, expected postoperative opioid requirement, and patient characteristics must be considered.[27] This decision should be discussed and agreed on between the patient, surgeon, and buprenorphine provider. If suboxone is discontinued prior to surgery, the drug should be restarted only once the patient no longer has acute pain requiring narcotic analgesics because suboxone can precipitate withdrawal.[28] If, however, suboxone is continued during the perioperative period, it is recommended that the patient's acute pain be treated with short-acting opioids. In this case, the patient likely requires significantly higher doses of opioids to achieve adequate pain control. Managing patients on suboxone is best achieved in consultation with the acute or chronic pain service.[29] For further discussion, the reader is referred to the chapter on Pre-Operative Optimization.

Naltrexone

Naltrexone is a long-acting competitive antagonist that has a high affinity for the μ-opioid receptor.[30] When taken prior to other opioids, naltrexone blocks the euphoric, sedative, and analgesic effects of opioids. Naltrexone may be prescribed for patients with mild opioid use disorder who do not demonstrate withdrawal symptoms.[31]

Oral naltrexone should be discontinued 2 days to 3 days prior to surgery to allow for intraoperative or postoperative opioids to effectively provide analgesia.[32] Extended-release naltrexone intramuscular injection is administered every 28 days, and elective surgeries should be postponed 4 weeks after administration.[33] The abrupt discontinuation of naltrexone may cause an increase in μ-opioid receptors, making patients more sensitive to perioperative opioids. Thus, patients previously taking naltrexone should be monitored closely and perioperative opioids should be titrated carefully to avoid sedation and respiratory depression.[34]

SUMMARY

The management of pain in patients with chronic pain syndromes who are on chronic opioid therapy or maintenance opioid therapy can be challenging for clinicians. Inadequate postoperative pain management in this population can have several adverse outcomes, such as increase hospital length of stay, precipitation of withdrawal in some cases, and overall increase in health care costs. In these patients, it is recommended to employ multimodal analgesic therapies whenever possible and to ensure baseline opioid requirements are met, while avoiding restricting opioid treatment of acute pain.

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