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A Practical Approach to Acute Postoperative Pain Management in Chronic Pain Patients

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Abstract

In the United States, more than 100 million people suffer from chronic pain. Among patients presenting for surgery, about one in four have chronic pain. Acute perioperative pain management in this population is challenging because many patients with chronic pain require long-term opioids for the management of this pain, which may result in tolerance, physical dependence, addiction, and opioid-induced hyperalgesia. These challenges are compounded by the ongoing opioid epidemic that has resulted in calls for a reduction in opioid use, with a concurrent increase in the number of patients with chronic opioid exposure presenting for surgery. This paper aims to summarize practical considerations for acute postoperative pain management in patients with chronic pain conditions. A patient-centered acute pain-management plan, including non-opioid analgesics, regional anesthesia, and careful selection of opioid medications, can lead to adequate analgesia and satisfaction with care. Also, a meticulous rotation from one opioid to another may decrease opioid requirement, increase analgesic effectiveness, and improve satisfaction with care.

Keywords

Postoperative Pain; Chronic Pain; Opioid Tolerance; Opioid rotation

Over 100 million people suffer from chronic pain in the United States, which results in an annual cost of up to $635 billion.[1] About one in four patients presenting for surgery suffer from chronic pain, and this number is expected to increase as the population ages, and cancer survival increases.[2] Understandably, postoperative pain is one of the most feared consequences of surgery.[3,4] Studies have estimated that up to 80 percent of patients experience moderate to severe pain after major surgery.[5,6] Poorly managed postoperative

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pain is associated with physiologic and psychological complications, including hypoventilation, infection, altered level of consciousness, myocardial infarction, oliguria, nausea, decreased gastrointestinal motility, depression, anxiety, decreased quality of life, and persistent postoperative pain among others.[7] Perhaps the high level of poorly controlled postoperative pain and associated chronic pain contribute to the ongoing opioid epidemic.

According to the Center for Disease Control and Prevention (CDC), about one-fifth of Americans received at least one opioid prescription for the management of acute or chronic pain in 2017.[8] Prescription opioids have been identified as the driving force behind the opioid epidemic. Analyses of prescription trends revealed that most opioids prescriptions were written by providers in pain medicine (48.6%) and surgery (36.5%).[9] Across all medical specialties, the most frequently prescribed opioids were hydrocodone and oxycodone.[10]

With chronic opioid administration, many patients experience decreased analgesic effects with opioid dosages that were previously therapeutic; thus, necessitating dose escalation to achieve the desired therapeutic effect. As the amount of opioids prescribed for pain management increases, so does the risk of tolerance, adversity, addiction, and overdose.[11] As a result, many health policy experts, regulatory agencies, professional associations, and health care providers now advocate limited use of opioids for pain management.[12] When a patient with chronic pain (and long-term opioids use) presents for major surgery, the stigma associated with opioid abuse increases the risk of under treatment.[13] Despite these challenges and the ongoing opioid epidemic, health care providers working in the perioperative setting must strive to provide adequate pain relief for all patients while limiting adverse medication effects.

The purpose of this review is not to replace practice guidelines or consensus statements by professional associations; instead, we discuss practical considerations for effective acute pain management in patients with chronic pain. To achieve this goal, we will first discuss the pathophysiologic changes associated with chronic opioid use. Second, the role of opioid rotation in acute pain management is explicated. Third, we discuss pain management considerations for patients on opioid abuse treatment. Finally, a hypothetical case study is presented to synthesize practical considerations with implications for clinical practice and research. It has been well established that psychosocial factors such as anxiety, depression, social support, and catastrophizing influence postoperative pain. [14–16] However, a detail discussion of these factors and their role in postoperative pain management is beyond the scope of this paper. Readers may refer to these excellent reviews for the influence of psychological preparation on postoperative outcomes.[15–17]

Pathophysiological Changes Associated with Chronic Opioid Use

Opioids exert most of their effects by binding to mu (μ), kappa (Κ), delta (δ), and opioid-like receptor type 1 (ORL1), which are located throughout the nervous system. Chronic opioid use is predictably associated with four closely related pathophysiologic changes: tolerance, physical dependence, addiction, and opioid-induced hyperalgesia.

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Opioid Tolerance

Acute and chronic administration of opioids results in a neuroadaptive response that contributes to tolerance, allodynia, and hyperalgesia.[18–20] There is evidence to suggest that hyperalgesia is a large contributor to the occurrence of tolerance.[18,21] Tolerance is a pharmacologically initiated phenomenon where exposure to a drug results in a reduction in that drug's clinical effect.[18–20] Opioid tolerance results in decreased analgesia and a reduction in side effects (e.g., respiratory depression, central nervous system depression, nausea, and constipation).[18,19,21]

Opioid administration may also result in cross-tolerance and incomplete tolerance.[22] Cross-tolerance occurs when tolerance to one opioid results in tolerance to other opioid medications.[22,23] For example, patients who have a tolerance to morphine are likely also to have a tolerance to codeine and remifentanil.[23] In this instance, patients will have similarly impaired pain relief to morphine, codeine, and remifentanil. Incomplete tolerance occurs when tolerance to a specific opioid has no impact on the analgesic effectiveness of another drug.[23] For example, patients who have a morphine tolerance will not necessarily have a similar tolerance to fentanyl or heroin.[23] When opioid medications are routinely rotated in intensive care unit patients (i.e., switching between specific opioids), the occurrence of tolerance is mitigated.[22] The occurrence of cross-tolerance and incomplete tolerance are determined by the specific molecular shape of the opioid drug and the specific opioid receptor types that are activated.[22]

The neuroadaptive response to opioid administration occurs via internalization, down-regulation of opioid receptors, and phosphorylation of other neurotransmitter receptor sites.[18] Internalization occurs when ligand-induced activation of cell membrane receptor sites results in phagocytosis of receptor proteins into the cell for degradation by lysozymes.[20] The result of internalization is receptor desensitization through diminished cellular signaling.[20] Downregulation of opioid receptors differs from internalization in that the total number of membrane receptors is decreased, and there is no alteration in cellular signaling.[19] Phosphorylation reactions can activate or deactivate proteins responsible for cellular signaling.[20,22]

All opioids have been implicated in acute tolerance.[18] Intraoperatively, the administration of high opioid doses results in acute tolerance that causes increased postoperative opioid requirements secondary to hyperalgesia.[18,21] Additionally, chronic preoperative opioid consumption results in a chronic tolerance that contributes to poorer surgical outcomes (e.g., longer length of stay and increased 30-day readmission rates), decreased patient satisfaction because of uncomfortable side effects, and reduced functional status.[18,20] Opioids have a bimodal clinical effect that results in simultaneous pain relief and a lowering of a patient's pain threshold.[18] The lowered pain threshold may last up to four days and prolong the duration of pain related to surgical wounds that have inflammation.[18]

Physical Dependence

Chronic administration of opioids can result in physical dependence.[24] Physical dependence is due to alterations in physiological functions, whereas psychological dependence is a

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mental craving.[24,25] The dopaminergic reward system is activated by opioids and plays a role in physical and psychological dependence.[25] Opioid receptors are present throughout the body, and physical dependence results from the physiological alterations at those sites.[25] Physical dependence is present when discontinuation or reduction of opioid medications results in withdrawal symptoms.[24,25] Patients may have physical dependence without psychological dependence.[25] A thorough description of withdrawal symptoms is discussed later.

Addiction

The American Society of Addiction Medicine describes addiction as "a primary, chronic disease of brain reward, motivation, memory and related circuitry [where] dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations." [26] Roughly 10 percent of patients with chronic pain are addicted to opioids and pathologically pursue the behavioral reward of taking medications rather than the intended analgesic effect.[27] Genetic and environmental factors influence an individual's predisposition to addiction by altering the release of dopamine from the substantia nigra. [26,28] Dopamine is a neurotransmitter that plays a crucial role in the usual pleasure and reward systems within the brain.[29] Chronic exposure to opioids coincides with decreased release of dopamine and changes in the circuitry of the dopaminergic system, which is characterized by an inability to abstain, impairment in behavioral control, craving, diminished problem recognition, and a dysfunctional emotional response. [26,30] Once the circuitry is altered, and dependence has been established, abstaining from opioids will lead to symptoms of withdrawal.

The signs and symptoms of opioid withdrawal include nausea, vomiting, diarrhea, abdominal cramping, myalgia, mydriasis, piloerection, hyperhidrosis, agitation, yawning, chills, rhinorrhea, insomnia, and anxiety.[31] These symptoms can occur in individuals who have taken opioids for as little as four consecutive days. For short-acting opioids such as morphine and heroin, withdrawal symptoms will usually develop within 6 to 12 hours after the last dose, while for long-acting opioids such as methadone, it occurs within 30 to 48 hours. [31,32] Although opioid withdrawal syndrome is generally non-life-threatening, the physical and psychological symptoms can be frightening to those undergoing withdrawal. [30,31] Pharmacologic interventions aimed at decreasing opioid withdrawal symptoms have been well documented. In addition to the mu-opioid receptor and alpha-2 adrenergic receptor agonists, patients can benefit from symptom-specific treatment with multimodal pain medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) and anti-anxiety medicines from the benzodiazepine drug class.[31]

Opioid Induced Hyperalgesia

Opioid-induced hyperalgesia (OIH) refers to a state of enhanced pain sensitization due to excessive pronociceptive input or prolonged exposure to opioids.[33] While the exact mechanism by which opioid administration induces OIH is yet to be fully understood, it is postulated that the primary mechanism of OIH involves inappropriate activation of the central glutaminergic system through the N-methyl-D-aspartate (NMDA) receptor. Another potential mechanism of OIH is an increase in spinal dynorphins after continuous opioid

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infusions, which releases excitatory peptides.[34] All opioids can cause OIH, but remifentanil, in particular, is one of the greatest culprits, especially when used in large doses (>0.5 μg/kg/min).[33]

Even though both OIH and opioid tolerance can result from chronic opioid abuse, the treatment approaches for OIH and opioid tolerance are very different. While increasing the opioid dose may improve the symptoms of opioid tolerance, higher doses of opioid can worsen the symptoms of OIH.[33,35] Prevention is the most effective approach in the treatment of OIH.[33] Whenever possible, non-opioid approaches should be utilized in pain management. When necessary, the minimal dose of opioids required to achieve analgesia should be used. In the perioperative setting, avoidance of the rapid administration of potent opioids such as remifentanil may prevent OIH. Studies have shown that administration of low dose remifentanil infusion has been associated with a lower incidence of OIH.[36] Several classes of medications have been employed to manage OIH: NMDA antagonist, opioid agonist-antagonists, and sodium channel blockers.[34]

Multimodal Pain Management

Multimodal pain management refers to the use of more than one pain medication with different mechanisms of action, as well as neuraxial and peripheral regional analgesia for pain control.[37] Studies have documented that patients with a history of opioid tolerance, dependence, and abuse who experience acute perioperative pain are frequently undertreated.[35] This under-treatment of pain results from many factors such as prejudice, fear of creating further dependence, and misunderstanding of the proper care of patients with opioid dependence by the practitioner.[38] A multimodal approach may improve acute pain management in these patients while alleviating some of the concerns associated with opioid use. However, it is worth noting that information and recommendations for most multimodal pain management regimens are based on anecdotal reports. While more empirical research is needed,[39] it is essential to recognize the functions of the multimodal approach, which include targeting multiple areas in the central and peripheral nervous system and blocking receptors and using alternative medications with different mechanisms of action to provide enhanced analgesia and pain control.[40] Multimodal analgesia is an essential component of enhanced recovery after surgery (ERAS) pathway[41] and opioid-sparing anesthesia.[42] A detailed discussion of ERAS and opioid-sparing anesthesia are beyond the scope of this paper. In the next section, we will review the role of regional anesthesia and commonly used medications in a multimodal pain management regimen.

Regional Anesthesia and Analgesia

Neuraxial (epidural and spinal) and peripheral nerve blockade are widely used techniques for the effective management of acute perioperative pain. Several studies have shown that regional anesthesia techniques are also useful in patients with chronic pain, opioid tolerance, opioid dependence, and OIH.[2,43,44] Table 1 summarizes several types of regional anesthetic techniques and surgical procedures that would be appropriate for opioid-free analgesia. Instituting regional anesthesia techniques and administration of local anesthetics can minimize or even negate the need for oral or intravenous opioids analgesics required for this

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patient population.[40,45] Clinical implications such as type of surgery and predicted pain level should guide the use of regional anesthesia techniques in the perioperative period.[46] The use of brachial plexus blocks for upper extremity procedures and lumbar and sacral plexus blocks for lower extremity surgical procedures have become standard for all patients as ultrasound-guided regional techniques have improved the speed, success, and safety of administration.[46] Neuraxial techniques such as spinal and epidural are also used safely and effectively. Truncal blocks such as the thoracic paravertebral block and the transversus abdominus plane block are commonly used to reduce postoperative pain for abdominal procedures, while the use of local infiltration analgesia for wound infiltration and intra-articular joint injection have added additional non-opioid methods to provide postoperative analgesia.[46]

Medications Used in Multimodal Approach

Medications used in the multimodal approach to pain management can be divided into opioid and non-opioid medications. As discussed below, opioids and non-opioids differ in their mechanisms of action along the numerous nociceptive pathways.

Non-Opioid Analgesia

Non-opioid analgesic medications provide some analgesia without the adverse effects associated with opioids. Many non-opioid medications are available for perioperative pain management in patients with chronic pain including acetaminophen, gabapentinoids, alpha-2 adrenergic agonists, NSAIDS, ketamine, intravenous lidocaine, and magnesium.[45–47] Many studies and meta-analyses have shown that the combination of multiple non-opioid medications reduces postoperative pain and postoperative opioid consumption.[48,49] Before any medication administration, the providers must be aware of the mechanism of action, side effects, and risks for their patients.

Acetaminophen prevents prostaglandin synthesis in the central nervous system and inhibits inflammation in the peripheral nervous system.[45,50] It has been shown to reduce postoperative opioid requirements with minimal side effects.[51] Acetaminophen may be administered by an oral or intravenous route at any point during the perioperative period.[45] Although the debate about the route of administration and analgesic efficacy continues, a systematic review by Jibril and colleagues reported that either route of medication administration was equally efficacious in a patient with normal gastrointestinal function.[50] As a result, the preoperative administration of oral acetaminophen is commonly administered as part of multimodal pain management regimen.[37] Intravenous, per rectal, and parental acetaminophen also decrease opioid requirement and improve perioperative pain control.[52]

Gabapentinoids, including gabapentin and pregabalin, were initially developed as anti-seizure medication but have been shown to possess excellent adjunctive analgesic and anxiolytic properties.[45] The exact mechanism by which gabapentinoids exert analgesic effects remains relatively unknown, but they are believed to work by inhibiting voltage-gated calcium channels and activating potassium channels. The US Food and Drug Administration classifies gabapentenoids as non-controlled substances.[53] However, gabapentin has been

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associated with an increased risk of abuse, overdose, and respiratory depression when used in combination with opioids.[53,54] As a result, many states have implemented rules and regulations controlling it uses.[53] There is not yet a consensus for optimal gabapentinoid dosing and further studies are needed.[43]

Alpha 2 adrenergic agonists such as clonidine and dexmedetomidine have sedative, anxiolytic, and analgesic properties and have been utilized perioperatively to reduce postoperative pain and to prevent opioid withdrawal symptoms.[55,56] Studies investigating the efficacy of preoperative administration of clonidine on postoperative pain have inconsistent results.[55,57] However, intraoperative administration of dexmedetomidine is effective at decreasing postoperative pain and postoperative opioid consumption.[44,58] Clonidine may be used to prevent withdrawal symptoms and promote comfort for patients on buprenorphine or methadone for the treatment of opioid dependence.[31,56,59] Caution must be exercised when using alpha-2-adrenergic agonists, especially in patients with cardiovascular comorbidity because of the risk for significant bradycardia and hypotension.[44]

NSAIDs such as cyclooxygenase 2 (COX-2) inhibitors, ketorolac, and ibuprofen are efficacious nonopioid analgesics that can be employed in the pain management plan for all patients, including those with chronic pain, to decrease opioid requirements.[45] The COX-2 inhibitors, such as Celecoxib should be administered preoperatively, rather than as a rescue analgesic because of its prolonged onset of action.[45] There is inconsistent evidence suggesting that NSAIDs may increase the risk of postoperative bleeding and poor bone healing.[60–62] Thus, communication with the surgical team regarding their use is essential.

Ketamine is an efficacious non-opioid analgesic that functions primarily by blocking NMDA receptors. Guidelines from the American Society of Regional Anesthesia and Pain Medicine, American Academy of Pain, and American Society of Anesthesiologists recommend the intraoperative infusion of ketamine for acute pain management in individuals with chronic pain and opioid tolerance.[63] It can be given intravenously either by continuous infusion or intermittent scheduled boluses.[44] At sub-anesthetic doses, the psychedelic effects of ketamine are minimized and do not affect patients' satisfaction with care.[64]

Intravenous lidocaine is a local anesthetic that is frequently infused perioperatively to reduce opioid use and enhance recovery from surgery. Besides analgesia, perioperative low dose infusion of lidocaine has been associated with a reduction in postoperative nausea and vomiting, ileus, and hospital length of stay.[65] The exact mechanism of systemic analgesia is not well understood but may be related to modulation of the inflammatory response during surgery.[45,65]

Magnesium sulfate is an NMDA receptor antagonist that is frequently administered intraoperatively as a bolus and infusion to reduce postoperative pain and opioid consumption.[44] A recent prospective randomized controlled double-blinded trial found that intravenous infusion of magnesium sulfate attenuates the surgical stress response and reduces postoperative pain.[66] Also, meta-analyses reported that magnesium and ketamine

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prevent the occurrence of OIH and opioid tolerance with increased patient satisfaction with care.[36,67]

Opioid Analgesia

Opioid analgesic medications are commonly used for the management of moderate to severe acute pain. Compared with opioid naïve patients, patients with chronic pain (who are being treated with opioids or have developed tolerance to opioids) will likely require higher doses of opioids to achieve the desired analgesic effect.[2,35] Such dose escalation may achieve the desired therapeutic effect; however, higher doses of opioids increase the risk for excessive sedation, respiratory depression, constipation, nausea, vomiting, and immunologic and hormonal dysregulation.[46,68] In the postoperative setting, these adverse effects of opioids may prolong hospital stay, delay recovery, and increase morbidity and mortality.[35] In the next section, we discuss an alternative approach to achieving analgesia with opioids without escalating the dose of a single opioid.

Role of opioid rotation in pain management

Opioid rotation refers "to the clinical practice of substituting one strong opioid with another when a satisfactory balance between pain relief and adverse effects is not achieved with the first opioid."[69] In other words, opioid rotation is the switching from one potent opioid to another to achieve the desired therapeutic effect. In a 2018 systematic review, Schuster and colleagues reported that switching chronic cancer patients from one level III opioid to another resulted in a significant reduction in the opioid dose required to achieve analgesia and a simultaneous increase in patient satisfaction.[70] Among non-cancer patients, opioid switching from one opioid to another has been shown to decrease opioid requirements and improvement in pain relief.[35] The higher analgesic effect may be due to differences in kappa, mu, and delta-opioid receptor interactions and incomplete cross-tolerance.[71]

Box 1 summarizes common indications for opioid rotation.[72] In the perioperative setting patients may be switched from one opioid to another because of the necessity to administer medication by a particular route (e.g., intravenously because of non-per os (NPO) status), provider/patient preference, and availability of some medications in the institution's formulary. For instance, a patient with chronic low back pain who is undergoing a bowel resection may be rotated from oral oxycodone to intravenous fentanyl because of the provider's familiarity with the pharmacology of fentanyl and the need for postoperative NPO status. Smith and Peppin (2018) proposed a systematic approach to opioid rotation that included determination of medical and non-medical causes of opioid intolerability, reduction or cessation of nonessential medications such as benzodiazepines, aggressive treatment of intolerable side effects, and selection of new opioid-based on pharmacological properties.[73] Given that the intolerability of side effects is less likely to be the reason for opioid rotation in the perioperative setting, the focus is on the pharmacological considerations for opioid rotation. A five-step approach to perioperative opioid rotation is summarized below:

1. **Determine current daily opioid dose–** In the health care setting, medication orders (dose and frequency) are frequently defined around a 24-hour (daily)

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period. The daily opioid consumption should include the typical dose of any as-needed opioids.

2. **Determine the morphine equivalent daily dose (MEDD) –** Given the variability in the degree of receptor binding affinity, potency, and efficacy, the total 24-hour dose of the opioid must be converted to its morphine equivalence for comparison. The MEDD is commonly used as an indicator of the risk of opioid-induced respiratory depression.[8,74] Patients taking more than 90 MEDD are at significant risk for opioid-induced respiratory depression.[8] There is no universally accepted opioid-conversion method.[75] Table 2 depicts the opioid conversion factors endorsed by the CDC[8] and the Center for Medicare and Medicaid Services.[74] *Multiply the daily dose of a given opioid with its conversion factor to obtain the MEDD.* Note that the conversion of methadone and transdermal fentanyl to its morphine equivalent are non-linear, and extra caution must be exercised when converting higher doses of methadone and transdermal fentanyl.[8] For a patient on multiple medications, the total MEDD is determined by adding the MEDD of each opioid.[8,74]

3. **Select new opioid (preferably of different class)-** Opioids are commonly classified into three broad classes based on chemical structure: phenanthrene derivatives (e.g., morphine, codeine, hydrocodone, hydromorphone, oxycodone, and oxymorphone), the phenylpiperidine derivatives (e.g., meperidine, fentanyl, alfentanil, remifentanil, and sufentanil), and the diphenylheptane derivatives (e.g., propoxyphene and methadone). Given the shared chemical structure, opioids within the same chemical class share a higher degree of cross-tolerance. Thus, when possible, an opioid should be rotated to an opioid of a different class. For instance, a patient on chronic hydrocodone (a phenanthrene derivative) may be rotated to fentanyl or alfentanil (a phenylpiperidine derivative).[76]

4. **Determine the MEDD of the new opioid**- Multiply the MEDD by the conversion factor of the desired opioids to obtain its daily opioid dose. Do NOT administer the calculated daily opioid dose. Instead, *decrease the calculated MEDD by 25 to 50 percent to obtain the starting dose*. A dose reduction is required because opioids have incomplete cross-tolerance, and administration of the full dose could lead to opioid toxicity.[8] As mentioned earlier, the dose reduction decreases the risk for opioid associated adverse effects such as respiratory depression, without sacrificing the analgesic effects.

5. **Divide the daily dose by desired frequency of administration**- The frequency of drug administration depends on drug pharmacokinetics and patient factors. Short-acting drugs such as fentanyl will require a more frequent administration, while long-acting drugs such as hydromorphone will require less frequent administration. Similarly, an extended-release formulation of an oral medication will require less frequent administration than the standard formulation. Patient factors such as knowledge of a patient's pharmacogenetics information would also affect the frequency of administration.[77] For instance, a patient who is

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identified as a CYP2D6 ultra-rapid metabolizer may require a more frequent and lower dose of tramadol, than a CYP2D6 poor metabolizer.[77]

Considerations for Patients on Methadone Maintenance Therapy

Methadone is a long-acting synthetic analgesic medication that is frequently used for the treatment of chronic pain and opioid addiction.[78] It exerts most of its analgesic effects as a partial mu-opioid receptor agonist and full agonist activity at kappa and delta receptors, and antagonist at NMDA receptors.[35,78] The oral formulation of methadone has a half-life of 24 to 36 hours in opioid-tolerant patients.[35] The long half-life helps control pain while preventing opioid cravings and opioid withdrawal symptoms. The metabolism of methadone is complicated and extensive involving highly polymorphic cytochrome p450 (CYP) enzymes such as CYP2D6, CYP3A4/3A5, and CYP2C19.[78] Many drugs inhibit or induce the activity of these enzymes, and thus affect the pharmacology of methadone. CYP enzyme inhibitors such as alcohol, barbiturates, benzodiazepines, cimetidine, erythromycin, fluoxetine, and grapefruits have been associated with higher plasma levels of methadone with increased clinical effects.[79] Conversely, enzymes inducers such as ketoconazole have been associated with a decrease in the plasma level of methadone.[80] In addition to the potential drug interactions, many patients on methadone maintenance therapy have pre-existing opioid tolerance, dependence, and addiction that present unique challenges for perioperative pain management.

Intraoperative administration of intravenous methadone decreases postoperative pain in patients undergoing multilevel spinal surgery.[81,82] A randomized control trial of patients undergoing total hip arthroplasty reported that compared to morphine patient-controlled analgesia (PCA), patients on methadone PCA reported lower pain scores and used fewer pain medications 24 hours postoperatively.[83] Among non-surgical patients, methadone has been reported to prevent OIH.[33] However, these findings are inconsistent as other researchers have reported methadone associated OIH.[84]

Patients on Buprenorphine and Naltrexone Therapy

Buprenorphine is a mu-opioid partial agonist, which also has kappa and delta-opioid antagonist properties.[85] A benefit of buprenorphine is its wide safety margin; minimal respiratory depression is seen with this drug.[86] Buprenorphine has a relatively long half-life of 20–60 hours and is well absorbed from sublingual administration.[38,85] Buprenorphine is about 25 to 100 times as potent as morphine, and produces adequate analgesia when 5 to 10 percent of the mu receptors are occupied.[87] Given its high affinity (and slow dissociation) for the mu-receptor, low doses of buprenorphine can displace most mu-opioid receptor agonists such as morphine.[85] On the other displacement of buprenorphine from the opioid receptor requires significantly higher doses of traditional opioids.[85,87] Thus, the recommendations for patients who take buprenorphine vary depending on the amount of postoperative pain expected. If only mild postoperative pain is expected, it is recommended to continue buprenorphine the morning of surgery and continue the patient's daily schedule.[38,86] Local anesthesia infiltration and non-opioid analgesics such as NSAIDs, acetaminophen, ketorolac, and ketamine can be used to manage mild postoperative pain in this population.[35,85] For those patients who are expected to experience high levels of

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postoperative pain, it is recommended that buprenorphine be discontinued for up to 72 hours before surgery to give enough for metabolism and excretion.[85] These patients can then receive traditional opioid treatment as well as adjunctive therapy with a multimodal approach, recognizing that the patient may still be opioid-tolerant.[85] Buprenorphine oral/sublingual is supplied alone and also in combination with naloxone, which is added to discourage patients from intravenous injection. The naloxone has a limited clinical effect on the opioid receptor when taken in orally or buccally.[88]

Naltrexone is an opioid antagonist used for the treatment of opioid abuse. The drug blocks the effects of opioids by competitively binding to the receptors, thereby reducing opioid activity and cravings if the patient receives an opioid.[89] Naltrexone is available in both oral and injectable forms; the latter is available as an intramuscular injection, which lasts for approximately 30 days.[90] Low dose naltrexone is also used in chronic pain conditions such as fibromyalgia to help reduce inflammation and discomfort.[90] Patients must be entirely opioid-free before this therapy is instituted, or they will experience immediate, profound withdrawal. The recommendations for caring for the patient receiving naltrexone depend on the route of administration. For patients who have received long-acting depot injection, it is best to postpone surgery for 30 days following the last injection.[86] This is best done in conjunction with an Addictionologist who is managing the patient so that relapse can be avoided. Patients on daily oral naltrexone can discontinue the medication 72 hours before surgery.[86] Finally, for a patient undergoing an emergency procedure, it must be recognized that the opioid receptors are blocked. Thus, different methods of pain control must be considered, such as regional nerve blocks, use of ketamine, intravenous acetaminophen, dexmedetomidine, and other non-opioid techniques to ensure adequate pain relief.

Successful Perioperative Pain Management in a Patient with Chronic Pain

Despite the advances in our pain mechanisms and the availability of potent opioid medications, up to 80 percent of patients report moderate to severe pain after major surgery.[7] Among patients with chronic pain, achieving optimal postoperative pain control is more challenging because of the biological and psychological changes associated with the disease process. Despite these challenges, effective postoperative pain management is not only the ethical responsibility of perioperative health care providers but also a fundamental right of the patients. As described in this paper, a comprehensive multimodal patient-centered approach is essential for optimal postoperative pain management in individuals with chronic pain. Table 3 summaries the perioperative pain management plan of a hypothetical individual (James) who presents to the operating room for an open bowel resection.

James is a 70-year-old male with a past medical history that is significant for non-specific chronic low back pain, type II diabetes, hypertension, and depression. His current home oral medications include gabapentin 300mg nightly, metformin 1000mg every 12 hours, Lisinopril 40mg daily, sertraline 200mg daily, hydrocodone/acetaminophen 10/325mg, two tablets by mouth, every 4 hours, and oxycodone 15mg by mouth every 3 hours as needed for breakthrough pain. He reports a baseline pain rating of 3 on a scale of 0 (no pain) to 10 (worst pain imaginable). Before coming to the hospital, James took his morning daily dose of hydrocodone as instructed by the provider during the pre-anesthesia visit. During the

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preoperative assessment, the nurse obtains and documents his medical and medication history. He reveals that he typically takes oxycodone two (2) times a day. As part of the multimodal pain management protocol, James is given Tylenol 1000mg PO, Celecoxib 400 mg PO, and Gabapentin 300 mg PO. Also, the CRNA performs an intrathecal injection of morphine sulfate 0.5mg and discusses the postoperative pain management goals with the patient.

The goals of the postoperative pain management plan include the prevention of withdrawal symptoms from opioids and optimal pain management using PCA. Together, they agreed that a return to a baseline pain rating of less than or equal to 3/10 would be optimal. To achieve this goal, the provider documents his daily opioid consumption and converts each dose into its morphine equivalents. James' current cumulative (hydrocodone plus oxycodone) MEDD is 165 mg (see postoperative phase on table 3 for details); this is the basal dose of opioids that the provider can administer to prevent withdrawals and achieve baseline pain relief during the postoperative period. James' postoperative orders include maintaining NPO, PCA morphine at 1mg per hour (a 50 percent MEDD reduction) with an on-demand 1mg bolus with a 4 hour lock time. On postoperative day one, James' bowel function returns, and he reports a pain rating of 0/10. Before discharge, James is transitioned to oral hydromorphone for ease of administration at home. Also, his dose of Gabapentin is increased to 600 mg two times a day. Using optimal multimodal pain management allowed James to leave the hospital on a lower dose of opioids with more pain relief and higher satisfaction with patient care.

Conclusion

This article described practical consideration for acute perioperative pain management in patients with chronic pain. Besides the multimodal approach, switching patients from one opioid to another may help decrease opioid requirements and increase satisfaction. Patients with opioid tolerance, dependence, and withdrawal therapy require special considerations. When patients with chronic pain present for surgery, adequate perioperative pain management is challenging. Historically, opioids have been the mainstay for perioperative pain control. However, the standard opioid-based techniques alone may not be sufficient to achieve adequate analgesia, especially in patients with opioid tolerance and opioid withdrawal maintenance therapy. Through careful consideration of the pharmacological properties of each medication, a patient-centered multi-modal perioperative pain management plan with realistic goals can greatly enhance perioperative pain management.

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References

1. Institute of Medicine. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington, DC: National Academies Press; 2011.
2. Jackman C Perioperative Pain Management for the Chronic Pain Patient With Long-Term Opioid Use. Orthop Nurs. 2019;38(2):159–163. [PubMed: 30933040]

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3. Davidson S, McKendrick D, French T. Preassessment clinic interview and patient anxiety. Saudi J Anaesth. 2016;10(4):402–408. [PubMed: 27833482]
4. Shafer A, Fish MP, Gregg KM, Seavello J, Kosek P. Preoperative anxiety and fear: a comparison of assessments by patients and anesthesia and surgery residents. Anesth Analg. 1996;83(6):1285–1291. [PubMed: 8942601]
5. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg. 2003;97(2):534–540, table of contents. [PubMed: 12873949]
6. Gan TJ, Habib AS, Miller TE, White W, Apfelbaum JL. Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. Curr Med Res Opin. 2014;30(1):149–160. [PubMed: 24237004]
7. Gan TJ. Poorly controlled postoperative pain: prevalence, consequences, and prevention. J Pain Res. 2017;10:2287–2298. [PubMed: 29026331]
8. Centers for Disease Control and Prevention. Prescription Opioid Data. In: Services USDoHaH, ed. Atlanta, GA2018.
9. Levy B, Paulozzi L, Mack KA, Jones CM. Trends in Opioid Analgesic–Prescribing Rates by Specialty, U.S., 2007–2012. Am J Prev Med. 2015;49(3):409–413. [PubMed: 25896191]
10. Nataraj N, Zhang K, Guy GP Jr., Losby JL. Identifying opioid prescribing patterns for high-volume prescribers via cluster analysis. Drug Alcohol Depend. 2019;197:250–254. [PubMed: 30875645]
11. Volkow ND, McLellan AT. Opioid Abuse in Chronic Pain — Misconceptions and Mitigation Strategies. N Engl J Med. 2016;374(13):1253–1263. [PubMed: 27028915]
12. Heins SE, Frey KP, Alexander GC, Castillo RC. Reducing High-Dose Opioid Prescribing: State-Level Morphine Equivalent Daily Dose Policies, 2007–2017. Pain Med. 2019.
13. Adesoye A, Duncan N. Acute Pain Management in Patients With Opioid Tolerance. US Pharmacist. 2017;42(2):28–32.
14. Khan RS, Ahmed K, Blakeway E, et al. Catastrophizing: a predictive factor for postoperative pain. Am J Surg. 2011;201(1):122–131. [PubMed: 20832052]
15. Sobol-Kwapinska M, Bąbel P, Plotek W, Stelcer B. Psychological correlates of acute postsurgical pain: A systematic review and meta-analysis. Eur J Pain. 2016;20(10):1573–1586. [PubMed: 27136510]
16. Powell R, Scott NW, Manyande A, et al. Psychological preparation and postoperative outcomes for adults undergoing surgery under general anaesthesia. Cochrane Database Syst Rev. 2016(5).
17. Theunissen M, Peters ML, Bruce J, Gramke H-F, Marcus MA. Preoperative anxiety and catastrophizing: a systematic review and meta-analysis of the association with chronic postsurgical pain. Clin J Pain. 2012;28(9):819–841. [PubMed: 22760489]
18. Lavand'homme P, Steyaert A. Opioid-free anesthesia opioid side effects: Tolerance and hyperalgesia. Best Pract Res Clin Anaesthesiol. 2017;31(4):487–498. [PubMed: 29739537]
19. Cahill CM, Walwyn W, Taylor AMW, Pradhan AAA, Evans CJ. Allostatic Mechanisms of Opioid Tolerance Beyond Desensitization and Downregulation. Trends Pharmacol Sci. 2016;37(11):963–976. [PubMed: 27670390]
20. Bian J, Zhang S, Yi M, Yue M, Liu H. The mechanisms behind decreased internalization of angiotensin II type 1 receptor. Vascul Pharmacol. 2018;103–105:1–7.
21. Colvin LA, Bull F, Hales TG. Perioperative opioid analgesia-when is enough too much? A review of opioid-induced tolerance and hyperalgesia. Lancet. 2019;393(10180):1558–1568. [PubMed: 30983591]
22. Martyn JAJ, Mao J, Bittner EA. Opioid Tolerance in Critical Illness. N Engl J Med. 2019;380(4):365–378. [PubMed: 30673555]
23. Nowoczyn M, Marie N, Coulbault L, et al. Remifentanil produces cross-desensitization and tolerance with morphine on the mu-opioid receptor. Neuropharmacology. 2013;73:368–379. [PubMed: 23792280]
24. Burma NE, Kwok CH, Trang T. Therapies and mechanisms of opioid withdrawal. Pain Manag. 2017;7(6):455–459. [PubMed: 29125396]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

25. Baconi DL, Ciobanu A-M, Vlăsceanu AM, Cobani OD, Negrei C, Bălălău C. Current concepts on drug abuse and dependence. J Mind Med Sci. 2015;2(1):18–33.
26. American Society of Addiction Medicine. Public Policy Statement: Definition of Addiction. In. Chevy Chase, MD2011.
27. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, Van Der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data analysis. Pain. 2015;156(4):569–576. [PubMed: 25785523]
28. Berridge KC, Robinson TE, Aldridge JW. Dissecting components of reward: 'liking', 'wanting', and learning. Curr Opin Pharmacol. 2009;9(1):65–73. [PubMed: 19162544]
29. Bressan RA, Crippa JA. The role of dopamine in reward and pleasure behaviour--review of data from preclinical research. Acta Psychiatr Scand Suppl. 2005(427):14–21.
30. Anderson-Mooney A, Dodd JN, Scott A, Guller L. The Nervous System and Addictions: Essentials for Clinicians In: Preedy VR, ed. Neuropathology of Drug Addictions and Substance Misuse. Vol 1 London, UK: Elsevier; 2016:3–13.
31. Kosten TR, Baxter LE. Review article: Effective management of opioid withdrawal symptoms: A gateway to opioid dependence treatment. Am J Addict. 2019;28(2):55–62. [PubMed: 30701615]
32. Gowing L, Ali R, White JM. Opioid antagonists with minimal sedation for opioid withdrawal. Cochrane Database Syst Rev. 2006(1).
33. Yi P, Pryzbylkowski P. Opioid Induced Hyperalgesia. Pain Med. 2015;16 Suppl 1:S32–36. [PubMed: 26461074]
34. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. Pain Physician. 2011;14(2):145–161. [PubMed: 21412369]
35. Coluzzi F, Bifulco F, Cuomo A, et al. The challenge of perioperative pain management in opioid-tolerant patients. Ther Clin Risk Manag. 2017;13:1163–1173. [PubMed: 28919771]
36. Liu Y, Zheng Y, Gu X, Ma Z. The efficacy of NMDA receptor antagonists for preventing remifentanil-induced increase in postoperative pain and analgesic requirement: a meta-analysis. Minerva Anestesiol. 2012;78(6):653–667. [PubMed: 22301767]
37. Yoo JS, Ahn J, Buvanendran A, Singh K. Multimodal analgesia in pain management after spine surgery. J Spine Surg. 2019;5(Suppl 2):S154–s159. [PubMed: 31656869]
38. Quinlan J, Cox F. Acute pain management in patients with drug dependence syndrome. Pain Reports. 2017;2(4):e611. [PubMed: 29392226]
39. Wachholtz A, Ziedonis D, Gonzalez G. Comorbid Pain and Opioid Addiction: Psychosocial and Pharmacological Treatments. Substance Use & Misuse. 2011;46(12):1536–1552. [PubMed: 21756033]
40. Baribeault T Opioid-Free Anesthesia for an Emergency Laparoscopic Cholecystectomy in a Patient Taking Buprenorphine-Naloxone for Opioid Addiction: A Case Report. Anesthesia eJournal. 2018;6:37–40.
41. Beverly A, Kaye AD, Ljungqvist O, Urman RD. Essential Elements of Multimodal Analgesia in Enhanced Recovery After Surgery (ERAS) Guidelines. Anesthesiol Clin. 2017;35(2):e115–e143. [PubMed: 28526156]
42. Kumar K, Kirksey MA, Duong S, Wu CL. A Review of Opioid-Sparing Modalities in Perioperative Pain Management: Methods to Decrease Opioid Use Postoperatively. Anesth Analg. 2017;125(5):1749–1760. [PubMed: 29049119]
43. Schmidt PC, Ruchelli G, Mackey SC, Carroll IR. Perioperative gabapentinoids: choice of agent, dose, timing, and effects on chronic postsurgical pain. Anesthesiology. 2013;119(5):1215–1221. [PubMed: 24051389]
44. Thomas DA, Boominathan P, Goswami J, Mukherjee S, Vadivelu N. Perioperative Management of Patients with Addiction to Opioid and Non-opioid Medications. Curr Pain Headache Rep. 2018;22(7):52. [PubMed: 29904819]
45. Afonso AM, Tokita HK, McCormick PJ, Twersky RS. Enhanced Recovery Programs in Outpatient Surgery. Anesthesiol Clin. 2019;37(2):225–238. [PubMed: 31047126]
46. Macres SM, Moore PG, Fishman SM. Acute pain management In: Barash PG, Cullen BF, Stoelting RK, et al., eds. Clinical Anesthesia. 8th ed. Philadelphia: Wolters Kluwer; 2017:1562–1606.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

47. Savarese JJ, Tabler NG. Multimodal analgesia as an alternative to the risks of opioid monotherapy in surgical pain management. J Healthc Risk Manag. 2017;37(1):24–30. [PubMed: 28719091]

48. De Oliveira GS Jr., Agarwal D, Benzon HT. Perioperative single dose ketorolac to prevent postoperative pain: a meta-analysis of randomized trials. Anesth Analg. 2012;114(2):424–433. [PubMed: 21965355]

49. Michelet D, Andreu-Gallien J, Bensalah T, et al. A meta-analysis of the use of nonsteroidal antiinflammatory drugs for pediatric postoperative pain. Anesth Analg. 2012;114(2):393–406. [PubMed: 22104069]

50. Jibril F, Sharaby S, Mohamed A, Wilby KJ. Intravenous versus Oral Acetaminophen for Pain: Systematic Review of Current Evidence to Support Clinical Decision-Making. Can J Hosp Pharm. 2015;68(3):238–247. [PubMed: 26157186]

51. Elvir-Lazo OL, White PF. The role of multimodal analgesia in pain management after ambulatory surgery. Curr Opin Anaesthesiol. 2010;23(6):697–703. [PubMed: 20847690]

52. Kaye AD, Cornett EM, Helander E, et al. An Update on Nonopioids: Intravenous or Oral Analgesics for Perioperative Pain Management. Anesthesiol Clin. 2017;35(2):e55–e71. [PubMed: 28526161]

53. Peckham AM, Ananickal MJ, Sclar DA. Gabapentin use, abuse, and the US opioid epidemic: the case for reclassification as a controlled substance and the need for pharmacovigilance. Risk Manag Healthc Policy. 2018;11:109–116. [PubMed: 30154674]

54. Gomes T, Juurlink DN, Antoniou T, Mamdani MM, Paterson JM, van den Brink W. Gabapentin, opioids, and the risk of opioid-related death: A population-based nested case-control study. PLoS Med. 2017;14(10):e1002396. [PubMed: 28972983]

55. Lambert P, Cyna AM, Knight N, Middleton P. Clonidine premedication for postoperative analgesia in children. Cochrane Database Syst Rev. 2014(1):Cd009633. [PubMed: 24470114]

56. Jain N, Chavan B, Sidana A, Das S. Efficacy of buprenorphine and clonidine in opioid detoxification: A hospital- based study. Indian J Psychiatry. 2018;60(3):292–299. [PubMed: 30405254]

57. Turan A, Babazade R, Kurz A, et al. Clonidine Does Not Reduce Pain or Opioid Consumption After Noncardiac Surgery. Anesth Analg. 2016;123(3):749–757. [PubMed: 27537762]

58. Bielka K, Kuchyn I, Babych V, Martycshenko K, Inozemtsev O. Dexmedetomidine infusion as an analgesic adjuvant during laparoscopic small es, Cyrillicholecystectomy: a randomized controlled study. BMC Anesthesiology. 2018;18(1):44. [PubMed: 29678158]

59. Kowalczyk WJ, Bertz JW, Moran LM, et al. Clonidine Increases the Likelihood That Abstinence Can Withstand Unstructured Time in Buprenorphine- maintained Outpatients. J Addict Med. 2017;11(6):454–460. [PubMed: 28759482]

60. McDonald E, Winters B, Nicholson K, et al. Effect of Postoperative Ketorolac Administration on Bone Healing in Ankle Fracture Surgery. Foot Ankle Int. 2018;39(10):1135–1140. [PubMed: 29972028]

61. Olds C, Spataro EA, Li K, Kandathil CK, Most SP. Nonsteroidal Antiinflammatory Drug Use after Nasal Surgery Is Not Associated with Increased Postoperative Complications. Plast Reconstr Surg. 2019;144(6):1130e–1132e.

62. Forsyth MG, Clarkson DJ, O'Boyle CP. A systematic review of the risk of postoperative bleeding with perioperative non-steroidal anti-inflammatory drugs (NSAIDs) in plastic surgery. Eur J Plast Surg. 2018;41(5):505–510.

63. Schwenk ES, Viscusi ER, Buvanendran A, et al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Acute Pain Management From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med. 2018;43(5):456–466. [PubMed: 29870457]

64. Aroke EN, Crawford SL, Dungan JR. Pharmacogenetics of Ketamine-Induced Emergence Phenomena: A Pilot Study. Nurs Res. 2017;66(2):105–114. [PubMed: 28252572]

65. Dunn LK, Durieux ME. Perioperative Use of Intravenous Lidocaine. Anesthesiology. 2017;126(4):729–737. [PubMed: 28114177]

66. El Mourad MB, Arafa SK. Effect of intravenous versus intraperitoneal magnesium sulfate on hemodynamic parameters and postoperative analgesia during laparoscopic sleeve gastrectomy-A

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prospective randomized study. J Anaesthesiol Clin Pharmacol. 2019;35(2):242–247. [PubMed: 31303716]

67. Wu L, Huang X, Sun L. The efficacy of N-methyl-D-aspartate receptor antagonists on improving the postoperative pain intensity and satisfaction after remifentanil-based anesthesia in adults: a meta-analysis. J Clin Anesth. 2015;27(4):311–324. [PubMed: 25824051]
68. Kershaw SG, Della Vedova CB, Majumder I, et al. Acute opioid administration induces hypothalamic-pituitary-adrenal activation and is mediated by genetic variation in interleukin (Il)1B. Pharmacol Biochem Behav. 2015;138:9–13. [PubMed: 26363312]
69. Dale O, Moksnes K, Kaasa S. European Palliative Care Research Collaborative pain guidelines: Opioid switching to improve analgesia or reduce side effects. A systematic review. Palliat Med. 2011;25(5):494–503. [PubMed: 21708856]
70. Schuster M, Bayer O, Heid F, Laufenberg-Feldmann R. Opioid Rotation in Cancer Pain Treatment. Dtsch Arztebl Int. 2018;115(9):135–142. [PubMed: 29563006]
71. Mercadante S, Portenoy RK. Opioid poorly-responsive cancer pain. Part 2: basic mechanisms that could shift dose response for analgesia. J Pain Symptom Manage. 2001;21(3):255–264. [PubMed: 11239748]
72. Fine PG, Portenoy RK, Ad Hoc Expert Panel on Evidence R, Guidelines for Opioid R. Establishing “best practices” for opioid rotation: conclusions of an expert panel. J Pain Symptom Manage. 2009;38(3):418–425. [PubMed: 19735902]
73. Peppin J Toward a systematic approach to opioid rotation. J Pain Res. 2014:589. [PubMed: 25378948]
74. Center for Medicare and Medicaid Services (CMS). Opioid Morphine Equivalent Conversion Factor. In: Services HaH, ed2015.
75. Fudin J, Pratt Cleary J, Schatman ME. The MEDD myth: the impact of pseudoscience on pain research and prescribing-guideline development. J Pain Res. 2016;9:153–156. [PubMed: 27042140]
76. Elbaridi N, Kaye AD, Choi S, Urman RD. Current Concepts of Phenylpiperidine Derivatives Use in the Treatment of Acute and Chronic Pain. Pain Physician. 2017;20(2s):Se23–se31. [PubMed: 28226339]
77. Aroke EN, Kittelsrud JM. A Primer to Pharmacogenetics of Postoperative Pain Management. AANA J. 2019;87(2):131–137. [PubMed: 31587726]
78. Kharasch ED. Current Concepts in Methadone Metabolism and Transport. Clin Pharm Drug Dev. 2017;6(2):125–134.
79. Volpe DA, Xu Y, Sahajwalla CG, Younis IR, Patel V. Methadone Metabolism and Drug-Drug Interactions: In Vitro and In Vivo Literature Review. J Pharmaceut Sci. 2018;107(12):2983–2991.
80. Lee H-Y, Li J-H, Wu L-T, Wu J-S, Yen C-F, Tang H-P. Survey of methadone-drug interactions among patients of methadone maintenance treatment program in Taiwan. Subst Abuse Treat Prev Policy. 2012;7:11–11. [PubMed: 22429858]
81. Gottschalk A, Durieux ME, Nemergut EC. Intraoperative Methadone Improves Postoperative Pain Control in Patients Undergoing Complex Spine Surgery. Anesth Analg. 2011;112(1):218–223. [PubMed: 20418538]
82. Stemland CJ, Witte J, Colquhoun DA, et al. The pharmacokinetics of methadone in adolescents undergoing posterior spinal fusion. Pediatr Anesth. 2013;23(1):51–57.
83. Neto JOB, Machado MDT, de Almeida Correa M, Scomparim HA, Posso IP, Ashmawi HA. Methadone patient-controlled analgesia for postoperative pain: a randomized, controlled, double-blind study. J Anesth. 2014;28(4):505–510. [PubMed: 24445560]
84. Manu E, Montagnini M, Vitale C. Methadone Induced Hyperalgesia: Is It Possible? (775). J Pain Symptom Manage. 2012;43(2):465–466.
85. Anderson TA, Quaye ANA, Ward EN, Wilens TE, Hilliard PE, Brummett CM. To Stop or Not, That Is the Question: Acute Pain Management for the Patient on Chronic Buprenorphine. Anesthesiology. 2017;126(6):1180–1186. [PubMed: 28511196]
86. Crabtree E, Hamilton A. Continuing Buprenorphine or Naltrexone-Containing Drugs in Peri-Operative Patients. In: Oregon Health and Science University; 2017.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

87. Khanna IK, Pillarisetti S. Buprenorphine - an attractive opioid with underutilized potential in treatment of chronic pain. J Pain Res. 2015;8:859–870. [PubMed: 26672499]

88. The Medical Letter. Management of Opioid Withdrawal Symptoms In. The Medical Letter on Drugs and Therapeutics: The Medical Letter, Inc; 2018.

89. Veilleux JC, Colvin PJ, Anderson J, York C, Heinz AJ. A review of opioid dependence treatment: pharmacological and psychosocial interventions to treat opioid addiction. Clin Psychol Rev. 2010;30(2):155–166. [PubMed: 19926374]

90. Younger J, Parkitny L, McLain D. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. Clin Rheumatol. 2014;33(4):451–459. [PubMed: 24526250]

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Box 1

Common Indications of Opioid Rotation

1.	Development of intolerable adverse events with current opioid
2.	Lack of analgesia following dose escalation
3.	The occurrence of drug-drug interactions
4.	Patient displays drug-aberrant behavior(s)
5.	Patient prefers an alternative route of administration
6.	Financial limitations or access barriers to certain medications

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By the end of the review, the learner would be able to

1. Discuss the multi-modal approach to acute pain management
2. Discuss the role of opioid rotation in opioid dose reduction and pain management
3. Articulate considerations for acute pain management in patients on partial opioid agonists and antagonists

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Table 1.

Surgical Site and Appropriate Regional Anesthesia Technique

Surgical Site		Type of Regional Technique (Block)
Head		Occipital
		Sphenopalpatine (topical, for migraine)
		Retrobulbar and peribulbar
Neck		Deep cervical plexus
		Superficial cervical plexus
Truncal	Chest	Intercostal
		Interpleural
		Paravertebral
		Quadratus lumorum (QL)
		Erector spinae
		Pec1 and Pec2
	Abdomen	Spinal
		Epidural
		Caudal
		Transversus abdominis plane (TAP)
		Quadratus lumborum (QL)
		Erector spinae
Upper Extremity	Shoulder	Interscalene
	Above the elbow	Supraclavicular
		Infraclavicular
	Below the elbow	Supraclavicular
		Infraclavicular
		Axillary
		Elbow- Selective blocks of ulnar, median, and radial
		Wrist- Selective blocks of ulnar, median, and radial
		Finger- Digital
Lower Extremity	Above the knee	Femoral
		3-in-1 Block (Femoral, obturator, lateral femoral cutaneous)
		Fascia Iliaca
	Below the knee	Saphenous- (begins just above knee) – also referred to as Adductor canal or Subsartorial blocks
		Sciatic – gluteal/posterior, anterior, popliteal, lateral approaches
		Ankle - (targets 5 nerves: saphenous, deep peroneal, superficial peroneal/fibular, sural, posterior tibial)
		Mid foot
		Toes-Digital

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Table 2

Determining Opioid Morphine Milligram Equivalent

Opioid[#]	Conversion Factor	Dose Equivalent to Morphine Sulfate (10mg)
Butorphanol[&]	7	1.4
Buprenorphine patch[&]	12.6	0.8
Buprenorphine tablet or film[&]	10	1
Codeine	0.15	66.7
Fentanyl buccal or SL tables or Lozenge	0.13	76.9
Fentanyl nasal spray	0.16	62.5
Fentanyl transdermal (in mcg/hr)	7.2	1.4mcg/hr
Fentanyl oral spray or film	0.18	55.5
Hydrocodone	1	10
Hydromorphone	4	2.5
Meperidine	0.1	100
Methadone		
1 – 20 mg/day	4	2.5
21 – 40 mg/day	8	1.25
41 – 60 mg/day	10	1
61 – 80 mg/day	12	0.8
Nalbuphine[&]	1	10
Oxycodone	1.5	6.7
Oxymorphone	3	3.3
Pentazocine	0.37	27
Tapentadol	0.4	25
Tramadol	0.1	100

From Opioid Oral Morphine Milligram Equivalent (MME) Conversion Factors," by Centers for Medicare and Medicaid Services, 2018 (https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Oral-MME-CFs-vFeb-2018.pdf). In the public domain.

Notes: mg = milligram, mcg/hr = microgram per hour

[#]doses in mg/day except where noted; Adapted from Opioid Morphine Equivalent Conversion Factors, Center for Medicare and Medicaid Services.

[&]Not included in the CDC MME table likely because they are associated with opioid overdose.

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Table 3:

Exemplar of a Perioperative Multimodal Pain Management Plan

Phase	Pharmacological plan	Rationale
Preoperative	Develop patient centered postoperative pain management plan.	Set realistic goals.
	Tylenol 1000mg PO	
	Celebrex 300mg PO	
	Neurontin 150mg PO	
	Morphine 5mg Intrathecal	
Intraoperative	Fentanyl – titrate to effect	Manage pain intraoperatively with choice of opioid.
	Morphine – titrate to effect	
Postoperative	**Opioid rotation from oral opioids to IV morphine**	The open bowel resection requires the patient to be NPO after the surgery.
	1. Patient taking oxycodone 200mg and tramadol 50mg.	
	○ Hydrocodone 120mg daily ➔ 120 × 1= 120mg morphine	The conversion of oral morphine to IV morphine is 3:1.
	○ Oxycodone 30mg daily ➔ 30 × 1.5 = 45mg morphine	
	○ Total MEDD = 120 + 45 = 165 MEDD	27.5mg IV morphine is the baseline rate that will be used to prevent withdrawal and manage chronic pain symptoms.
	2. 165mg of oral morphine is equivalent to 55 mg IV morphine.	
	3. Decrease the dose by 50% due because of incomplete tolerance ➔ (50% $of 55mg = 27.5mg$).	
	4. Infuse 27.5 mg over 24 as the basal rate of PCA ($^{27.5}/_{24} = 1.15mg$).	1mg IV bolus helps manage acute postoperative pain
	○ Run baseline PCA at 1 to 1.25mg per hour	
	○ Program 1mg bolus as needed with a 4-hour lock time	
	Postoperative day 1: Summary of opioid consumption	A summary of the last 24 hours opioid consumption is used to determine the discharge opioid requirement.
	- 24mg morphine from the infusion	
	- 3 mg in boluses	
	- Total daily IV use = 27 mg	
	Postoperative day 2: Discharge orders	The importance of teaching the patient about the need to reduce opioid consumption cannot be overemphasized.
	- Gabapentin 600 mg two times a day	
	- Convert IV morphine to oral equivalence ➔ 27 × 3 = 81mg	- Some patients may rationalize their opioid dependence by requesting the same opioid. Good knowledge of pharmacogenetics would enhance patient teaching.
	- 81 mg of oral MEDD ➔ $^{81}/_{4} = 20mg$ oral Hydromorphone	
	- Hydromorphone extended-release 8 mg by mouth 2 (or 3 depending on assessment) times a days	
		- Increasing the dose of non-opioid analgesics should help decrease opioid requirements.

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Notes: PCA= patient controlled analgesia; IV = intravenous; NPO = nothing by mouth; MEDD= morphine equivalent daily dose; PO = oral