**Lesson S31: Perioperative Pain Management of the Patient With Chronic Pain—Part 2**

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Read this article, reflect on the information presented, then go online and complete the lesson post-test and course evaluation before the termination date below. (CME credit is not valid past this date.) You must achieve a score of 80% or better to earn CME credit.

TIME TO COMPLETE ACTIVITY: 2 hours
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**Practice Gaps**

This 2-part series reviews the perioperative management of pain. Part 1 (presented last month) defines pain and the descriptors of pain terminology. Appropriate evaluation of the chronic pain patient is outlined and alternatives for anesthetic plans presented. The concept of multimodal analgesia is discussed and a conversion table for commonly used analgesic agents is presented.

In Part 2, narcotic metabolism and toxicity will be delineated and perioperative adjuvants discussed. Additional sections will deal with the special concerns of postoperative analgesia in the obese patient and drug interactions caused by concomitant administration of St. John’s wort. Finally, the differences between addiction, pseudoaddiction, tolerance, and secondary gain will be presented.

**Objectives**

At the end of the lesson, the participant will be able to:

1. Present post-operative benefits/risks of PCA use
2. Identify concerns and risk factors of obesity on choices of anesthetics
3. Be aware of the potential effects of St. John’s Wort
4. Differentiate between addiction, pseudo-addiction, tolerance, and secondary gain
5. Describe the metabolism of different opioids
6. List the clinical triad of opioid toxicity
7. Know the common side effects of opioid administration
8. Understand the mechanism of action of ketorolac and possible adverse side effects
9. Present a plan for postoperative pain management of the patient with chronic/acute pain
10. List advantages and disadvantages of dexmedetomidine
Case Presentation

A 65-year-old man was scheduled for multilevel laminectomies and instrumentation. Suffering from severe back pain for years, he had been receiving chronic methadone therapy, opioid patches, and oxycodone/acetaminophen. His pain specialist had prescribed several antidepressants, and the patient reported that he also self-administered several herbal preparations, including St. John’s wort. His underlying disease limited his exercise tolerance. Although there was no formal diagnosis of obstructive sleep apnea, his wife reported that he snored loudly and often stopped breathing for a few seconds at night. He weighed 265 lb (120 kg) and was 69 inches (175.26 cm) tall. He was very concerned about pain and postoperative pain control.

Narcotic Metabolism and Toxicity

Three major classes of opioid receptors – mu, kappa, and delta – interact with opioids and enhance neurotransmission, each with characteristic effects. Mu receptors produce euphoria, analgesia, miosis, and respiratory depression. Kappa receptors produce sedation, analgesia, miosis, and respiratory depression. Delta receptors induce euphoria, analgesia, and seizures. Other poorly-defined classes of receptors produce relatively minor effects. Sigma receptors mediate dysphoria, hallucinations, and psychosis. Opiate antagonists such as naloxone act on all four types of opiate receptors, thus providing an important remedy for adverse effects.

Pharmacokinetic drug-drug interactions may reduce or increase the effects of opioids that are metabolized by enzymes of the cytochrome P450 (CYP450) system, such as codeine, oxycodone, hydrocodone, fentanyl, tramadol, and methadone. Opioids that are not metabolized by the CYP450 system (such as morphine, oxymorphone and hydromorphone) have fewer CYP450 adverse drug interactions.16

Opioid toxicity is typically manifested as a clinical triad of CNS depression, respiratory depression (bradypnea and/or hypopnea), and pupillary miosis. Respiratory depression is the most specific and identifiable sign. Respiratory rates as low as 4-6 breaths per minute may be observed with moderate-to-severe intoxication. The natural drive to breathe may be overridden by CNS sedative effects secondary to polypharmacy or a severe opioid overdose.

Physicians should be vigilant for signs of opioid toxicity in their patients, even if specific signs and symptoms are not present. Opioid exposure does not always produce miosis. With overdose, pupillary dilation from CNS hypoxia may mask miosis. Morphine, meperidine, pentazocine, and diphenoxylate/atropine (Lomotil) may be associated with mydriasis or midpoint pupils.

Other common symptoms of opioid toxicity include drowsiness, conjunctival injection, and euphoria. Depending on the opioid compound, patients may also present with ventricular arrhythmia (e.g. methadone) and seizures (e.g. meperidine). The patient may also demonstrate mild peripheral vasodilation and orthostatic hypotension. Severe or persistent hypotension may indicate toxicity from other substances. Propoxyphene was withdrawn from the United States market in 2010 due to an increased risk of QT prolongation.

Common side effects from opioids include decreased gastrointestinal motility and ileus, which may both delay and prolong opioid absorption. Nausea and emesis are usually transient in opioid-naïve
patients. Neuro-psychological phenomena such as anxiety, agitation, dysphoria, paranoia, and hallucinations may be seen sporadically, and are typically associated with higher doses. Pruritus, flushed skin, and urticaria may manifest secondary to histamine release.

The opioid associated with the highest risk of mortality is methadone. The Center for Disease Control (CDC) reports that methadone contributed to 31.4% of all opioid-related deaths in the U.S. from 1999-2010, and 39.8% of all single-drug opioid-related deaths, despite comprising a very small fraction of opioids prescribed. The mortality rate from methadone overdose was also considerably higher than other opioid-related deaths from overdose, for both mult-drug and single-drug deaths. Methadone should be prescribed when benefit outweighs risk. Methadone and other extended-release opioids should also not be used for mild pain, acute pain, "breakthrough" pain, or on an as-needed basis. For chronic non-cancer pain, methadone should not be considered a drug of first choice by prescribers or insurers.17

Perioperative Adjuvants

Multi-modal analgesia can be accomplished via many routes and can involve combinations of different drug classes which act synergistically to alleviate pain.

Ketorolac

Ketorolac is an NSAID, imparting analgesia via suppression of prostaglandin synthesis. It may be given orally, intravenously, intramuscularly, or intranasally. A standard intravenous dose is 30 mg every 6 hours and is not recommended for ≥5 days, due to risk of renal impairment or failure. Its onset of action is roughly 10 minutes, and duration of action is approximately 6-8 hours. The estimated analgesic effect may be equivalent to 4-6 mg of morphine or more.18

Side effects commonly include headache, gastrointestinal pain, dyspepsia, and diarrhea. Adverse effects may also include increased risk of gastrointestinal bleed and bleeding at the surgical site; hence it should not be given pre-operatively. It is also associated with allergic reactions in susceptible individuals (e.g. those with asthma and nasal polyps). Renal effects, including acute interstitial nephritis, papillary necrosis and acute renal failure, preclude its use in renal insufficiency.

Ketorolac carries a black box warning for patients with known cerebrovascular bleed, hemorrhagic diathesis or incomplete hemostasis. Its use is also contraindicated in patients with a prior history of hypersensitivity to NSAIDs.

Ketamine

Ketamine is a non-opioid adjuvant for pain control, an N-methyl D aspartate (NMDA) receptor antagonist and analogue to the compound phencyclidine (PCP). Ketamine, unlike PCP, has a relatively short elimination half-life and is extensively metabolized by hepatic enzymes and excreted renally. Ketamine has been used primarily in alleviating neuropathic pain conditions in chronic pain populations. The current literature hypothesizes that ketamine may have a perioperative opioid-sparing effect, with opioid dosages decreased by roughly 10% to 60%, and patients reporting generally moderate improvements in pain score.19
Various providers have quoted effective doses for its analgesic administration. Doses may range from 0.2 mg/kg or less to as high at 0.75 mg/kg. It may also be infused at rates of roughly 2-7 mcg/kg/minute. Ketamine offers less cardiac and respiratory depression compared to opioids. Cons to its use include hallucinations and/or nightmares, which occur rarely at analgesic doses and may be mitigated but not eliminated completely by general anesthesia or benzodiazepine. Compared to opioid use alone, there is no reduction in nausea and vomiting. Diplopia and nystagmus may also occur in a small percentage of patients receiving ketamine.19

**Dexmedetomidine**

Another drug available for perioperative pain management is dexmedetomidine (Precedex®). It is an intravenous alpha-2 agonist agent with excellent sedative effects, a complex analgesic profile, and sympatholytic properties. For sedation and mild analgesia, it is typically given as an infusion at a rate of 0.2 to 0.7 mcg/kg/hour.

The major advantage of dexmedetomidine is that respiratory physiology remains near-normal. Concentrations producing significant sedation may reduce minute ventilation, but do not alter the slope of the CNS response curve to carbon dioxide. Drawbacks to dexmedetomidine include its sedative properties, high cost, and possibility of causing bradycardia and hypotension in susceptible patients. As such, caution should be used when bolusing dexmedetomidine.

**Patient-Controlled Analgesia**

Patient-controlled analgesia (PCA) refers to delivery of small but potent doses of analgesic agents via sophisticated infusion pumps, at the discretion of the patient and at set intervals. The method provides the smallest plasma concentration of an analgesic compound at which pain is relieved (known as the minimum effective analgesic concentration or MEAC). By maintaining the MEAC with intermittent small boluses, effective analgesia can be maintained while avoiding both the side effects of over-medication and the risks associated with under-treating pain.20

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**Fig 2. Pharmacodynamic theory of PCA [Illustration by David B. Turk, M.D. Adapted from Ferrante at al.]20**

Key: PCA dose → PRN or standing dose ← Analgesia

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![Pharmacodynamic theory of PCA diagram](Image)
Intravenous (IV) PCA is currently the favored mode of pain control as many patients prefer this method over the conventional pro re nata (PRN) dosing schedules. Greater patient satisfaction may result from superior analgesia, and/or perceived control over analgesic medications.

Post-surgical opioid-tolerant patients with acute-on-chronic pain may require a baseline continuous PCA infusion in order to control pain effectively in addition to demand dosing. Baseline opioid infusions should generally be avoided in opioid-naïve patients and patients with obstructive sleep apnea because of the risk of adverse respiratory events.

Patients on maintenance opioid therapy should first receive their basal opioid requirements before adding post-operative PCA dosing. Opioid tolerant patients can safely receive higher dosing schedules.

**Obesity and Perioperative Pain Control**

Obese patients present the anesthesiologist with significant concerns. Altered physiology and body composition affects drug distribution, plasma protein binding and regional blood flow. When drug pharmacokinetic and pharmacodynamic parameters are unknown, initial dosing in obese patients should begin based upon lean body weight.

One obvious concern regarding the obese patient is obstructive sleep apnea (OSA), in which the flow of air ceases or decreases during sleep because the airway has become narrowed, blocked, or floppy. Patients with OSA are often obese or possess a large neck or collar size (≥17 inches in males and ≥16 inches in females). Other anatomical risk factors for OSA include: retrognathia, wide craniofacial base, tonsillar hypertrophy, adenoid hypertrophy, narrowed palate, narrow nasal cavities, and macroglossia. The prevalence of sleep disordered breathing in adults is estimated to be 9% in women and 24% in men, whereas the prevalence of overt OSA has been estimated at 2% in women and 4% in men.

For obese patients or those with a high likelihood of OSA, it is recommended that the anesthesiologist avoid long-acting opioids and sedatives that place the patient at risk of respiratory depression, pulmonary hypertension, and adverse cardiac events. ASA guidelines for the perioperative management of patients with OSA advocate regional analgesic techniques over systemic opioids, secondary to fewer adverse outcomes in patients with OSA. Non-steroidal anti-inflammatory drugs are also useful due to their opioid-sparing effect. There have also been case reports of patients who received successful analgesia with dexmedetomidine.

**St. John’s Wort and Drug Interactions**

St. John’s Wort is a common perennial wildflower found throughout Europe (Fig 3). It is used in the treatment of dysthymia (chronic low-grade depression) and major depressive disorder. A systematic review found that use of St John’s Wort was superior to a placebo in treating major depression; and some studies reported it to be as effective with less side effects when compared to standard antidepressants. No standardized dosing exists but therapeutic doses may range from 300 mg to 1800 mg daily. Active compounds act similarly to SSRIs and mono-amine oxidase inhibitors.
(MAOIs). It is classified as a drug in Germany. In the United States, it is considered an herb and thus classified as a food and not subject to federal drug regulations.

As with many other herbal substances, the side effect profile has not been fully determined. Potential symptoms may range from photosensitivity to induction of CYP450 hepatic enzymes and altered metabolism of other drugs, including warfarin, cyclosporine, theophylline, digoxin, HIV protease inhibitors, anticonvulsants, SSRIs, tryptans, and oral contraceptives. Patients taking these medications should be advised to stop taking St John's Wort. Dose adjustment of conventional treatment may be necessary.

St. John’s Wort may also precipitate serotonin syndrome in individuals taking selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs) tramadol, meperidine, levorphanol, triptans, and 5-HTP. Such a combination is not recommended but difficult to control as the herb is easily available over-the-counter. St. John’s Wort should be avoided in bipolar patients, as Wort–related mania has been described.25

Patients on Highly Active Antiretroviral Therapy (HAART) should be monitored carefully as St John’s Wort may lower the concentration of antiretroviral agent resulting in ineffective treatment and rapid onset of drug resistance.26,27

Anesthesia providers should routinely inquire about consumption of herbal and over-the-counter medications, being mindful of possible adverse effects and drug interactions.

Addiction, Pseudo-addiction, Tolerance, Secondary Gain

The American Society of Addiction Medicine (ASAM) defines addiction as a primary disease of brain reward, motivation and memory, leading to characteristic biological, psychological, and social manifestations. As a chronic disease, addiction often involves cycles of relapse and remission.28

ASAM characterizes the ABCDE’s of addiction as:

- Inability to consistently Abstain;
- Impairment in Behavioral control;
- Craving; or increased “hunger” for drugs or rewarding experiences;
- Diminished recognition of significant problems in one’s behaviors and relationships; and
- A dysfunctional Emotional response.

Pseudo-addiction is a drug-seeking behavior in patients with pain who are receiving inadequate analgesia. It is an iatrogenic abnormal behavior that develops as a direct consequence of inadequate pain management.29

Pseudo-addiction may be seen in three consecutive phases:

1. Inadequate provision of analgesics to treat pain stimulus
2. Increased analgesic demands by patient, and behavioral changes to convince others of the pain’s severity, and
3. Mistrust between patient and health care team.
Pseudo-addiction can be managed by establishing trust between the patient and health care team, including provision of appropriate and timely analgesia to effectively manage the patient’s pain.

A separate physiological phenomenon that may overlap both addiction and pseudo-addiction is tolerance. Tolerance is the capacity of the body to become less responsive to a substance with repeated use or exposure. The patient on chronic opioid therapy may become tolerant to medication effects over time, and thus the patient may ask for escalation of a regimen. It is important for a practitioner to be sensitive when differentiating between malingering and tolerance in patients with opioid abuse problems.

**Management of the Case**

In the case presented, there was no clear “best” choice given the wide variety of anesthetic options available. Several facets require consideration -- the patient’s history, co-morbidities and medication regimen, the specifics of the surgery, and the patient’s wishes.

In the pre-op clinic, the patient’s medical history was reviewed, and an updated medication list was ascertained. The surgical plan was discussed with the patient, and he voiced his interest to proceed with an anesthetic plan created in conjunction with his anesthesiologist. A sleep study was performed several weeks pre-operatively and the patient was positive for obstructive sleep apnea. He was given a continuous positive airway pressure (CPAP) machine for home use and told to bring his fitted mask with him on the day of surgery.

Due to his history of prior significant back injuries, obesity, and multi-level procedure, neuraxial anesthesia was not elected, although the surgeon agreed to place an epidural catheter at the end of the case for postoperative analgesia. The patient was provided his home medications, including methadone, and the fentanyl patch was continued into the operating room. In addition, preoperative gabapentin was provided. Intraoperatively, a general anesthetic was provided with concurrent ketamine infusion and a multi-modal analgesic plan.

The post-operative management included a multi-modal approach to treat acute and chronic pain. To address chronic pain, the patient was re-started on his oral (PO) home regimen on post-operative day one. As there had been no break from his home regimen, there was decreased concern for opioid withdrawal in the perioperative period. The patient continued to receive his home dose fentanyl patch 25 mcg every 72 hours for basal maintenance and methadone. It was decided that this regimen could be continued safely since it was part of his chronic pain care. The perioperative team was made aware.

To address acute pain, an IV-PCA hydromorphone for post-operative pain control was provided with no continuous basal PCA dose provided due to the patient’s documented sleep apnea. He also received intravenous acetaminophen at the conclusion of surgery and low-dose basal dexmedetomidine in the post-anesthesia care unit. Ketorolac was not chosen at the neurosurgeon’s request due to a theoretical adverse effect of NSAIDs on post-operative bone healing, even though several studies have shown no effect on bone healing and long-term ossification if short-term or low-dose ketorolac is used (<120mg).30

Finally, he was also advised by the team about the risks of therapy with St. John’s Wort (and herbal medications) and to slowly taper his use in the weeks before surgery. As St. John’s Wort may account for faster metabolism of his other medications, he was advised to call his physician should he or his
wife note new side effects such as increased sedation, mental status changes or respiratory depression.

In the days and weeks after his surgery, his pain management physician discussed a plan to taper his basal opioid requirements and return to his basic narcotic requirements. With the success of the surgery, a plan was made to send the patient to an addiction specialist to begin the process of a narcotic wean.

**Conclusion**

Addressing this patient’s post-operative pain provides unique challenges to the anesthesiologist. One must be aware of signs of narcotic overdose as well as adverse drug effects stemming from polypharmacy. These patients are complicated to treat in acute-on-chronic pain states, but through vigilance, multimodal analgesia, and use of neuraxial and peripheral blocks when applicable, the anesthesiologist can provide good care to minimize postoperative pain and optimize the analgesia of a challenging narcotic tolerant patient population.

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References


POST-TEST

1. An obese patient taking oxycodone 35 mg daily for chronic lumbar back pain after failed back surgeries is scheduled for prostatectomy. Planning multi-modal perioperative pain management for this patient does not include:
   a. Evaluating for the presence of obstructive sleep apnea
   b. Evaluating opioid tolerance
   c. Initial dosing of sedatives and analgesics based on lean body weight
   d. Initial dosing of sedatives and analgesics based on actual weight

2. During a pre-op evaluation, an HIV-positive patient taking HAART and escitalopram 10 mg for depression asks the anesthesiologist if St. John’s Wort would help his depression. The proper response would be:
   a. “St. John’s Wort is a safe, cost-effective, efficacious medication.”
   b. “St. John’s Wort may interfere with HAART therapy and interact with escitalopram.”
   c. “A psychiatry consult is necessary to make a decision.”
   d. “The correct dosage of St John’s Wort’s must be based on your weight.”

3. A 39-year-old patient with a history of depression demonstrates drug-seeking behavior and asks for more frequent dosing of opiates. Which of the following would not be useful in the treatment of this patient?
   a. Establish trust
   b. Provide adequate and timely level of analgesia
   c. Acquire criminal background information on patient
   d. Determine likelihood of tolerance

4. Methadone:
   a. Can be used safely for breakthrough pain
   b. Is most effective for post-surgical acute pain
   c. Has a higher risk of mortality compared to other opioids
   e. Is a drug of choice for chronic non-cancer pain
5. **Baseline continuous PCA infusion is best used for:**
   a. Opioid-tolerant patients with acute-on-chronic pain
   b. All patients undergoing abdominal surgical procedures
   c. Opioid-naïve patients
   d. Patients with pseudo-addiction

6. **A 69 year old overweight Caucasian male with a history of day-time sleepiness is being evaluated in the pre-op clinic for elective penile implant. Which of the following would not yield information on OSA?**
   a. Smoking history
   b. Examination of the patient’s tongue
   c. Patient’s shirt and collar size
   d. Preoperative head and neck x-rays

7. **What is the most specific finding in opioid toxicity?**
   a. Respiratory depression
   b. Pupillary miosis
   c. Ileus and constipation
   d. CNS depression

8. **Which of the following opioids is likely to have a drug-drug interaction related to cytochrome P450 metabolism?**
   a. Morphine
   b. Hydromorphone
   c. Oxymorphone
   d. Oxycodone

9. **Which of the following opioid effects tends to be transient in naïve patients started on opioid therapy?**
   a. Euphoria
   b. Nausea
   c. Respiratory depression
   d. Constipation

10. **In which example would use of ketorolac likely be contraindicated?**
    a. 40 year old male with history of hepatitis C and allergy to morphine
    b. 32 year old female healthy female with a positive urinary tract infection.
    c. 29 year old male in the SICU with a cerebrovascular bleed after a motor vehicle accident
    d. 69 year old male with a history of BPH