Pharmacology Review: In-Hospital Opioid Management

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- I hereby certify that, to the best of my knowledge, no aspect of my current personal or professional circumstance places me in the position of having a conflict of interest with this presentation. I hereby certify that, to the best of my knowledge, neither I (including any member of my immediate family) nor any individual or entity with whom or with which I have a significant working relationship have (has) received something of value from a commercial party related directly or indirectly to the subject of this presentation.

Opioid Overview

- What are opioids?
- Misuse of Opioids have been prominent within the last two decades.
  - In 2017, the department of health and human services declared a public health emergency for Opioid use
  - 2019:
    - 70,630 people died of drug overdoses
    - 10.1 million people admitted to misusing opioids
    - 1.6 million people were diagnosed with OUD
- This presentation will focus on acute pain management for the hospitalized patient.

Presentation Focus:

- Opioid Pharmacokinetics
- Misuse of Opioids
- Commonly prescribe opioids
- MME conversions
- Multimodal Pain Management Strategies
- Acute Pain Management in different populations:
- Tapering strategies
- Discharge
- Resources for Prescribers

Opioid Pharmacokinetics

- Mechanism of action — Opioids produce analgesia by acting on central and peripheral mu-, kappa-, and delta-opioid receptors to inhibit the transmission of nociceptive input and the perception of pain.
- Properties of Mu Receptors
  - Mu1
    - Supraspinal analgesia
    - Bradycardia
    - Sedation
  - Mu2
    - Respiratory suppression
    - Euphoria
    - Physical Dependance
- Properties of Delta Receptors
  - Respiratory suppression
  - Spinal Analgesia
- Properties of Kappa Receptors
  - Spinal Analgesia
  - Respiratory Suppression
  - Sedation

Pharmacokinetics continued…

- Based upon their effects on the mu receptor, opioids are often divided into pure agonists and agonist-antagonists (see next slide).
- Buprenorphine is a unique opioid with high affinity but low intrinsic activity at the mu opioid receptor and antagonism at the kappa opioid receptor.
- Tramadol and tapentadol are centrally acting analgesics whose mode of action is based both on the mu opioid receptor binding and monoamine (serotonin and norepinephrine) reuptake blockade (mixed mechanism).

Classification of opioids for pain management

Opioid type	Medications	Notes about therapy
Pure agonists	Codeine	Mainstay of therapy for moderate to severe cancer pain. No clinically relevant ceiling effect for analgesia; as dose is raised, analgesic effects increase until analgesia is achieved or dose-limiting side effects supervene. Meperidine and propoxyphene are not preferred due to potential effects of toxic metabolites. Methadone must be used with caution; only clinicians who are knowledgeable about the risks posed by long and variable half-life, unpredictable potency, and potential for QTc prolongation should use this drug without guidance.
	Hydrocodone	
	Dihydrocodeine	
	Morphine	
	Hydromorphone	
	Fentanyl	
	Oxycodone	
	Oxymorphone	
	Levorphanol	
	Methadone	
	Meperidine	
Mixed agonist-antagonists	Buprenorphine	Agonist-antagonists include mu receptor agonists with lower intrinsic efficacy (partial agonists) and drugs that have agonist effects at one opioid receptor and antagonist effects at another (mixed agonist-antagonists). Most were developed to be less attractive to individuals with the disease of addiction; this characteristic does not rationalize widespread use for cancer pain. All have the potential to induce acute abstinence in patients with physical dependency on agonist opioids. Most of the mixed agonist-antagonists have a ceiling effect for analgesia. However, buprenorphine does not have a ceiling effect. It is available as a transdermal patch and in a buccal formulation and may be of use in relatively opioid-naïve cancer patients. Some mixed agonists-antagonists (pentazocine and butorphanol) have a high risk of psychotomimetic side effects.
	Butorphanol	
	Dezocine	
	Nalbuphine	
	Pentazocine	
Mixed-mechanism drugs	Tramadol	Centrally acting analgesics that have agonist actions at the mu receptor and block reuptake of monoamines.
	Tapentadol	

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Pharmacokinetics cont’d

- Opioid formulations — Opioids come in immediate-release/short-acting (IR/SA) and extended-release/long-acting (ER/LA) formulas. Opioids can be administered through a wide variety of routes; with the most common being oral and transdermal administration when it is to treat pain that is **not** related to cancer/palliative management.
- Short-acting
- Long-acting

Misuse of Opioids

- Can lead to…
  - Addiction
  - Physical Dependence
  - Tolerance
  - Opioid use disorder (OUD)

Most Commonly Prescribed Opioids

- Hydrocodone (Vicodin®)
- Oxycodone (OxyContin®, Percocet®)
- Oxymorphone (Opana®)
- Morphine (Kadian®, Avinza®)
- Codeine
- Fentanyl
- Hydromorphone
- Tapentadol
- Methadone

Opioid Conversion Table

Chronic Pain Management Toolkit

Calculating total daily doses of opioids is important to appropriately and effectively prescribe, manage, and taper opioid medications. There are a number of conversion charts available, so caution is needed when performing calculations. As with all medications, consulting the package insert for dose titration instructions and safety information is recommended. Treatment should be individualized and begin with lower doses and gradual increases to manage pain.

Once the dose is calculated, the new opioid should not be prescribed at the equivalent dose. The starting dose should be reduced by 25-50% to avoid unintentional overdose due to incomplete cross-tolerance and individual variations in opioid pharmacokinetics. This dose can then be gradually increased as needed.

To calculate the total daily dose:

1. Determine the total daily doses of current opioid medications (consult patient history, electronic health record, and PDMP as necessary).
2. Convert each dose into MMEs by multiplying the dose by the conversion factor.
3. If more than one opioid medication, add together.
4. Determine equivalent daily dose of new opioid by dividing the calculated MMEs of current opioid by new opioid's conversion factor. Reduce this amount by 25-50% and then divide into appropriate intervals.

Calculating Morphine Milligram Equivalents (MME)*

Opioid	Conversion Factor (convert to MMEs)	Duration (hours)	Dose Equivalent Morphine Sulfate (30mg)
Codeine	0.15	4-6	200 mg
Fentanyl (MCG/hr)	2.4		12.5 mcg/hr**
Hydrocodone	1	3-6	30 mg
Hydromorphone	4	4-5	7.5 mg
Morphine	1	3-6	30 mg
Oxycodone	1.5	4-6	20 mg
Oxymorphone	3	3-6	10 mg
Methadone†			
1-20 mg/d	4		7.5 mg
21-40 mg/d	8		3.75 mg
41-60 mg/d	10		3 mg
≥61 mg/d	12		2.5 mg

**The dose conversions listed above are an estimate and cannot account for an individual patient's genetics and pharmacokinetics.*
***Fentanyl is dosed in mcg/hr instead of mg/day, and absorption is affected by heat and other factors.*
†Methadone conversion factors increase with increasing dose.

Sample Case

Your patient is a 45-year-old man who is taking oxymorphone 10 mg 4 times a day for chronic pain. You have determined he is an appropriate candidate for a long-acting regimen and decide to convert him to extended release oxycodone.

1. Total daily dose of oxymorphone → 10 mg X 4 times /d = 40 mg/d
2. Convert to MMEs (oxymorphone conversion factor = 3) →40 X 3 = 120 MME
3. Determine MMEs of oxycodone (oxycodone conversion factor = 1.5) → 120/1.5 = 80 mg/d
4. Decrease dose by 25% → 25% of 80 = 20 → 80 – 20 = 60
5. Divide by interval (q 12 hours) → 60/2 = 30

The starting dose of extended release oxycodone is 30 mg q 12h.

Additional Resources

CDC Opioid Conversion Guide
https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf

Prior to Prescribing…

- It is important to discuss risks and benefits of beginning an opioid regimen on a patient so they fully understand the plan of initiation, management, and tapering, and eventual discontinuation.
- Opioid analgesic risk evaluation and mitigation strategy (REMS)
- There are also other 16 other assessment tools for risk of OUD. Those recommended include:
  - Current Opioid Misuse Measure (COMM)
  - Opioid Risk Tool (ORT)
  - Patient Medication Questionnaire (PMQ)
  - Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP®-R)

Multimodal Pain Management Strategies

- NSAIDS
- Tylenol
- Tramadol
- NMDA Receptor Blockers
  - Methadone
  - Ketamine
  - Magnesium
  - Gabapentin/Pregabalin
- Glucocorticosteroids
- Fixed dose combination: hydrocodone/oxycodone+Tylenol; hydrocodone+ibuprofen
- Regional Anesthesia

Acute Pain Management: Opioid Naïve

- What are the goals of the patient?
- Try non-opioid management as first line
  - NSAIDs, Gabapentin/Lyrica, Tylenol
- If opioid management is necessary, initiate multimodal therapy
  - Opioid + one or more of the above medication regimens
  - Start with IR drugs at lowest effective dose
  - Must NEVER start ER release for first line treatment
- Along with pain management, address other ways of improving function for acute pain management
- If patient has meaningful improvement of function and pain, continue treatment and wean as function improves

Acute Pain Management in the Chronic Pain Patient: Chronic Opioid Use

- It is important to take reliable history, check PDMP for compliance, take baseline UDS, and **assess baseline pain scores**
- Evaluate what the patient's baseline opioid dose is, reach out to their primary provider for these medications to obtain valid history
- Assess for psychological sources of acute pain
- Once acute pain source is identified, avoid increasing opioid dosing initially. Treatment should start with nonopioid alternatives
  - Non-opioid pain medications (NSAIDs, Tylenol, gabanoids) and nonpharmacological intervention (ice, heat, immobilization, PT, OT, acupuncture, meditation).

Acute Pain Management in the Chronic Pain Patient: Chronic Opioid Use

- If pain control is inadequate with nonopioid methods of analgesia in addition to the patient's baseline opioid, and it is determined that benefits outweigh the risks, a short-acting opioid should be prescribed to supplement the patient's baseline opioid. Short-acting opioids such as these are better able to meet fluctuating demands for analgesia during episodes of acute pain than are extended-release or long-acting formulations of opioids.
- Patients who chronically use opioids may be expected to have some degree of analgesic tolerance, and thus to require higher doses of opioids than opioid naïve patients, but the degree of tolerance is unpredictable.
- Doses of opioids should be titrated rapidly as necessary
- Most healthy opioid-tolerant patients will not experience sedation or respiratory depression as a result of an incremental increase in opioid dose but that is difficult to predict. Patients who are more vulnerable to respiratory depression, including older adults, patients with sleep apnea, and pulmonary, hepatic, or renal dysfunction should be monitored more carefully.

Acute Pain Management in the Chronic Pain Patient: Chronic Opioid Use

- Treatment must be a multidisciplinary approach
  - Address the insult – aggravating factor for acute pain
    - Patients on chronic opioids may require hospitalization for parenteral opioids or regional anesthesia for injuries and surgeries that are often managed on an outpatient basis in other populations
    - Continue with the patient's baseline opioid dosing when admitted inpatient
      - For hemodynamically stable patients ONLY
  - Utilize Multimodal Pain Management Strategies
  - Offer psychological/emotional support and how their acute pain is impacting the effects of their chronic pain

Acute Pain Management: Patient on Medication Assisted Therapy

- Combine with Behavioral Health Services and Substance Abuse specialists
- The only opioid agonists approved for the treatment of OUD in the United States are methadone and buprenorphine.
- The opioid antagonist naltrexone is also approved for maintenance treatment of OUD, as well as for treatment of alcohol use disorder. Naltrexone can be administered as a daily oral dose, or as a monthly intramuscular injection.
- Management of acute pain in patients who take naltrexone poses distinctive challenges, as naltrexone blocks the effects of opioid agonists.

Acute Pain Management: Patient on Medication Assisted Therapy

- Similar approach to those on Chronic Opioid Management for Acute Pain
- Methadone
  - Because opioid cross-tolerance may be present in patients who take methadone patients on methadone typically require higher doses of opioid than opioid naïve patients.

Acute Pain Management: Patient on Medication Assisted Therapy

- Buprenorphine
  - A retrospective study of patients on MMT or buprenorphine maintenance therapy (BMT) undergoing total knee arthroplasty found that patients in the MMT/BMT group required sevenfold greater doses of opioids in the perioperative period than opioid naive patients (793 milligram morphine equivalents [MME]/24 hours versus 109 MME/24 hours)
- For both methadone and buprenorphine, it is important to recognize that we can continue these medications when inpatient and add other modalities, as necessary.
  - If opioids are needed, titrate up as needed and once pain begins to resolve, titrate down appropriately

Acute Pain Management: Patient on Medication Assisted Therapy

- For patients who take buprenorphine for OUD once per day
  - Mild to moderate pain
  - For severe or undertreated pain
  - Escalation when improvement is not found
    - Medications should be ordered scheduled, holding for sedation and respiratory depression as stated prior.

Acute Pain Management: The Patient in Full Remission from OUD

- Some patients successfully achieve sustained remission from OUD without medication.
- Acute pain can be difficult to treat in this population.
- With severe pain that cannot otherwise be controlled, it is sometimes necessary and appropriate to initiate opioid medications.
- If initiation of opioids are necessary:
  - **This needs to be a collaboration between prescriber and patient. Involvement with an addiction care team is also recommended.**

Acute Pain Management: OUD Patients

- All patients presenting to the acute care setting should be screened for OUD. If identified, patient's must also be screened to identify psychological reasons for acute pain
- In the hospitalized patient, pain should be treated aggressively to achieve effective analgesia in patients with OUD, with opioid doses titrated upwards rapidly as necessary.
  - Withdrawal can happen
- It is imperative to involve addiction counselors in order to treat appropriately. Many states/institutions do not allow the initiation of methadone/buprenorphine in the hospital setting. Arranging for outpatient care is essential.

Tapering strategies

- Tapering during admission
  - Opioid naïve
  - Chronic pain patients
    - On chronic opioids
    - On MAT
    - In full remission
- At discharge
  - As mentioned above, 5 days worth of the initial prescription can be given, however, this can be more difficult for patients with chronic pain on chronic opioid management, patient's with OUD on treatment, or patient's with OUD without treatment. It is always beneficial to have behavioral therapists, addiction resources, and communication with outpatient prescribers to produce a comprehensive plan.
- Follow up
  - If patient's transition from acute pain to chronic pain (lasting greater than 3 months), there should be follow up visits prior to 3 months of opioid refills, a comprehensive Pain Contract, and follow up as described above.

Post-Acute Care

- Pain agreement if long term opioids are indicated (transitioning to chronic pain)
  - Understand the agreement and what is expected during treatment
  - Urine drug screens
  - Random pill counts for compliance
  - Describe how and under what circumstances the patient will void the agreement and be discharged from the service
    - You must give 4 weeks worth of prescription if patient is discharged until they find a new practice to avoid withdrawal
  - **Best Practice:**
    - Review and reassess on a frequent basis and NO MORE than 3 months between visits

Discharge:

- Some states now require prescribing Nalaxone at time of discharge for opioid use of greater than 90mme/day or opioid use with concurrent benzodiazepine use
- Follow up appointments necessary to evaluate use, misuse, and effectiveness of treatment if they are discharged on opioids
- Check the prescription monitoring program each time you prescribe opioids
- If patient is on chronic opioid management and changes are made, you must contact their primary doctor prescribing these medications
  - Most practices have pain contracts, and the original prescriber must be informed of new prescriptions

Resources for Prescribers

- Urine Drug Tests
- PDMP – Drug monitoring programs
  - To determine concurrent opioid use
- DAST, AUDIT – Drug abuse screening test, alcohol use disorders identifications test
- SAMHSA
    - Substance Abuse and Mental Health Services Administration

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