


All About Opioids: Optimizing Analgesia, Minimizing Side Effects, and Keeping it Legal

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Objectives

- 1) Review the evolution of opioids and current landscape.
 - 2) Understand patient selection criteria and guidelines for opioid therapy.
 - 3) Understand individual opioid medications.
 - 4) Explore strategies for managing poor opioid response.
 - 5) Learn methods to minimize and treat side effects.
 - 6) Review legal guidelines for prescribing and documentation.
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Brief History of Opioids



Ancient Use

- The opium poppy was first cultivated around 3400 BC by the Sumerians, who called it the "joy plant."
- By 1300 BC, ancient Egyptians documented opium's medicinal uses
- Opium spread through trade routes to ancient Greece and Rome, where Hippocrates described its use as a narcotic around 400 BC.

Medieval Period

- Opium was a key ingredient in remedies like laudanum, a tincture of opium used widely in 16th-century Europe.



Brief History of Opioids

American Civil War (1861–1865)

- Morphine was used extensively for pain and surgery → "soldier's disease," a term for opioid addiction among returning soldiers.

World War II:

- Opioids like morphine and heroin were used for pain and sedation, though heroin was later banned due to addiction concerns.

Post-War Era:

- Introduction of synthetic opioids like fentanyl (1960), oxycodone (1917), and hydrocodone (1920s) provided additional options for severe pain.

Current Landscape



- **Opioid Use in the United States**
- Uses 80% of the world's opioid supply, makes up less than 5% of population.
- **Addiction and Misuse:**
- 8.9 million people ages 12 and older misused RX pain relievers (SAMHSA NSDUH 2022).
- 21–29% of patients prescribed opioids for chronic pain misuse them
- About 8–12% develop an opioid use disorder (NIDA, 2023).
- **Overdose Crisis**
- From 1999 to 2023, over 645,000 opioid overdose deaths in the U.S. (CDC).
- Synthetic opioids are involved in more than 75% of all opioid-related deaths.
- **New Guidelines from CDC 2022**
- Individualized, patient-centered care, reduced emphasis on rigid dose limits.



Opioids are Safe & Effective with Proper Use

Efficacy: Opioids are standard for post-surgical pain and trauma; Up to 90% of cancer patients achieve significant pain relief with opioid therapy.

Chronic Pain Management: Opioids improve function and quality of life in patients with chronic conditions.

Low Risk of Addiction in Short-Term Use: Risk of addiction in acute pain treatment is as low as 0.6% with careful prescribing.

Patient-Centered Approach: With proper education and monitoring, opioid-related side effects are manageable, ensuring safe, effective pain control.

Mechanism of Action of Opioids

Action on Opioid Receptors:

- Opioids bind to mu-opioid receptors in the brain, particularly in ventral tegmental area (VTA) and the nucleus accumbens (reward pathway).

Inhibition of GABAergic Neurons:

- In the VTA, opioids inhibit GABAergic neurons. GABA is an inhibitory neurotransmitter that normally suppresses the activity of dopamine-producing neurons.
- By inhibiting GABA, opioids remove the "brake" on dopamine production.

Dopamine Release:

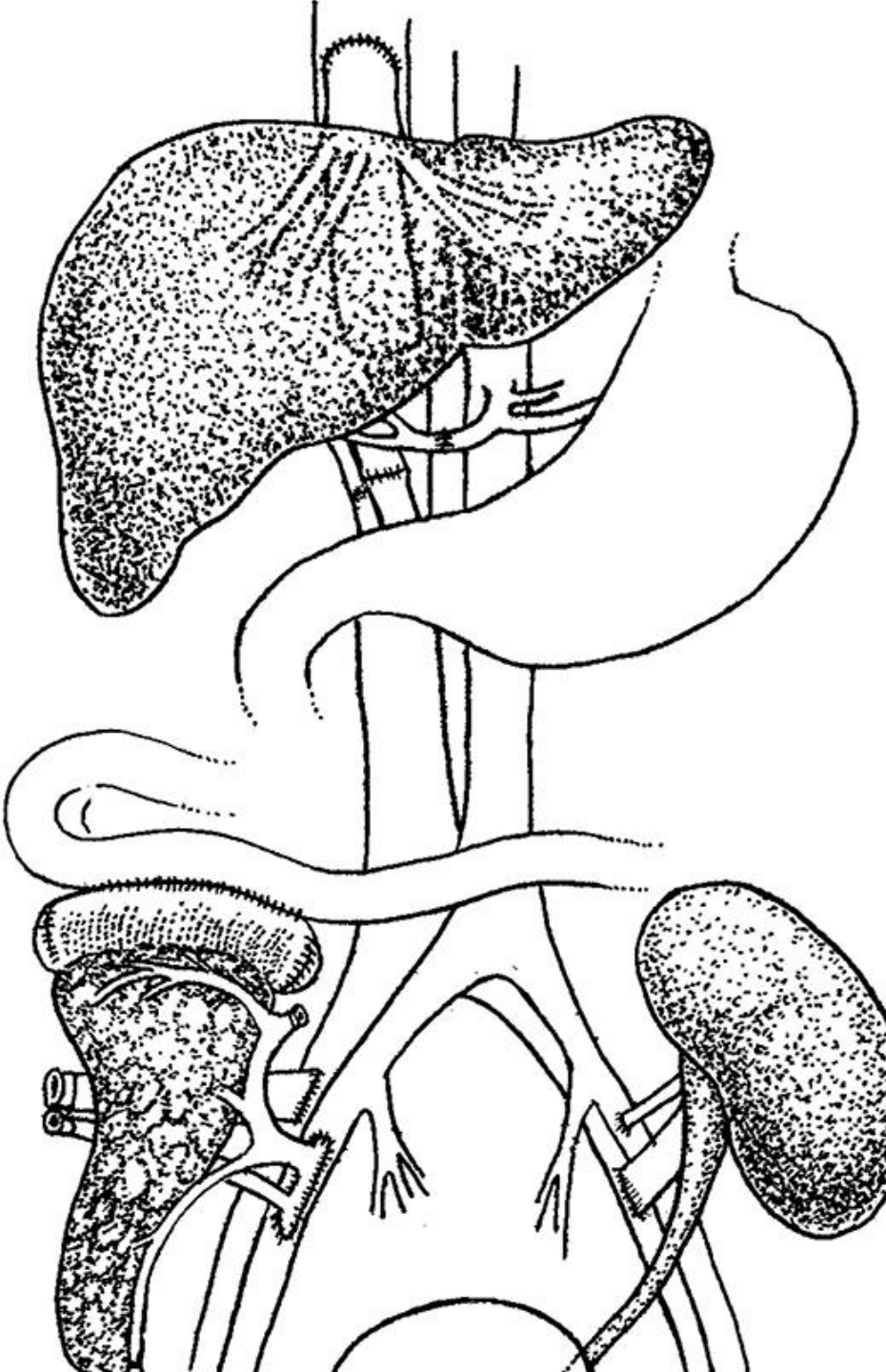
- Once uninhibited, dopamine neurons in VTA become more active → increased dopamine release into nucleus accumbens and other parts of the brain.
- Dopamine surge = feelings of euphoria, pleasure, and well-being.

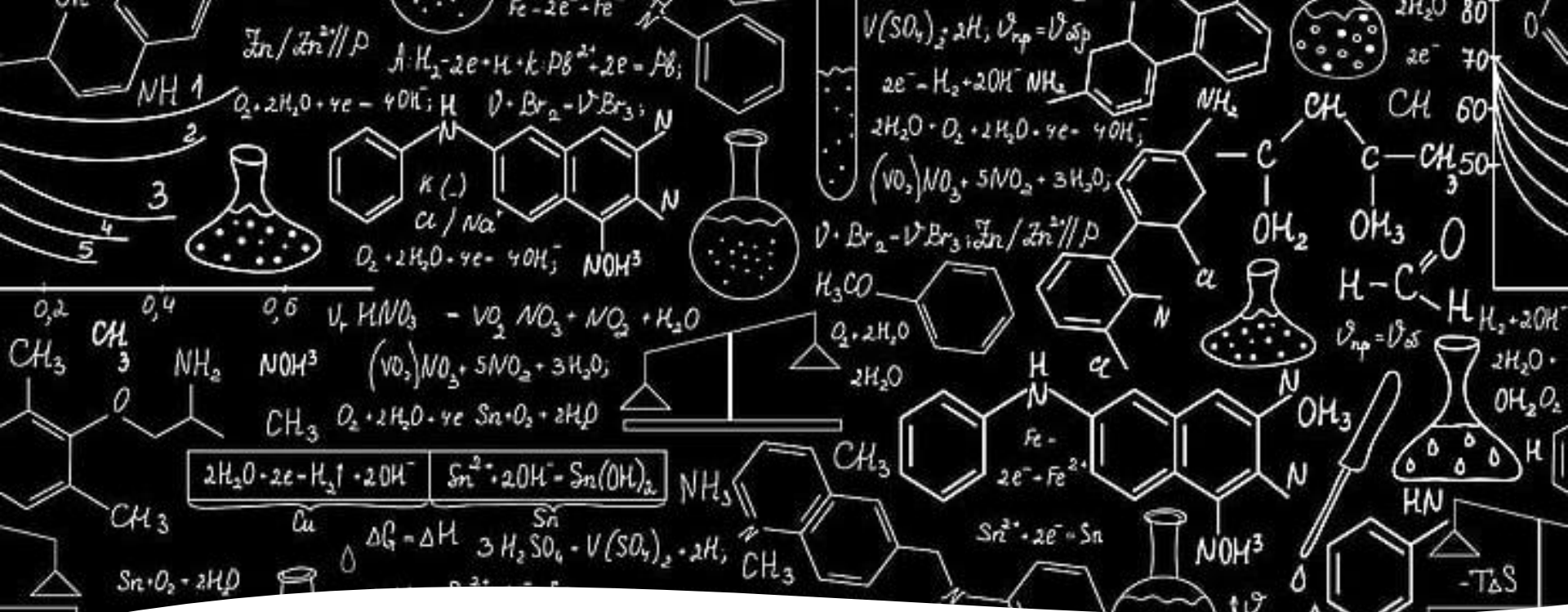
Clinical Implications

- **Pain Relief:** Dopamine release enhances the analgesic effects of opioids by reducing the perception of pain and increasing a sense of comfort.
- **Addiction Potential:** Dopamine release = addictive properties of opioids, reinforces desire to use for same rewarding effects.
- **Tolerance and Dependence:** Over time, chronic opioid use alters the brain's dopamine system, reducing its sensitivity to natural rewards and increasing dependence on opioids for dopamine release.

Opioid Pharmacokinetics

- Absorption: Oral, transdermal, IV, subcutaneous.
- Distribution: Lipid-soluble opioids cross blood-brain barrier.
- Metabolism: Primarily in liver (e.g., morphine via glucuronidation).
- Excretion: Mostly renal.





Advances in Opioid Therapies

- Abuse-deterrent formulations
- Combination therapies
- Novel delivery methods
- Research on non-opioid alternatives, or more selective opioids to reduce adverse effects and dependency.

Patient Selection & General Principles

Criteria for opioid therapy include:

- Cancer-related pain (somatic, visceral, neuropathic).
- Severe chronic non-cancer pain (evaluated case-by-case).

General Principles:

- Initiate therapy with a clear risk assessment.
- Continuous monitoring and adjustment for safety.

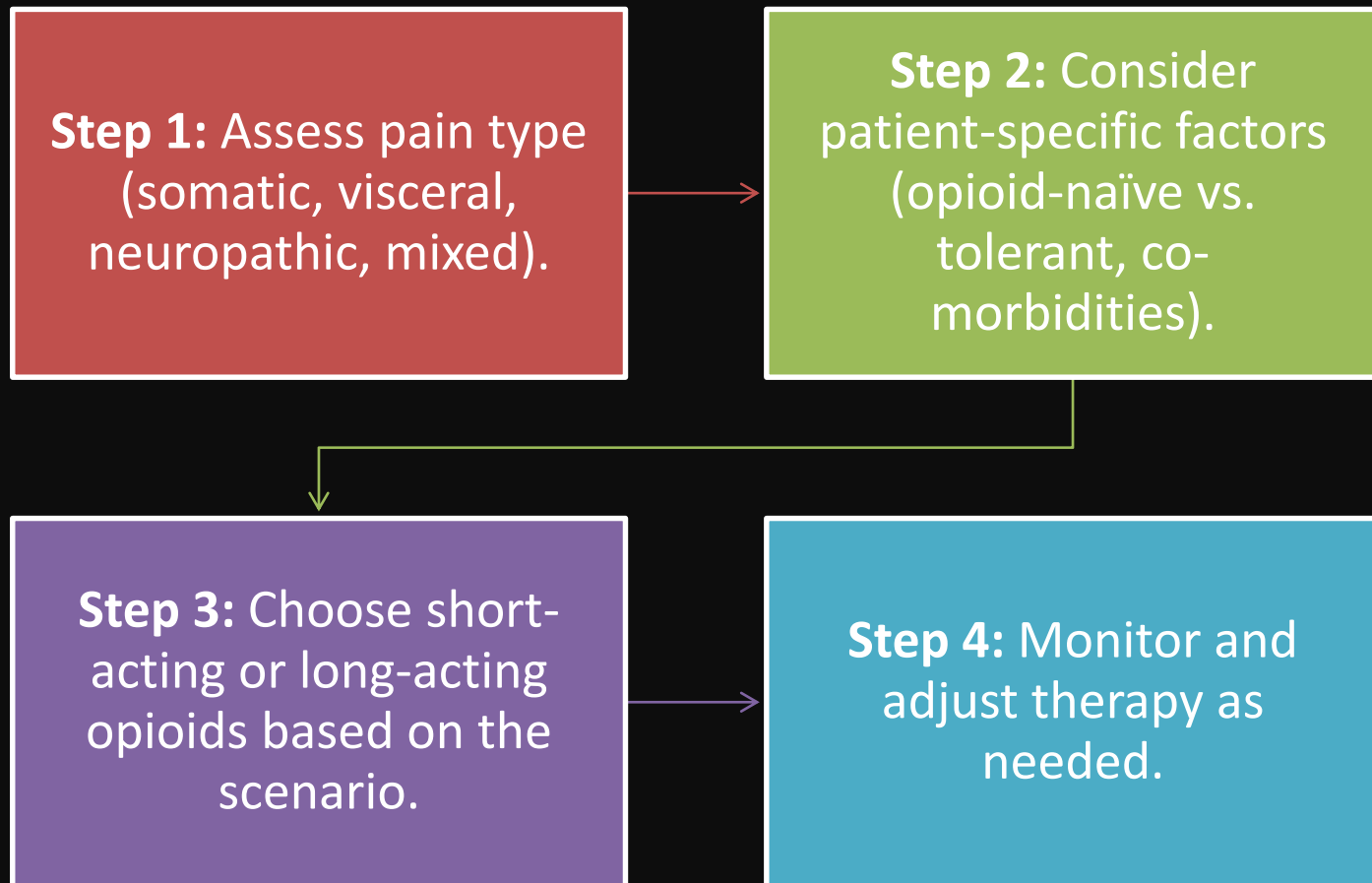


Opioid Selection Basics

Selecting the right opioid depends on pain type, patient tolerance, and co-morbidities.

Short-acting vs. long-acting: when each is appropriate.

Opioid Selection Basics



Opioid Selection Basics: Step 1

Assess Pain Type

Pain Type	Definition	Description	Examples
Somatic Pain	Arises from bones, muscles, or soft tissues. Localized.	Aching, throbbing, or sharp.	Bone fractures, arthritis, post-surgical pain.
Visceral Pain	Originates from internal organs. Poorly localized.	Cramping, pressure, or deep aching.	Pancreatitis, gallbladder pain, dysmenorrhea.
Neuropathic Pain	Results from nerve damage or dysfunction.	Burning, shooting, or tingling.	Diabetic neuropathy, sciatica, postherpetic neuralgia.
Nociplastic Pain	Pain without clear evidence of tissue damage or nerve injury.	Deep, widespread, aching or burning.	Fibromyalgia, chronic pelvic pain, non-specific LBP.
Mixed Pain	Combination of somatic/visceral and neuropathic components.	Sharp, aching, and burning sensations.	Cancer pain, CRPS, chronic low back pain with radiculopathy.

Opioid Selection Basics: Step 2

Consider patient-specific factors

1) Level of Opioid Tolerance

Opioid-Naïve: Patients with no/limited opioid exposure

- Low doses, short-acting opioids to gauge response, close monitoring for sedation and side effects
- **Examples:** Hydrocodone/Acetaminophen 5/325 1 tab PO q6 hrs PRN pain.

Opioid-Tolerant: Patients on regular opioid therapy for prolonged time, usually average of 30-60 MME (or more) per day

- Higher starting doses, adjusted on tolerance
- Long-acting opioids/extended release for baseline pain control and short-acting opioids for breakthrough pain.
- **Examples:** Oxycodone ER 10mg PO BID and Hydrocodone/Acetaminophen 5/325 1 tab PO q4 hrs PRN breakthrough pain.

Opioid Selection Basics: Step 2

Consider patient-specific factors

2) Renal Impairment:

- Avoid medications with active metabolites that accumulate (e.g., morphine).
- **Preferred Options:** Fentanyl, hydromorphone.

2) Hepatic Impairment:

- Use opioids with minimal hepatic metabolism.
- **Preferred Options:** Hydromorphone, oxycodone.

3) Cardiac Risk (e.g., QT Prolongation):

- Avoid methadone unless closely monitored with ECG.

4) Elderly Patients:

- Start at 25-50% of the usual dose; increased sensitivity, slower metabolism.

5) Respiratory Conditions:

- Avoid long-acting opioids initially; monitor for respiratory depression.

6) Substance Use Disorder: Consult pain specialist and/or pain psychiatrist.

Opioid Selection Basics: Step 3

Choose Short-Acting or Long-Acting opioids

Short-Acting Opioids	Long-Acting Opioids
Rapid onset	Slow onset but prolonged action
Ideal for acute or breakthrough pain in Opioid-Naïve and Opioid-Tolerant patients	<i>Ideal for chronic, persistent pain in Opioid-Tolerant patients only!</i>
Examples: Morphine IR, Oxycodone IR	Examples: Oxy ER, Fentanyl patch, Methadone

Opioid Selection Basics: Step 4

Choose opioid; Monitor and adjust therapy as needed.

- Balance analgesia and side effects.
- Titrate up if inadequate analgesia
- Titrate down or rotate to a different opioid if side effects.

Opioid Classifications

Pure agonists:

Morphine, oxycodone,
oxymorphone, hydrocodone,
hydromorphone, fentanyl,
methadone

Mixed agonist- antagonists:

Buprenorphine, nalbuphine

Mixed mechanism:

Tramadol, tapentadol

Morphine

- Widely used for its effectiveness and reliability.
- Many formulations and applications. IR and ER options.
- Be cautious with renal impairment → active metabolites.

Oxycodone

- Available as single-agent and combination (with acetaminophen); IR and ER options.
- Higher oral bioavailability than morphine → better oral option.
- Similar efficacy to morphine for moderate to severe pain.

Hydrocodone

- A semi-synthetic opioid mu-opioid receptor agonist in combination products with acetaminophen or ibuprofen; IR and ER forms.
- Metabolizes to hydromorphone (active metabolite).
- Effective in opioid-naïve patients for mild to moderate pain.

Hydromorphone

- Highly potent, 5-7 times potency of morphine
- IR and ER forms; good for moderate to severe pain.
- Can be effective with neuropathic pain when combined with adjuvants.
- Preferred in renal impairment → fewer active metabolites.

Fentanyl

- A synthetic mu-opioid receptor agonist with 50–100 times the potency of morphine.
- Highly lipophilic → rapid absorption → fast acting.
- Transdermal option reduces constipation risk; provides relief for up to 72 hours, ideal for stable, chronic pain.
- Buccal tablets, nasal sprays, and lozenges: Rapid onset of action for breakthrough cancer pain
- Not recommended for opioid-naive patients due to risk of respiratory depression.

Methadone

- Unique pharmacology with NMDA antagonist properties
→ good for neuropathic pain.
- Also works like SSRI/SNRI
- Has a long half-life (15–60 hours), but its analgesic duration is shorter, requiring careful dosing to avoid accumulation and toxicity.
- Requires careful titration, ECG monitoring due to QT prolongation risk, additional education.

Buprenorphine

- Partial agonist at the mu receptor and antagonist at the kappa receptor
- Effective for mixed nociceptive and neuropathic pain.
- Good for opioid-naïve patients or
- Safe in **renal dysfunction** due to hepatic metabolism and lack of active metabolites.
- Lower potential for tolerance compared to full agonists (e.g., morphine or fentanyl).

Tapentadol

- Dual mechanism: Mu-opioid receptor agonist and norepinephrine reuptake inhibitor.
- A strong option for moderate-to-severe pain, good for both nociceptive and neuropathic pain.
- Reduced risk of opioid-induced constipation; fewer GI side effects.

Tramadol

- Dual mechanism: Weak mu-opioid receptor agonist and serotonin-norepinephrine reuptake inhibitor (SNRI).
- Best for mild-to-moderate pain, neuropathic pain
- Avoid in patients with seizure disorders or those taking serotonergic drugs (e.g., SSRIs, MAOIs).

Codeine

- Weak mu agonist; less often used.
- Available in combination products with acetaminophen or ibuprofen (e.g., Tylenol #3).
- Prodrug → Relies on CYP2D6 for activation; variable efficacy.
- Not recommended in renal or hepatic impairment due to metabolite accumulation.

Monitoring and Patient Evaluation

Pain level and function assessments at each visit.

A large blue downward-pointing arrow connecting the first step to the second.

Screen for signs of misuse or addiction.

A large blue downward-pointing arrow connecting the second step to the third.

Regular evaluations of side effects and overall response to opioids.

Addressing Poor Opioid Response

Options include: Adjust dosing or formulation.

Rotate to a different opioid.

Combine with non-opioid adjuncts.

Use interventional therapies where appropriate.

Titrating Opioids

- **Start low, go slow:** Initial low doses to minimize side effects.
- **Individualize dosage:** Based on patient response and tolerance.
- **Monitor closely:** Regular reassessment to adjust dosage or rotate opioids as needed.



Opioid Rotation: What is it?

Switching a patient from one opioid to another opioid to achieve better pain control or reduce side effects.



Opioid Rotation: When to Consider

- **Poor pain control:** Pain remains uncontrolled despite dose adjustments.
- **Side effects:** Intolerable side effects, such as excessive sedation, nausea, or itching.
- **Development of tolerance:** Increased doses are required to achieve the same analgesic effect.
- **Renal or hepatic dysfunction:** Current opioid is metabolized or excreted in a way that worsens toxicity.
- **Drug availability:** Access issues, cost considerations, or formulary restrictions.

Opioid Rotation: How?

Steps in Opioid Rotation

- 1. Assess the need:** Why is current opioid suboptimal?
- 2. Calculate the equianalgesic dose**
Use an equianalgesic dosing chart/app to determine dose of the new opioid that provides equivalent analgesia to the current one.
- 3. Adjust for incomplete cross-tolerance**
Reduce the calculated dose of the new opioid by 25-50% to account for incomplete cross-tolerance.
- 4. Titrate the new opioid**
Start with the adjusted dose and titrate upward based on patient response and side effects.
- 5. Monitor closely**
Observe the patient for changes in pain control, side effects, or signs of withdrawal or toxicity.

Opioid Rotation: Example

A patient on morphine 60 mg/day with uncontrolled pain is rotated to oxycodone.

Step 1: Determine total daily dose of morphine

- 60 mg morphine/day (oral)

Step 2: Use the conversion ratio – from an oral equianalgesic chart:

- 30 mg morphine = 20 mg oxycodone
- Ratio is: 1 mg morphine = $20 / 30 = 0.6667$ mg oxycodone
- Now convert: 60 mg morphine $\times 0.6667 = 40$ mg oxycodone (equianalgesic dose)

Step 3: Apply safety dose reduction for incomplete cross-tolerance

- Reduce by 25% $\rightarrow 40 \text{ mg} \times 0.75$ (percentage we want to keep) = 30mg oxycodone/day

Step 4: Divide the dose appropriately

- 30mg oxycodone/day \rightarrow 10mg TID, or 5mg q4 hours PRN, for example

Caveats about Rotation: Approach with Caution or Consult Experts

Scenario

Methadone to another opioid

Fentanyl patch to oral opioid

Converting between routes

Why It's Risky

Nonlinear kinetics; adjust with caution; consult pain/pharmacy

Long half-life; residual effect lingers after discontinuation

IV to oral often requires bioavailability correction (e.g., morphine IV:oral = 1:3)



A black and white photograph of a spiral staircase. The staircase is viewed from above, showing the circular pattern of the steps and the railing. The floor is covered in a grid of small, square tiles. The railing is made of metal and follows the curve of the stairs. The lighting creates strong shadows, emphasizing the three-dimensional structure of the staircase.

Managing Side Effects

Managing Opioid-Related Side Effects

Constipation

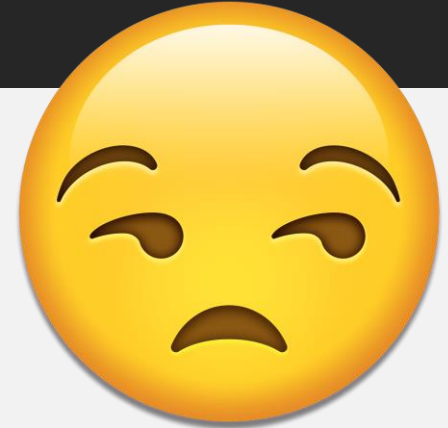
Nausea

Somnolence
& “Brain Fog”

Respiratory
Depression

Pruritis

Managing Side Effects: Constipation



How opioids contribute to constipation:

- Bind to mu-opioid receptors in the gut, slowing gastrointestinal motility
- Slower transit time allows fluid resorption from stool

Diagnostic Criteria for Opioid-Induced Constipation (OIC):

- New/worsening constipation when initiating, changing, or increasing opioid therapy which includes two or more of the following:

In greater than 25% of bowel movements, client experiences:

- Straining
- Lumpy or hard stools
- Feeling of incomplete evacuation
- Sensation of anorectal blockage
- Need for manual assistance (e.g., digital disimpaction);
or
- Fewer than three spontaneous bowel movements weekly

Managing Side Effects: Constipation



Non-Pharmacologic Strategies:

- Increase fluid intake, mobility, soluble dietary fiber (unless debilitated, limited oral fluid intake, or bowel obstruction is suspected).

Pharmacologic Strategies:

Prevent: Use a contact cathartic (e.g., senna, two tablets qhs), an osmotic laxative (e.g., polyethylene glycol, lactulose, or magnesium sulfate), or both. Start when initiating opioids.

Treat:

- **Conventional laxatives:** senna, polyethylene glycol, or lactulose; patient preference.
- **Stool softeners:** Docusate sodium allows water to easily enter the stool. Fewer side effects but less effective than other laxatives. Use when patients describe hard, dry stools.
- **For OIC unresponsive to conventional methods:** Peripherally Acting Mu-Opioid Receptor Antagonists (PAMORAs); counteract the peripheral side effects of opioids without affecting the central pain-relieving effects.
 - **Methylnaltrexone:** Subcutaneous or oral formulation; Quick onset, within hours.
 - **Naloxegol:** Oral once-daily tablet.
 - **Naldemedine:** Oral once-daily tablet.

Managing Side Effects: Nausea



How Opioids Contribute to Nausea

- Activation of chemoreceptor trigger zone (CTZ)
- Delayed gastric emptying
- Vestibular sensitivity

Non-Pharmacologic Strategies

- **Dietary adjustments:** Encourage small, frequent meals; Avoid greasy, spicy, or heavy foods.
- **Hydration:** Maintain adequate hydration to prevent dehydration, which can exacerbate nausea.
- **Positioning:** Encourage sitting upright after eating.
- **Reduce triggers:** Minimize strong odors or other nausea triggers in the environment.

Managing Side Effects: Nausea



Pharmacologic Management

Antiemetics

- **First-Line Options:**
 - **Ondansetron:** Serotonin 5-HT₃ receptor antagonist.
 - **Prochlorperazine:** Dopamine antagonist.
 - **Metoclopramide:** Dopamine antagonist that promotes gastric motility, helps if nausea is related to delayed gastric emptying.
- **Second-Line or Adjunct Options:**
 - **Haloperidol:** Effective at low doses for opioid-induced nausea.
 - **Promethazine:** Histamine H₁ receptor antagonist, also sedating.
 - **Scopolamine Patch:** Useful for nausea associated with vestibular sensitivity.

Glucocorticoids:

- **Dexamethasone:** Sometimes used for refractory nausea.

Benzodiazepines:

- **Lorazepam:** Can be used in patients where anxiety contributes to nausea.

Managing Side Effects: Nausea



Adjusting opioid therapy

- **Opioid rotation:** Switch to opioid with a lower likelihood of causing nausea (e.g., fentanyl or hydromorphone).
- **Route of administration:** Consider transdermal options (e.g., fentanyl patches) or intravenous opioids if oral forms are causing significant nausea.

Prevention

- Start antiemetics preemptively in patients with a history of opioid-induced nausea.
- Titrate opioid doses slowly to allow the body to adapt.

Managing Side Effects: Somnolence



How opioids contribute to somnolence:

- **Bind to mu receptors in brain:** Affect brain areas involved in alertness, suppressing arousal and promoting drowsiness.
- **Inhibition of neurotransmitter release:** Reduce circulating excitatory neurotransmitters like glutamate, acetylcholine, and norepinephrine → CNS depression and decreased alertness.
- **Modulation of the reticular activating system (RAS):** Suppress RAS activity, responsible for maintaining wakefulness.
- **Dysregulation of sleep:** Reduce REM and deep slow-wave sleep, increasing lighter stages of sleep → non-restorative rest.

Clinical presentation: Variable; Sedation is a dose-dependent side effect of opioids, particularly in opioid-naïve patients. Sedation with initiation or dose escalation usually resolves within a week.

Proceed with caution and remember: Sedation precedes respiratory depression!

Managing Side Effects: Somnolence



Management:

- Prevent: Titrate doses gradually and do not co-prescribe with other sedating meds.
- Rule out underlying causes (CNS pathology, metabolic disturbances, dehydration, other drugs). Eliminate or reduce nonessential CNS depressants.
- Evaluate the opioid regimen. If good pain relief, try 25% dose reduction and re-evaluate. If poor pain relief, try opioid rotation, or an adjuvant to reduce amount of opioid needed.
- Consideration of a stimulant (methylphenidate, modafinil) may be appropriate.

Managing Side Effects: Respiratory Depression



How opioids contribute to respiratory depression:

- Suppression of respiratory center
- Reduced sensitivity to carbon dioxide
- Impaired upper airway reflexes
- Dose-dependent effect

Clinical presentation: Preceded by sedation, presents with obtundation combined with a respiratory rate of less than 8 breaths per minute. Other signs include hypoventilation, cyanosis, hypoxia, hypercapnia.

Risk factors:

- Opioid-naïve patients.
- High-dose opioid therapy or rapid dose escalation.
- Combination with sedatives or alcohol.
- Underlying conditions (e.g., sleep apnea, COPD).
- Advanced age or renal/hepatic impairment (slower metabolism).

Managing Side Effects: Respiratory Depression



Management:

- **Prevent:** AVOID! Rarely occurs when therapy is administered according to accepted guidelines, and dose titration is done in small increments (25-50%) and at long enough intervals to observe the effects of a dose at steady state. Pay attention to somnolence which precedes this.
- **Reverse with Naloxone (Narcan):**
 - Short-acting opioid antagonist
 - FDA recommendation: Discuss availability of naloxone (over the counter or prescribed) with all patients when prescribing opioids.
 - Educate about naloxone: Rapid reversal; also precipitates severe pain and acute withdrawal. Self-administer only when an excessive opioid dose has been taken and the goal is to prevent respiratory depression.
 - Reserve naloxone for symptomatic respiratory depression.

Managing Side Effects: Pruritis



How opioids contribute to pruritis:

- Mechanism uncertain. Morphine → histamine release from mast cells; other opioids less likely to cause histamine release but still associated with pruritus. Increasing evidence that opioid-induced pruritus is mediated by mu-receptors.

Clinical presentation: Itching after taking opioids

Management:

- Non-sedating anti-histamines: loratadine, cetirizine, or fexofenadine.
- Opioid rotation
- Low doses of opioid antagonists (hospitalized patients)

Legal Implications and Documentation Obligations

- Detailed pain assessments and rationale for opioid RX, dose adjustments, and rotation.
- Document compliance with state-specific opioid prescribing laws.
- Legal Standards: Medical boards and the DEA provide guidelines on compliance and record-keeping.



2022 CDC Guideline: Opioids & Pain Management

Initiating and Continuing Opioid Therapy

1. **Non-opioid therapies are preferred** for subacute and chronic pain.
(Use opioids only when benefits outweigh risks.)
2. **Establish treatment goals** with patients, focused on function—not pain elimination.
3. **Discuss risks and benefits** of opioid therapy with patients before starting.
4. **Start with immediate-release opioids** when initiating therapy.

Dosing and Duration

5. **Use the lowest effective dose** — no rigid MME thresholds. but caution around higher doses.
6. **Prescribe short durations for acute pain** — typically 3–7 days is sufficient.

Risk Assessment and Mitigation

7. **Evaluate benefits and risks regularly** and taper when risks outweigh benefits.
8. **Use strategies to mitigate risk**, like naloxone coprescribing and considering PDMPs.
9. **Review patient's history of controlled substances** using state RX Drug Monitoring Programs.

Monitoring and Special Considerations

10. **Use toxicology screening** when appropriate to monitor therapy.
11. **Avoid concurrent opioid and benzodiazepine use** when possible.
12. **Offer treatment for opioid use disorder** if it's identified (e.g., buprenorphine, naltrexone).

Legal Considerations in Opioid Prescribing

Consent: Obtain written informed consent before starting opioid therapy.

Consider a treatment agreement!

Consider co-prescribing naloxone for patients at increased risk of overdose.

- Naloxone HCl 4 mg nasal spray — Use 1 spray intranasally as needed.
- Prescribe: ≥ 50 MME/day, benzo use, hx of SUD, respiratory/renal issues.
- Store safely, educate family, emphasize naloxone saves lives.

Monitoring:

- Review Prescription Drug Monitoring Programs (PDMPs) – don't co-prescribe with benzodiazepines.
- Regular drug testing for compliance.
- Document monitoring practices.

Conclusion

Optimize analgesia with appropriate patient and opioid selection.

Address poor responses with individualized adjustments.

Minimize side effects through recognition, prevention, and tailored treatments.

Comprehensive documentation and compliance with legal standards are essential.

Balancing pain relief with safety is the foundation of effective opioid therapy.



Thank you!

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