Opioid Risks and Side Effects

Appropriate Opioid Prescribing for Acute Pain: Limiting Use and Duration

In general, opioids should not be considered first line therapy for mild to moderate pain in patients with limited opioid exposure. If other nonpharmacologic and nonopioid pharmacologic options are not effective or appropriate for acute pain, and the provider determines that opioids may be effective, the following recommendations should be considered:

1. **Evaluate the patient**
   - Identify the type and cause of the acute pain, along with severity
   - Determine likely recovery period and duration of the acute pain
   - Assess age and medical comorbidities that might affect opioid dose or lead to avoidable opioid-related adverse drug events (ORADEs)
   - Assess patient's use of alcohol or sedative medications and prescribe opioids with caution in these patients
2. **Maximize other therapies**
   - Optimize use of multimodal nonopioid agents, nonpharmacologic agents, and other pain interventions
   - Even when prescribing an opioid, continue other pain interventions thought to be effective
3. **Assess the risk of developing opioid use disorder (OUD)**
   - Assess the patient for history of substance use disorder
4. **Consult the PDMP**
   - Review dispensed controlled substance prescription history
   - Take note of concurrent benzodiazepine prescription and any chronic opioid use
5. **Educate the patient**
   - Counsel patient about pain, expected duration, and course of recovery
   - Goal = improve function + decreased pain + minimize side effects and harms
   - Review the risks and side effects of opioids
   - Provide an opioid safety handout and review with the patient
   - Provide information on safe storage and disposal of opioid medications
6. **Choose a type and amount**
   - Prescribe the lowest effective dose of short-acting opioids, usually for a duration of < 3 days
   - In cases of more severe acute pain, prescribe < 7-day supply
   - Preferentially use an immediate-release mono-product opioid, such as oxycodone, tramadol, or morphine sulfate
     - Allows for continued utilization of multimodal nonopioid agents such as APAP and NSAIDs
7. **Establish a follow-up plan**
   - Refer for appropriate intervention (i.e. dental, physical therapy, specialist)
   - Before providing a refill, reassess the patient's pain, level of function, response to treatment, and healing process
     - Evaluate with a functional pain screening tool (PEG)"

- Evaluate for side effects and risks (i.e., rapid risk assessment for ORADEs and OUD - must be documented in EHR)
- Patients must sign a controlled substance agreement when opioids are first prescribed > 7 days

8. **Have a plan in place for tapering or discontinuation**

Other Recommendations

When deciding whether or not to prescribe an opioid keep in mind the following facts:

- *Opioids are inherently dangerous drugs* with numerous side effects, rapid development of tolerance, debilitating withdrawal symptoms, significant potential for misuse and addiction, and lethality in overdose. Clinicians are encouraged to reserve opioids for the treatment of severe pain, pain that has not responded to nonopioid therapy and cases where nonopioid therapy is contraindicated or anticipated to be ineffective.
  - Opioids are among the three broad categories of medications with potential for misuse, dependence and addiction, the other two being stimulants and CNS depressants. Opioids act by attaching to opioid receptors on nerve cells in the brain, spinal cord, gastrointestinal (GI) tract and other organs, triggering a spike in dopamine that not only reduces the perception of pain but can also produce a powerful sense of well-being and pleasure by affecting the brain's limbic reward system.
  - When used repeatedly opioids induce tolerance, as higher doses are necessary over time to produce the same effect.[1] This mechanism also contributes to the high risk of overdose following a period of abstinence.[2] Tolerance can be lost in times of abstinence, leading relapsed users to take a previously "safe" dose with tragic results.[3] The effects of opioids are mediated by specific subtype opioid receptors (mu, delta and kappa) that are also activated by endogenous endorphins and enkephalins. The production of endogenous opioids is inhibited by the repeated administration of outside opioids, which accounts for the discomfort that ensues when the drugs are discontinued.
  - Besides the significant abuse potential, rapidly developing tolerance and agonizing withdrawal symptoms that accompany opioids, patients also experience serious side effects such as nausea, vomiting, constipation, respiratory depression, impaired judgment, sedation and coma (Table 3).[4,5] These complications, which often necessitate additional medical care, can prevent patients from performing daily tasks and remaining active in the workforce.

Table 1 | Common and Serious Side Effects of Opioids

Common Side Effects	Serious Side Effects of Chronic Opioid Use
+ Nausea/vomiting + Constipation + Pruritus + Euphoria + Respiratory depression, particularly with the simultaneous use of alcohol, benzodiazepines, antihistamines, muscle relaxants, or barbiturates	+ Cardiac abnormalities, including prolonged QTc and torsades de pointes[57] + Sudden cardiac death with the concomitant use of benzodiazepines and methadone[57] + Hormonal disruptions, including decreased testosterone in males[58] + Decreased luteinizing hormone, follicle-stimulating hormone, and fertility in women[59] + Musculoskeletal compromise, including an increased risk of osteoporosis[60] + Immunosuppression[61] + Inhibition of cellular immunity via delta and kappa receptors[62] + Hyperalgesia (ie, upregulation of receptors and increased tolerance)[63] + Sleep disturbances (eg, shortened deep sleep cycle)[64]

+ Lightheadedness + Dry mouth	+ Delayed or inhibited gastric emptying, increased sphincter tone, and blockade of peristalsis[65]

Source: *Martin PR, Hubbard JR. Substance-related disorders. In: Ebert MH, Loosen PT, Nurcombe B: Current Diagnosis & Treatment in Psychiatry. McGraw Hill; 2000:233-259*

- *Opioids are not effective* as a long-term option for pain, and lack evidence for many acute pain indications.[6,7] It is recommended that individual providers and provider groups have a "no" list, i.e. painful conditions lacking evidence of benefit for which they do not routinely prescribe opioids, including but not limited to acute musculoskeletal injuries (including low back pain), neuropathic pain, post traumatic headache, previously reduced fractures or dislocations, dental pain, headache/migraine, and cyclic vomiting.
  - Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to be safer and equally or more effective in managing many types of pain when compared to opioid medications.[8–12]
  - Opioids should not be routinely prescribed for uncomplicated low back pain and dental pain.
    - Many studies have demonstrated the superiority of opioid alternatives, including NSAIDs and acetaminophen, for both dental and uncomplicated back pain.[13,14]
    - Opioids are correlated with decreased function at six months and prolonged disability at one year in patients with uncomplicated lower back pain.[15,16]
  - Opioids should not be prescribed for migraine headache and post-traumatic headache (headache associated with trauma to the head and/or neck).
    - Opioids can cause acute migraine medications to be less efficacious.[17,18]
    - Opioids have detrimental effects when used to treat headache, and it is recommended they be avoided. Potential complications include the precipitation of depression, anxiety, disability and medication-overuse headaches.[19]
    - Use of opioid analgesia also correlates with the progression of migraine headache from acute to chronic.[20]
    - The American Academy of Neurology, American Headache Society and ACEP caution against the use of opioids for headache treatment. These agents are best reserved for extraordinary situations in which all other options fail or are contraindicated.[21,22]
  - For patients experiencing cyclic vomiting, continued use of opioid therapy is a poor prognostic indicator that may contribute to disease progression. Dependence and withdrawal are also associated with recurrent episodes.[23]
  - Opioids should not be routinely prescribed for previously reduced dislocations and fractures.
    - A 2017 study comparing pain levels at two hours for acute extremity pain showed no statistically significant or clinically important differences in pain reduction among single-dose treatment with ibuprofen and acetaminophen or with three different opioid and acetaminophen combination analgesics (oxycodone and acetaminophen, hydrocodone and acetaminophen, codeine and acetaminophen).[8]
- *Opioid prescribing patterns should be collected and shared with peers or fellow clinicians within a practice.*
  - Opioid prescribing practices vary among clinicians. While little research exists examining provider-level variations in opioid prescribing patterns in primary care practice, some clinicians are minimizing or eliminating use of opioids while others continue to rely heavily on opioid analgesia.[25–29]
  - Knowledge of current ordering patterns can be critical for protocol implementation, clinician education and quality improvement.

- Tracking prescribing patterns and providing the comparative data to every clinician within the practice may help reduce discrepancies and identify clinicians who can benefit from further education in multimodal analgesia and opioid stewardship. Clinicians are advised to approach opioid prescribing with the same stewardship they employ when making other medical decisions.
- Physicians are encouraged to monitor the opioid prescribing patterns of other clinicians providing care under their license, including resident physicians and advanced practice providers.
- Information on prescribing patterns should not be used punitively but rather to help clinicians understand their own treatment habits, facilitate change and improve care. Local sharing has been shown to significantly reduce the number of opioids prescribed at discharge in emergency medicine practice.[24]

- If and when a decision is made to use an opioid, then the question is *which one, as all opioids are not the same*.
  - Each opioid moiety has differential effects on the opioid receptors mu, kappa, delta, and nociceptin. These receptors have differential effects on analgesia and adverse effects[30-31] due to variable affinity, intrinsic activity, and potency, though the mu receptor is generally the most important.
  - It is useful to consider which opioid worked best in the past; however, a patient's insistence on a particular opioid is very likely to indicate problematic use, if not addiction.
  - With respect to efficacy and potential adverse effects, genetics at some point in the future may have predictive value, though today that value has not been realized[32-33].
  - On the other hand, initial opioid selection can be based in part on presence of certain co-existing non-pain medical conditions or concerns (data limited), though relative safety in one domain may be risky in another (Table 2).
  - Opioid selection otherwise is based on more practical considerations: cost, coverage, formulary, prior authorization requirements, and availability.

Table 2 | Opioid Selection Considerations based on Medical Condition

- Constipation[34-37]

Worse:	Methadone	Morphine			
Better:	Buprenorphine TD	Fentanyl TD	Oxycodone CR	Tapentadol	

- Renal Disease[38-42]

Avoid:	Morphine	Codeine	(also avoid NSAIDs)
Safer:	Buprenorphine	Methadone	Fentanyl

- Hepatic Disease[43-45]

Avoid:	Methadone	Codeine	(also avoid NSAIDs, APAP)
Safer:	Fentanyl		

- Serotonin syndrome risk more likely: Tramadol, Tapentadol
- Depression less likely: Buprenorphine
- Respiratory depression less significant: Buprenorphine, Tapentadol, Tramadol[31,46]
- Hypogonadism less likely: Buprenorphine, Tapentadol[46]
- Addiction liability lower: Buprenorphine, Tapentadol, Tramadol, Methadone, Abuse Deterrent Formulations[47-53]

Resources

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