Analgesia for the critically ill patient

August 9, 2020 by Josh Farkas

CONTENTS

- Introduction (#introduction)
- Diagnosis & monitoring of pain (#diagnosis_and_monitoring_of_pain)
- Concept of multimodal analgesia (#concept_of_multi-modal_analgesia)
- Analgesic ladder for critically ill patients (#analgesic_ladder_for_critically_ill_patients)
- Agents
  - Acetaminophen (#acetaminophen)
  - Pain-dose ketamine infusion (#pain-dose_ketamine_infusion)
  - Alpha-2 agonists (#alpha-2_agonists_as_analgesics_-_overview)
    - Alpha-2 agonist plus ketamine (#alpha-2_agonist_plus_ketamine)
  - Opioids (#opioids)
    - Avoiding opioid infusions (#avoiding_opioid_infusions)
    - Opioid PCA (Patient-Controlled Analgesia) (#opioid_patient-controlled_analgesia_(PCA))
  - NSAIDs (#NSAIDs)
  - Lidocaine (#lidocaine)
  - Gabapentinoids (#gabapentinoids)
- Other measures (#other_measures)
- Podcast (#podcast)
- Questions & discussion (#questions_&_discussion)
- Pitfalls (#pitfalls)

introduction
Most ICU patients have some pain, particularly intubated patients. Inadequate pain control or overmedication are both problematic, so this requires thoughtful management.

Opioids have traditionally been front-line analgesics in the ICU. However, these cause numerous side effects (delirium, constipation/ileus, vomiting, delayed extubation).

For patients with ongoing pain, combining drugs from different pharmacologic classes may allow for effective analgesia while avoiding drug toxicity (multimodal analgesia).

Whenever possible, the ideal approach is removal of the cause of pain (e.g., removal of unnecessary tubes/drains, management of constipation).

diagnosis and monitoring of pain

This can be tricky in a patient with undifferentiated agitation: is the patient delirious, anxious, or in pain?

- Make sure that analgesics (especially opioids) are being used for pain control, and not as a blunt instrument to calm down agitated patients. Anxiety or delirium should be managed with an anxiolytic or antipsychotic – not an opioid.

 Patients able to communicate should be asked directly about pain.

 Among patients unable to communicate, behavioral pain scores may be used to assess pain (e.g., table below). This isn't perfect, but it provides a systematic approach to assess pain and titrate medication accordingly.

<table>
<thead>
<tr>
<th>Table 1 Description of the Critical-Care Pain Observation Tool</th>
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<tbody>
<tr>
<td>Indicator</td>
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<tr>
<td>Facial expression</td>
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<td></td>
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<tr>
<td>Body movements</td>
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<td>Muscle tension</td>
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<tr>
<td>Compliance with the ventilator (intubated patients)</td>
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<tr>
<td>Vocalization (intubated patients)</td>
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<tr>
<td></td>
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<tr>
<td>Total, range</td>
</tr>
</tbody>
</table>

See the chapter on buprenorphine for general principles of management.

Considerations regarding the use of non-opioid analgesia discussed below apply well to these patients (e.g., ketamine, alpha-2 agonists, lidocaine).

concept of multi-modal analgesia

Multi-modal therapy is a useful principle which may be applied to a variety of topics (e.g., sedation, hemodynamic support, antiemetics).

foundational concept #1: low doses to optimize risk/benefit
Increasing medication dosing increases both therapeutic and toxic effects, as shown above. Using lower medication doses can often allow substantial clinical benefit, with minimal toxicity (optimizing the risk/benefit ratio). This also creates a safety buffer; even if drug concentrations increase a bit, they will remain within a safe range.

**foundational concept #2 = different agents function synergistically**

- Different analgesics frequently work in a synergistic fashion (i.e., 1+1 = 3).
- Synergy allows moderate doses of several different agents to have a large combined impact.

**putting it together: multi-modal therapy**

- A multi-modal strategy therefore involves using moderate doses of several different agents, in order to maximize efficacy while minimizing toxicity. This is in contrast, for example, to a traditional approach of drowning patients with super-human doses of a single opioid (a strategy which is effective, albeit at the cost of considerable toxicity).
- Multi-modal therapy is more work, because it involves administration of more medications. This may be confusing to practitioners who aren’t familiar with it (“why are we using four drugs when we could use one?”). However, the evidentiary basis for multi-modal therapy is reasonably robust (based largely on RCTs performed in operative and post-operative patients).

**analgesic ladder for critically ill patients**

The concept of an analgesic ladder was developed by the World Health Organization in 1986, as a theoretical construct to encourage rational use of opioids. It focused on optimizing the use of non-opioid analgesics, before escalating to opioids. This may be adapted for critically ill patients as shown here:
There is no one-size-fits-all solution to analgesia among critically ill patients. For example, patients with neuropathic pain may benefit from upfront initiation of a gabapentinoid, whereas most other patients probably won’t. That said, the above schema may provide a rough guide to when different types of medications may be initiated. In particular, the typical progression from PRN opioids straight to an opioid infusion should be avoided.

acetaminophen

**general comments & mechanism of action**

- Acetaminophen is a mild-moderately effective analgesic with an excellent safety profile. It forms the first level of the analgesic ladder due to its safety, rather than its efficacy. Acetaminophen is often overlooked because it isn’t very potent. However, scheduled acetaminophen may nonetheless play a useful role in multi-modal analgesia. RCTs and meta-analyses demonstrate that acetaminophen is an effective analgesic in a variety of contexts, with benefits which may include reduced opioid requirements, avoidance of delirium, and avoidance of nausea/vomiting. ([20189753](https://pubmed.ncbi.nlm.nih.gov/20189753/), [30726545](https://pubmed.ncbi.nlm.nih.gov/30726545/), [30305124](https://pubmed.ncbi.nlm.nih.gov/30305124/), [30778597](https://pubmed.ncbi.nlm.nih.gov/30778597/)).

- Acetaminophen is a centrally acting, noncompetitive reversible inhibitor of cyclooxygenase (COX) enzymes, with analgesic and antipyretic effects. ([30845871](https://pubmed.ncbi.nlm.nih.gov/30845871/)).

**dose**

- The usual dose is 650-1,000 mg q6hr. For patients with ongoing pain this should be scheduled, to provide a baseline level of analgesia.

- Acetaminophen may be given PO, PR, or IV. PO is preferred, because IV is expensive (although this varies in different countries).


**contraindications & complications**

- In severe alcoholism, stable cirrhosis, or low body weight (<50 kg), the dose should be reduced to 2 grams per day (at most). ([25477978](https://pubmed.ncbi.nlm.nih.gov/25477978/))

- In acute liver injury or decompensated cirrhosis, acetaminophen should be entirely avoided.

- In neutropenia, acetaminophen might be avoided, to allow for early detection of neutropenic fever.

**pain-dose ketamine infusion**

**general comments & mechanism of action**

...
Ketamine functions as an NMDA inhibitor. At very low doses, ketamine provides analgesia without other neurologic effects.

Pain-dose ketamine infusions provide a mild to moderate level of analgesia (with some variation between patients). This often isn't sufficient to control the pain entirely, but it may provide a continuous basal level of analgesia with opioid-sparing effects. (25530168)

Increasing evidence supports the use of pain-dose ketamine infusions among critically ill patients. (12933413, 26025196, 28468568)

Pain-dose ketamine infusions are extraordinarily safe, especially in an ICU environment (noting that low-dose ketamine infusions can be given safely on the wards). Of all the medications described in this chapter, ketamine is arguably the safest one. Ketamine doesn't suppress respiration or airway protection. Ketamine doesn't cause hypotension (occasionally ketamine may increase the blood pressure, but generally not substantially).

The main limitation of pain-dose ketamine infusions is that they're a bit of a hassle to set up (compared, for example, to opioid boluses, which are faster to give and more immediately gratifying).

**Benefits of a pain-dose ketamine infusion**

- **1.** Mild-moderate analgesic effect, reducing the required dose of opioids.
- **2.** Ketamine may inhibit the development of tolerance to opioids and the emergence of opioid induced hyperalgesia. (15983467, 16854557, 23269131, 14581110) Thus, ketamine may mitigate some side effects of opioids.
- **3.** Ketamine exerts antidepressant effects, which may improve patient mood and promote participation in rehabilitation. (26025196, 23428794, 16894061)

**Risks of pain-dose ketamine infusion: psychomimetic side effects**

- The only true risk of pain-dose ketamine infusion is psychomimetic side effects. At the higher dosing end (around 0.2-0.3 mg/kg/hr), ketamine may cause somnolence, agitation, euphoria, or hallucinations. Often these effects may be beneficial (e.g., mild sedation or euphoria). However, some patients may experience disturbing hallucinations.
- Psychomimetic side effects will abate rapidly after pausing the ketamine infusion, so this isn't a major problem if managed appropriately.
- One randomized controlled trial found that pain-dose ketamine infusions reduced the risk of delirium. (30268528) This suggests that the possibility of psychomimetic side effects doesn't imply a danger of more serious neurologic complications from ketamine.

**Nuts & bolts of pain-dose ketamine infusions**

- The typical dosing range is 0.1-0.3 mg/kg ketamine per hour (e.g., ~8-20 mg/hour).
- If you're extremely worried about psychomimetic side effects, you could just leave the infusion at a fixed rate of 0.12 mg/kg/hour. Several studies suggest that the risk of psychomimetic effects at that dose is close to zero. (25530168, 15983467, 21676160) This strategy might be reasonable in an intubated patient with baseline agitation, where it may be difficult to determine whether the patient is experiencing psychomimetic side effects.
- For most patients, it's useful to start at the lower end of this dosing range, and then uptitrate the ketamine gradually over a period of hours as needed. If troublesome psychomimetic side effects occur, then pause the ketamine infusion for an hour or two and resume at a lower dose (a dose which didn't cause psychomimetic side effects).
  - Psychomimetic side effects are dose related, and therefore not a contraindication to using ketamine.
  - Resuming ketamine at a lower dose can often still allow the patient to receive substantial benefit from ketamine, without experiencing any side effects.
- The combination of ketamine with a central alpha-2 acting sedative (dexametomidine or clonidine) or with propofol appears to prevent the occurrence of psychomimetic side effects. (15235947) This may allow higher doses of ketamine to be given (e.g., doses up to ~0.5 mg/kg/hr). More on this below (alpha-2_agonist_plus_ketamine).

**Alpha-2 agonists as analgesics – overview**

[Back to contents]
Alpha-2 agonists exert analgesic effects by affecting central alpha-2 receptors and imidazoline receptors. Depending on their activity upon different receptors, they have a spectrum of overlapping clinical effects.

The analgesic potency of alpha-2 agonists is mild. However, they may be beneficial within a multi-modal analgesic scheme, where they augment the efficacy of other agents (e.g., ketamine, as discussed further below).

Central alpha-2 agonists cause varying degrees of sedation (table below). Among outpatients this is a side effect, but among critically ill patients this is often extremely useful. This combination of analgesia plus sedation has also allowed clonidine to be useful in treating opioid withdrawal.

Alpha-2 agonists can cause bradycardia and hypotension. Aside from boluses of dexmedetomidine, this is generally relatively mild and manageable. However, these agents are generally unsuitable for patients with pre-existing bradycardia or heart block.

tolerance and withdrawal to alpha-2 agonists

Perhaps the greatest drawback of alpha-2 agonists is the possibility of developing tolerance and withdrawal. Over time, patients may become tolerant to the medication, causing reduced clinical efficacy. If the medication is then stopped abruptly, this may cause a withdrawal syndrome (e.g., with tachycardia, hypertension, and anxiety). Withdrawal is predominantly an issue among patients taking these medications on a chronic, outpatient basis – but it can occur to a lesser extent among inpatients (especially patients on higher doses of dexmedetomidine).

These issues may be avoided as follows:

1. Consider limiting the duration of dexmedetomidine infusions (e.g., to less than ~5 days). Dexmedetomidine is an excellent medication to facilitate extubation, but it may not be the optimal agent to serve as a maintenance analgesedative for indefinite periods of time. Discontinuation of dexmedetomidine can be facilitated by transitioning to oral clonidine.
2. For patients who have been on oral alpha-2 agonists for several days, it may be preferable to taper off gradually (or taper abruptly with careful observation for withdrawal).
3. It's essential to actively wean alpha-2 agonists as soon as possible (e.g., as patients are recovering and have decreasing needs for analgesia and sedation). All efforts should be made to ensure that patients aren't continued on these agents indefinitely on an outpatient basis.
4. Avoid high doses of these medications (this is consistent with the bedrock concept of multi-modal analgesia, which is to use moderate doses of several agents in order to minimize toxicity from any single agent).

Fear of tolerance and withdrawal shouldn't generally dissuade practitioners from using these agents. However, these limitations must be understood to maximize the safe and efficacious use of alpha-2 agonists.
Dexmedetomidine is a titratable, infused analgosedative agent which is commonly used in the critical care unit. It is generally used predominantly as a sedative. However, it has proven efficacy in promoting multimodal analgesia (e.g., reducing opioid requirements).

Dexmedetomidine doesn't suppress respiration or airway reflexes, allowing it to be used in patients who aren't intubated. For example, dexmedetomidine may be a safe agent for a non-intubated patient with pain and anxiety, who is at risk for respiratory suppression (e.g., due to COPD or obesity hypoventilation syndrome).

Boluses of dexmedetomidine may cause bradycardia and hemodynamic collapse, so these should generally be avoided. Instead, the infusion may be started at a high rate (e.g., 1-1.4 mcg/kg/min) and down-titrated as the drug takes effect (within an hour).

In rare situations, dexmedetomidine may be a uniquely useful and necessary sedative (e.g., control of agitation in a hypercapnic patient in efforts to improve tolerance of BiPAP). What should be done if dexmedetomidine is deemed to be mission-critical, but is causing bradycardia? A dexmedetomidine infusion may be combined with a simultaneous infusion of low-dose epinephrine or dobutamine (to offset the bradycardic effects).

Clonidine is similar to dexmedetomidine, but it has a longer half-life and greater hemodynamic effects (bradycardia and hypotension).

In many countries, intravenous clonidine is used in a similar fashion to intravenous dexmedetomidine. In the United States, only oral clonidine is available.

Oral clonidine is often used as a means of weaning patients off intravenous dexmedetomidine. The main limitation of clonidine is that oral administration limits the ability to rapidly increase or decrease doses. However, clonidine is absorbed fairly rapidly (e.g., within ~2 hours), so accelerated oral dose titration is possible.

Clonidine may actually have a U-shaped effect on blood pressure, with lower doses causing hypotension but higher doses having less effect on blood pressure — discussed further here (https://emcrit.org/pulmcrit/ketadex/). (28833346 https://pubmed.ncbi.nlm.nih.gov/28833346/)

If a patient is temporarily unable to take oral medication, clonidine may also be given sublingually (achieving similar pharmacokinetics compared to oral clonidine). (7986518) https://pubmed.ncbi.nlm.nih.gov/7986518/

Tizanidine appears to offer analgesic efficacy, with far less effect on hemodynamics. (18671474 https://pubmed.ncbi.nlm.nih.gov/18671474/), 25849473 (https://pubmed.ncbi.nlm.nih.gov/25849473/). Tizanidine also has muscle relaxant properties and mild sedating effects. Among the alpha-2 agonists, tizanidine might arguably be the best analgesic.

Tizanidine has traditionally been used for pain syndromes involving muscle spasm (e.g., back pain or myofascial pain). However, recent research shows efficacy in somatic pain as well (e.g., pain following cholecystectomy or hernia repair). (26555871)
Drug interactions:
- Tizanidine is metabolized by the hepatic CYP1A2 system.
- Tizanidine levels may be low in patients taking inducers of CYP1A2 enzyme (especially rifampin and carbamazepine).
- Tizanidine may be excessive in patients taking inhibitors of CYP1A2 (especially: some fluoroquinolones, fluvoxamine, mexiletine, and some oral contraceptives).

Drawbacks of tizanidine:
- Reversible liver function abnormalities are seen in ~5% of patients.
- Bioavailability is somewhat variable (food may increase absorption of tizanidine tablets).
- Normally the majority of tizanidine is removed via first-pass metabolism in the liver, so hepatic dysfunction could lead to increased drug levels.
- Rebound hypertension may occur if doses >20 mg/day are used for extended periods.

Alpha-2 agonist plus ketamine

Combining ketamine plus clonidine or dexmedetomidine may be synergistically useful for several reasons:

- **Synergistic analgesia**: The combination of ketamine plus an alpha-2 agonist provides more effective analgesia than either agent alone.
- **Hemodynamic stability**: Ketamine tends to increase blood pressure, whereas alpha-2 agonists tend to reduce blood pressure.
- **Avoidance of ketamine's psychomimetic side effects**: The major treatment limiting side effect of ketamine infusions is psychomimetic effects, which occur at higher doses (typically >0.2-0.3 mg/kg/hr). These side effects are generally minor and easily managed by pausing the infusion and then resuming at a lower rate. Alpha-2 agonists can exert a sedative effect which avoids ketamine induced psychomimetic effects, thereby widening the margin of safety when administering ketamine.
- **Avoidance of tolerance to alpha-2 agonists?** Within 1-2 weeks, patients will develop tolerance to the sedative effects of alpha-2 agonists. Animal models suggest that ketamine may prevent this, thereby allowing alpha-2 agonists to maintain ongoing efficacy over time.
Opioids have traditionally been the backbone of pain management in critical illness. However, this selection is based more on inertia and ease of use, rather than on evidentiary support. Anesthesiologists have long recognized that avoidance of opioids may improve recovery after surgery, with intensivists only gradually beginning to follow suit.

PRN bolus-dose opioids will often be required for the management of critically ill patients. Opioid toxicity increases substantially with the use of a continuous opioid infusion, so these should be avoided whenever possible.

A series of studies in Europe have demonstrated that it's possible for critically ill, intubated patients to be maintained on extremely low doses of opioids or no opioids at all. (https://pubmed.ncbi.nlm.nih.gov/20116842/), (https://pubmed.ncbi.nlm.nih.gov/32068366/) This implies that many ICUs are using vastly more opioids than are actually necessary.

**pharmacokinetics, dosing, and selection**

<table>
<thead>
<tr>
<th>intravenous opioids commonly used in critical illness</th>
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<tbody>
<tr>
<td>Fentanyl</td>
</tr>
<tr>
<td>Typical dose</td>
</tr>
<tr>
<td>Bolus: &quot;50-100 mcg is 10-60 min infusion; ~25-100 mcg/hour</td>
</tr>
<tr>
<td>Infusion: ~0.4-1 mg q2-3 hours infusion; ~0.4-4 mg/hour</td>
</tr>
<tr>
<td>(Note: Dose will vary depending on patient size, severity of pain, and tolerance of opioids.)</td>
</tr>
<tr>
<td>Bolus: ~4-8 mg q2-3 hours infusion; ~3-30 mg/hour</td>
</tr>
<tr>
<td>Equianalgesic dose</td>
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<tr>
<td>(7x more potent than IV morphine)</td>
</tr>
<tr>
<td>Onset</td>
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<tr>
<td>~5-10 minutes</td>
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<tr>
<td>Peak effect</td>
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<tr>
<td>~10-20 minutes</td>
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<tr>
<td>~15-30 minutes</td>
</tr>
<tr>
<td>Duration of action</td>
</tr>
<tr>
<td>Longer in liver failure or after prolonged infusion.</td>
</tr>
<tr>
<td>~2-4 hours</td>
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<tr>
<td>Longer in liver failure or advanced renal failure.</td>
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<tr>
<td>~3-5 hours</td>
</tr>
<tr>
<td>Longer in liver failure or advanced renal failure.</td>
</tr>
<tr>
<td>Metabolism</td>
</tr>
<tr>
<td>(Hydromorphone-3-glucuronide).</td>
</tr>
<tr>
<td>Renal failure</td>
</tr>
<tr>
<td>In renal failure, accumulation of hydromorphone-3-glucuronide may cause seizure, mydriasis, or agitation.</td>
</tr>
<tr>
<td>Avoid in severe renal failure.</td>
</tr>
<tr>
<td>In renal failure, accumulation of morphine-6-glucuronide may cause respiratory suppression and seizure.</td>
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<tr>
<td>Hepatic failure</td>
</tr>
<tr>
<td>Use caution and consider extending the time interval between doses.</td>
</tr>
<tr>
<td>Contraindication</td>
</tr>
<tr>
<td>(All are relatively contraindicated in pts at risk for respiratory suppression - esp. chronic hypoxemia)</td>
</tr>
<tr>
<td>Advantages</td>
</tr>
<tr>
<td>Promotes hemodynamic stability.</td>
</tr>
<tr>
<td>No toxic metabolites accumulate in renal failure.</td>
</tr>
<tr>
<td>When infused, fentanyl accumulates in fat and half-life extends; may cause delayed awakening.</td>
</tr>
<tr>
<td>CYP3A4 inhibitors may reduce metabolism (problematic with infusion, but not PRN boluses).</td>
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<tr>
<td>PCA demand dose</td>
</tr>
<tr>
<td>~0.2-0.5 mg</td>
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<tr>
<td>~1-3 mg</td>
</tr>
<tr>
<td>PCA lockout interval</td>
</tr>
<tr>
<td>~10-15 minutes</td>
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<tr>
<td>~10-30 minutes</td>
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</tbody>
</table>

Opioids commonly used in critical care are listed above. These are overall fairly similar agents. The most important aspect of opioid administration is dose-titration, rather than the selection of any particular drug.

Other opioids, especially tramadol and meperidine, have numerous side effects and no role in managing critically ill patients.

It is commonly taught that there is no "maximal dose" of opioids. This is only partially true. At high doses, opioids may rapidly cause opioid-induced hyperalgesia (a paradoxical process whereby excess opioid doses exacerbate pain). This seems to be most problematic with remifentanil and fentanyl, with one study showing that a single, large dose of fentanyl was capable of inducing hyperalgesia. (26654943) Whenever giving an opioid dose equivalent to >50 mg oral oxycodone daily, consider whether the dose is necessary and beneficial. Especially among medical patients, there's little rational explanation why such massive doses of opioid should be needed. A common error is to use large-dose opioids for their sedative properties (when such patients would be better served by receiving less opioid and more sedation).

**complications of greatest concern in the ICU:**

- Respiratory suppression
  - Opioids suppress the respiratory drive relatively potently. Unfortunately, even with chronic use, this effect remains strong.
  - Patients at greatest risk are those with chronic hypercapnia and a blunted respiratory drive (e.g., obesity hypoventilation syndrome or chronic hypercapnic respiratory failure due to COPD).
Among intubated patients, respiratory suppression can be beneficial by facilitating ventilator synchrony. However, persistent respiratory suppression may delay extubation.

(2) Gastrointestinal failure
Opioids are a major risk factor for nausea/vomiting, gastroparesis, ileus, and colonic pseudo-obstruction. In severe cases, the latter can cause colonic perforation and death.

(3) Opioid dependence and withdrawal
- The brain very rapidly adapts to continuous opioid exposure, leading to dependence. When the opioid dose is reduced, this may cause withdrawal and rebound analgesia.
  - Opioid withdrawal may be an under-recognized factor which contributes to pain and depression after critical illness.
  - Ongoing use of opioids throughout the patient’s hospital course may lead to chronic outpatient opioid use, which exposes the patient to a host of long-term problems.

avoiding opioid infusions

the use of continuous infusions of opioids for days on end lacks a strong evidentiary basis. For example:

- No prospective, high-quality study has demonstrated a benefit from using a continuous opioid infusion. It's often assumed that more is better, but a continuous exposure to opioid may merely blunt the brain's responsiveness to it (rather than improving efficacy).
- Among patients being treated with patient-controlled analgesia (PCA) for acute pain, the addition of a continuous opioid infusion has been shown to increase complications, without improving pain control! (21074739)
- Replacing fentanyl infusions with methadone was shown to accelerate extubation, implying that fentanyl infusions prolong intubation. (22420584)

major reasons to avoid opioid infusions include the following:

- Continuous exposure to opioids rapidly causes tolerance, which may eventually lead to problems with withdrawal and dependence.
- Infusions will be up-titrated with the patient is in pain, but less aggressively down-titrated when the patient isn't in pain. This will inevitably increase opioid exposure, compared to a PRN-only strategy (which only provides opioid when the patient has pain).
- High cumulative opioid exposure from infusions (especially fentanyl) may cause opioid-induced hyperalgesia leading to a vicious spiral (figure above).
- Continuous infusions of fentanyl will lead to drug accumulation in the fat tissue, which makes it impossible to rapidly withdraw the opioid when the patient is otherwise ready for extubation.

strategies to avoid problems with opioid infusions:

1. Avoid infusions whenever possible (favoring a bolus-only strategy, even if that involves using relatively generous opioid boluses).
2. If an infusion is necessary, use a rational dose (e.g., 25-50 mcg/hour fentanyl). Note that 100 mcg/hr fentanyl infusion is roughly equivalent to ~400 mg of oral oxycodone daily.

3. Aggressively wean down the infusion at least once daily (but optimally more often).

4. It takes an infusion 4-5 half-lives to reach steady state. Therefore, for severe uncontrolled pain the first line therapy is PRN boluses of opioid, combined with up-titration of opioid infusion. Merely up-titrating the infusion without PRN doses is the wrong approach here, because it will lead to delayed and excessive opioid dosing.

5. Pay attention to how much opioid is being used as PRN doses vs. infusion. Ideally at least a moderate fraction of the total opioid given should be given as PRN doses. Alternatively, if the patient is receiving no PRN doses, then that suggests that the infusion rate is excessively high.

6. Ketamine may reduce the development of tolerance and opioid induced hyperalgesia. Thus, co-infusion of pain-dose ketamine with an opioid may limit opioid dose and toxicity.

**opioid infusions may be beneficial in the following situations:**

1. Among intubated patients with profound respiratory failure with a need to suppress the respiratory drive (e.g., severe status asthmaticus), opioid infusions may be beneficial. Use of an opioid infusion to suppress respiratory drive may allow for avoidance of paralysis, thereby constituting the lesser of two evils.

2. For patients on chronic opioids prior to admission, some basal amount of opioid may be necessary to prevent withdrawal.

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**opioid patient-controlled analgesia (PCA)**

Patient-controlled analgesia (PCA) may be useful for severe pain in a patient who is awake enough to understand how to use the PCA. PCAs don't play a large role among critically ill patients, as our patients are often too ill to use them. Nonetheless, it's worth understanding how to set one up.

**general concepts behind a PCA**

- (1) Small doses of opioid provided on-demand may allow for finer dose titration against the patient's pain requirements. This may actually lead to reduced opioid consumption over time.

- (2) Small doses are provided, with a defined lock-out interval between doses (during which time, activating the PCA will not result in delivering additional medication). Using a lock-out interval prevents multiple doses from accumulating (“stacking”) and thereby leading to intoxication.

- (3) Also to ensure safety, a patient who becomes mildly intoxicated will fall asleep and stop activating the PCA. In order for this safety mechanism to function optimally, the PCA should ideally have no basal rate (more on this below).

**basic setup**

- (1) Select an agent based on the same considerations as are generally used (e.g., renal dysfunction, interacting drugs). All other things being equal, morphine might be a good choice (it causes less euphoria, making it a bit less prone towards inappropriate reinforcement).

- (2) Choose a demand dose and lockout interval (see table below). Doses and intervals may vary a bit depending on how sensitive the patients are to opioids and what their opioid requirement has been. However, relatively similar doses can be used overall, with the expectation that patients will titrate their own doses by operating the PCA.

- (3) **The basal (continuous) rate of the PCA should always be set to zero** unless the patient has been on chronic opioids. For patients who were previously on chronic opioids, their chronic dose may be converted into an appropriate basal rate using various calculators (e.g., this one [https://clincalc.com/Opioids/](https://clincalc.com/Opioids/)). This can be a bit tricky though, so if in doubt be sure to discuss this with your unit pharmacist and err on the low side.

- (4) Discontinue all other opioid orders. Also, remove potentially sedating medications if possible (e.g., benzodiazepines).
common mistakes

1. The PCA is designed to maintain analgesia – not to rescue the patient from uncontrolled pain.
   - If the patient has severe, uncontrolled pain, then this should be treated immediately by clinician-titrated boluses of opioid.
   - Patients often require loading with a moderate dose of opioid before initiation of the PCA. The PCA delivers only small doses of opioid, so it’s not adequate to “catch up” to entirely uncontrolled pain.
2. Never use a continuous infusion in a patient who is opioid naive.
   - Continuous opioid infusions probably don’t help improve analgesia, as explored above. In the case of PCAs, it has been specifically shown that adding a basal rate doesn’t improve analgesia – but it does increase toxicity! (16334492, 21074739)
   - Basal rates should be used only for patients who are on chronic opioids.
   - If the patient’s pain isn’t controlled, then consider increasing the demand dose – or better yet – adding a non-opioid analgesic (e.g., ketamine).
3. Ensure that only the patient is activating the PCA (and not, for example, relatives or friends). A safety mechanism of PCAs is that as patients become sedated they will stop activating the PCA.
4. Pumps can malfunction, rarely leading to opioid intoxication. If the patient is demonstrating features of opioid intoxication, then disconnect the PCA and treat the patient appropriately.

NSAIDs

NSAIDs inhibit prostaglandin synthesis via COX enzymes, thereby exerting antipyretic, analgesic, and anti-inflammatory effects. NSAIDs are generally not preferred in the ICU due to risks of gastrointestinal hemorrhage, platelet dysfunction, or (especially) renal failure. However, they may be considered selectively for patients at low risk of complications.

candidates for receiving NSAIDs in the ICU

| NSAIDs inhibit prostaglandin synthesis via COX enzymes, thereby exerting antipyretic, analgesic, and anti-inflammatory effects. | NSAIDs are generally not preferred in the ICU due to risks of gastrointestinal hemorrhage, platelet dysfunction, or (especially) renal failure. However, they may be considered selectively for patients at low risk of complications. | candidates for receiving NSAIDs in the ICU |
• (1) The patient is on no other nephrotoxic medications (ideally, allow only one nephrotoxin per patient at a time).
• (2) The patient has excellent and stable renal function (i.e., good urine output and creatinine values).
• (3) There are no sources of hemodynamic instability or impaired perfusion.
• (4) Absence of cirrhosis or inflammatory bowel disease.
• (5) No history of GI ulceration.
• (6) No active hemorrhage or severe coagulopathy (especially, no platelet dysfunction).

**Selection and dosing**

- Different NSAIDs seem to have similar safety and efficacy. However, intravenous ketorolac may take effect considerably faster than oral agents.
- The key principle of NSAID dosing is the concept of the *dose ceiling*. Above a certain dose, further increases will only increase toxicity (without increasing efficacy). Recent evidence demonstrates that the dose ceiling is often lower than was previously thought. This is useful, because it reveals that we can obtain the same efficacy while using smaller, safer doses. Dose ceilings for some commonly used NSAIDs are:
  - Ketorolac: 10 mg IV Q6hr PRN, [Medscape monograph on ketorolac](https://reference.medscape.com/drug/ketorolac-343292) (27993418)
  - Ibuprofen: 400 mg PO q6hr PRN, [Medscape monograph on ibuprofen](https://reference.medscape.com/drug/advil-motrin-ibuprofen-343289) (31383385)
  - Don’t give a dose higher than the dose ceiling! Doses below the dose ceiling may still remain useful, however (e.g., 300 mg of ibuprofen).
  - Discontinue the NSAID as soon as possible (in particular, avoid ketorolac administration for >5 days).

**Lidocaine**

- [Back to contents](#top)

**General Comments & Mechanism of Action**

- Lidocaine is a type Ib antiarrhythmic and also an amide local anesthetic. It functions by inhibiting voltage-gated sodium channels, but at low systemic doses used for analgesia it likely acts via other mechanisms (e.g., modulation of calcium channels or NMDA receptors).
- Systemic lidocaine has been used increasingly for a variety of painful conditions (e.g., neuropathic pain, renal colic, and post-operative pain). It has analgesic, anti-inflammatory, and antihyperalgesic properties (30845871, 28114177).
- The best evidence for lidocaine infusions for pain management exists in the postoperative context. Various studies have demonstrated that lidocaine may reduce pain, decrease opioid requirements, avoid ileus, decrease nausea/vomiting, and reduce hospital length of stay (28114177).
- Lidocaine is not recommended in the PADIS guidelines for *routine* use among critically ill patients (30113379). However, it may be beneficial in selected patients who fail to respond to more conventional strategies.

**Pharmacokinetics**

- Lidocaine undergoes hepatic metabolism into two active metabolites (monoethylglycinexylidide and glycinexylidide). These are subsequently eliminated by the kidney. In renal failure, activate metabolites can accumulate.
- Lidocaine undergoes roughly biphasic distribution.
  - Initially, lidocaine has a half-life of 7-30 minutes, as drug distributes into body tissues.
  - Eventually the half-life increases to ~1.5-3 hours. This reflects saturation of the tissues and elimination of drug by the liver and kidneys. The terminal half-life may be up to 8 hours in patients with hepatic failure (26335213).

**Dose**

https://emcrit.org/ibcc/pain/
1. Initial loading dose
   - ~1.5 mg/kg infusion over 10-30 minutes (may use 1-2 mg/kg).

2. Continuous infusion at a low, fixed rate
   - ~1 mg/kg/hour ideal body weight appears to be a reasonable dose. This will often be close to 1 mg/min, with some correction based on body size.
   - Many sources recommend titration of the infusion based on pain. However, lidocaine has a relatively narrow therapeutic window (e.g., therapeutic level of ~2.5-3.5 ug/ml and toxic level of >5 ug/ml). Therefore, unless there is a high level of expertise regarding monitoring and dose-adjustment, it might be safest to use a fixed rate (especially at centers which are unable to measure a lidocaine level). The whole concept of multi-modal analgesia is to use low doses of several medications, to avoid toxicity from any individual agent. Use of a relatively low, fixed lidocaine infusion rate may fit within this overall strategy.
   - Caution: Many sources list higher infusion rates (e.g., 2-3 mg/kg/hour), but accumulation and shifts in metabolism over time may make these rates unsafe for extended infusion (e.g., >24 hours).
   - Caution: Monitor the patient's organ function while on the lidocaine infusion. If acute organ failures occur (e.g., renal failure or multiorgan failure), then either close monitoring of drug levels or discontinuation of the infusion may be required.

3. Duration of lidocaine infusion?
   - This is unclear. Most studies in the anesthesia literature have limited lidocaine infusions to 48 hours in duration. However, some studies have reported the use of a continuous lidocaine infusion for four days or even 1-2 weeks!
   - Over time, the half-life of lidocaine may extend slightly (due to accumulation in various body compartments and also due to the inhibition of lidocaine metabolism by some of its own metabolites). Therefore, if lidocaine is continued beyond 48 hours, it may be sensible to reduce the rate slightly (to 0.8 mg/kg/hr ideal body weight) or monitor serum lidocaine levels.

- Medscape monograph on Lidocaine

adverse effects

- Early signs of toxicity: Perioral paresthesias, visual or auditory disturbance, metallic taste, tinnitus, lightheadedness, and sedation. These should serve as triggers to discontinue the lidocaine infusion, and thus avoid more severe toxicity.
- Organ system manifestations:
  - Cardiac: Bradycardia, QRS widening, sinus node suppression
  - Neurologic: Delirium, tremor, visual disturbances, numbness/tingling, metallic taste, tinnitus, seizure.
  - Gastrointestinal: Nausea and vomiting
  - Hematologic: Methemoglobinemia (rare)
- Mild-moderate toxicity should resolve after discontinuing the infusion. Severe toxicity may be managed by administration of intralipid.
**contraindications**

- Allergy to lidocaine.
- Heart block (including PR >200 ms or QRS >120 ms).
- Increased risk of seizure (e.g., seizure history).
- Hepatic dysfunction (bilirubin >1.5 mg/dL).
- Renal dysfunction (GFR <30 ml/min or acute-onset oliguria).
- Severe heart failure, shock, or multiorgan failure.
- Acute porphyria.
- Drug interactions:
  - Medications involving CYP1A2 or CYP3A4 systems – check for interactions using an electronic tool (e.g., the MedScape drug interaction tool [here](https://reference.medscape.com/drug-interactionchecker)).
  - Other class I antiarrhythmics (including phenytoin) [26335213](https://pubmed.ncbi.nlm.nih.gov/26335213/).

**general comments & mechanism of action**

- Gabapentinoids refer to gabapentin and pregabalin.
- These drugs *don’t* actually interact with GABA receptors – they function to inhibit voltage-dependent calcium channels.
- Gabapentinoid use is largely limited to *neuropathic pain* (e.g., Guillain-Barre Syndrome, diabetic neuropathy, post-herpetic neuralgia).
- Although occasionally used for post-operative pain, there is little evidentiary support for their use in post-operative or acute somatic pain. ([27426431](https://pubmed.ncbi.nlm.nih.gov/27426431/)).
- Rapid discontinuation of gabapentinoids can cause withdrawal. Patients who were on these medications *prior* to ICU admission should generally be continued on them (with dose-adjustment as needed based on renal function).

**pharmacokinetics**

- Gabapentin has a half-life of 5-7 hours, which is prolonged in renal dysfunction.
- Pregabalin may have a faster onset, with 90% bioavailability and peak concentration within an hour.

**dose**

- Gabapentin: 300-1200 mg q8hr
- Pregabalin: 75-150 mg q12hr
- Both agents should be dose-reduced in renal dysfunction.
- Additional information:

**contraindications & complications**

- Limiting side effects include somnolence, respiratory depression, hypoactive delirium, and less often myoclonus.
- Risks are compounded by renal dysfunction and other CNS-suppressive medications. However, mild sedation may be a beneficial effect for intubated patients.

**other measures**

- Nerve blocks are excellent measures when they can be used.
- Local measures (e.g., lidocaine patches, TENS units) are safe and may be helpful.
- Early mobilization and physical therapy could improve back pain.

**summary**
NSAIDs promote renal failure and gastric ulceration. They should be used only in rare and well-selected patients within the ICU.

Tramadol and meperidine (Demerol) have uniquely unfavorable side effect profiles and should be avoided. If you're looking for an anti-shivering agent, fentanyl is preferable to meperidine.

Opioid infusions cause a host of problems (e.g., tolerance, withdrawal, opioid-induced hyperalgesia, ileus, delayed extubation). They should be a last resort for most patients.

Acetaminophen and pain-dose ketamine infusions are effective analgesics with excellent side effect profiles. Their use should be encouraged, particularly among patients at high risk for opioid toxicity (e.g., patients with tenuous respiratory drive or abdominal pathology that increases the risk for ileus).

Bowel motility must be carefully attended to among patients receiving opioids.

Pain should be assessed carefully. Make sure that the analgesic medication is being used to treat pain, rather than to treat agitation or delirium.

Don't give a loading dose of dexmedetomidine (this may cause hemodynamic instability, particularly bradycardia).

Going further:

- **Reengineering the analgesic ladder for critically ill patients** ([https://emcrit.org/pulmcrit/analgesic-ladder/](https://emcrit.org/pulmcrit/analgesic-ladder)) (PulmCrit)
- **Editorials about tramadol from Matthew DeLaney** ([http://empharmd.blogspot.com/2015/05/three-reasons-not-to-prescribe-tramadol.html](http://empharmd.blogspot.com/2015/05/three-reasons-not-to-prescribe-tramadol.html)) & **David Juurlink** ([http://www.cmaj.ca/content/185/8/E352.full](http://www.cmaj.ca/content/185/8/E352.full))

References

Analgesia for the critically ill patient - EMCrit Project


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https://emcrit.org/fbcc/pain/
The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.