Sedation

November 3, 2016 by Josh Farkas

causes of agitation in the ICU are numerous

- Acute neurological catastrophe
- Multifactorial delirium, for example:
  - Sepsis
  - Medications
  - Sleep fragmentation due to frequent neurologic checks, blood pressure monitoring, or loud noises
- Air hunger from ventilator dysynchrony
- Pain
- Thirst due to hypernatremia
- Withdrawal syndromes
  - Alcohol withdrawal
  - Withdrawal of chronic medications (e.g., benzodiazepines, opioids, or gabapentin)

general approach to an agitated patient:

approach to the agitated patient
1. Consider whether this could be a manifestation of a new neurologic or medical problem (e.g., review vital signs, perform a focused neurologic examination).
   - Does this represent a major change in the patient's neurologic status, or has the patient been agitated for days?
   - If this appears to represent a significant change from prior neurologic status, perform an evaluation for delirium.
   
2. Look for anything easily modifiable that could make the patient more comfortable, for example:
   - Changing to a more comfortable ventilator mode.
   - Removing painful devices.
   - Treatment of hypernatremia.
   - Ear plugs at night.

3. Try to determine whether the patient may be suffering from pain, anxiety, or delirium.

   **general principles of ICU sedation**

   **agitated delirium or anxiety?**
   - Ideally, we should be able to differentiate between agitated delirium versus anxiety:
     - **Agitated delirium** refers to an acute confusional state marked by agitation. If medication is required, the optimal medication is arguably an antipsychotic.
     - **Anxiety** refers to fear or uneasiness in the absence of confusion. If medication is required, the optimal medication is a sedative (e.g., propofol or dexmedetomidine).
   - Among patients who aren't intubated, agitated delirium and anxiety can often be differentiated based on the presence or absence of delirium (although combinations of both processes may remain vexing). Among intubated patients, sorting out these two processes can be even more difficult.
   - In practice, it may be impossible to differentiate precisely between anxiety versus agitated delirium. The ultimate goal is to keep the patient comfortable and calm, while avoiding iatrogenic harm from medications. It may be necessary to empirically trial various medications, prior to selecting the medication(s) which work best for a specific patient.

   **long-term versus short-term sedation**
   - **Short-term sedation**
     - Refers to patients who will be intubated for a limited timeframe (e.g., one or two days).
     - A shorter duration leads to fewer problems with medication accumulation, tolerance, and withdrawal.
     - The choice and construction of a sedative regimen is less challenging and less important.
   - **Long-term sedation**
     - Refers to patients who remain intubated for several days.
     - A longer duration of intubation leads to increasing problems with medication tolerance, accumulation, toxicity, and withdrawal.
     - Carefully engineering a sedative regimen is often essential in minimizing iatrogenic harm and facilitating prompt extubation.
   - The same general considerations apply to both short-term and long-term sedation. However, meticulous construction of a sedation regimen is much less important for short-term sedation. This chapter is overall focused a bit more on long-term sedation, since this is more challenging.

   **multimodal sedation**

   As with analgesia, a multi-modal approach to sedation may often be useful (more on multimodal analgesia here).
   - Sedative agents often function synergistically. By using several agents, efficacy can be maximized while minimizing toxicity.
   - For example:
     - Propofol monotherapy may require using a high dose of propofol. This may cause hypotension, and eventually it may cause hypertriglyceridemia (which requires shutting off the propofol infusion entirely).
     - Combining a low dose propofol infusion with an antipsychotic may avoid the toxic effects of propofol, allowing the use of propofol for an extended duration.

   **sedation targets & circadian rhythm**
   - The Richmond Agitation-Sedation Scale (RASS) is a standardized description of the level of arousal. Many ICUs use this for documentation and titrating medications:
     - +4 = combative
     - +3 = very agitated
     - +2 = agitated
     - +1 = restless
     - 0 = alert and calm

   **Risk/Benefit ratio varies as a function of dosage**

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https://emcrit.org/ibcc/sedate/
#2) initiate a cornerstone sedative infusion

- Most patients will require a sedative infusion. The best agents appear to be propofol or dexmedetomidine. There is no solid evidence that either of these agents is superior to the other.
- Factors which could favor propofol:
  - Anticipated long duration of intubation
  - Seizures
  - Elevated intracranial pressure
  - Need for deep sedation to facilitate ventilator synchrony
- Factors which could favor dexmedetomidine:
  - Patient is approaching extubation

#1) treat pain and remove irritation

- Treat pain as necessary with a multi-modal analgesia strategy (more on this [here](https://emcrit.org/ibcc/pain/)).
- Remove sources of irritation as possible (see above); for example, removal of unnecessary lines and tubes.

**Basal sedation versus titratable sedation**

- When engineering a sedative regimen, it might be useful to divide sedation conceptually into two parts: basal sedation and titratable sedation.

**Basal sedation**

- This refers to a mild degree of sedation which may be used continuously.
- Basal sedation alone should be mild enough that it doesn't compromise the ability to protect the patient's airway. The functional definition of basal sedation is that the patient could be safely extubated on this level of sedation.
- Basal sedation can be provided by a long-acting medication (e.g., phenobarbital), or it can be achieved using a short-acting infusion (e.g., propofol). Within long-term sedative regimens, it's often useful to use oral medications to contribute at least part of the basal sedative requirements.

**Titratable sedation**

- This refers to a deeper level of sedation, which will compromise the patient's ability to protect their airway.
- Titratable sedation is generally provided by short-acting agents (e.g., propofol or ketamine). The short half-life of these agents allows titratable sedation to be lifted prior to extubation.

**Nonsedation?!**

- The above sections may give the impression that all intubated patients require a complex multi-agent sedative regimen. This is often true, but some patients can do fine with much less sedation at all.
- Two studies from Denmark demonstrated the ability of most patients to tolerate intubation with minimal medication requirements (small boluses of morphine and haloperidol). ([23068366](https://pubmed.ncbi.nlm.nih.gov/23068366/)), ([20116842](https://pubmed.ncbi.nlm.nih.gov/20116842/))

This practice isn’t generalizable to most ICUs, due to the high intensity of nursing care required. However, it’s important to emphasize that the sedative regimen must always be personalized to each patient. Some patients may require high doses of several agents, whereas other patients may require no sedatives at all.

**Daily sedation interruption?**

- The basic concept here is to stop sedative and opioid infusions and re-titrated daily, to make sure that we’re using the lowest possible dose.
- Sedation interruption was extremely critical when we were using long-acting infusions (e.g., midazolam and fentanyl drips). The general concept remains useful today but should probably be applied in a modified fashion. Specifically, we should be continuously titrating drugs such as propofol or dexmedetomidine to achieve a target level of sedation – so stopping entirely doesn’t make a lot of sense.

**Key concepts:**

- Re-assess the sedation regimen frequently (at least daily – but ideally more often).
- Always seek to use the lowest doses possible of all medications.
- Don’t necessarily shut off everything in a robotic fashion. For example, if the patient is awake and comfortable (RASS = 0), then shutting off all the sedation could cause them to become agitated with no real benefit.

**Bridging the intubated patient towards extubation**

- For a patient with problematic agitation, extubation can be challenging. Specifically, propofol infusions may need to be lightened prior to a spontaneous breathing trial. This can elicit agitation, interfering with the extubation process.
- The following agents can be continued throughout the extubation period, since they don’t suppress respiration. It may be helpful to shift the patient toward these agents in anticipation of extubation:
  - Dexmedetomidine
  - Ketamine infusion
  - Antipsychotics

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There is little evidence indicating precisely how to engineer a sedative regimen. Consequently, large geographic variation exists. Below is one reasonable approach for intubated patients – but this is intended merely as one possible example. Progress down the steps until the patient is comfortable.

**#1) treat pain and remove irritation**

- Treat pain as necessary with a multi-modal analgesia strategy (more on this [here](https://emcrit.org/ibcc/pain/)).
- Remove sources of irritation as possible (see above); for example, removal of unnecessary lines and tubes.

**#2) initiate a cornerstone sedative infusion**

- Most patients will require a sedative infusion. The best agents appear to be propofol or dexmedetomidine. There is no solid evidence that either of these agents is superior to the other.
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- Factors which could favor dexmedetomidine:
  - Patient is approaching extubation
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3) basal agent(s)
- Many patients will do fine with a low or moderate dose of propofol or dexmedetomidine – so they will require no additional medication. However, some patients may benefit from the addition of one or more basal agents. The role of basal agents may include:
  1. In some cases, these are required to achieve control of refractory agitation.
  2. More commonly, basal agents may be used to reduce the required dose of propofol or dexmedetomidine. Decreasing the dose of propofol or dexmedetomidine may avoid problems with these agents (e.g., hemodynamic instability, propofol infusion syndrome, or dexmedetomidine tolerance/withdrawal).
- These agents may include one or more of the following:
  - **Atypical antipsychotic** (quetiapine or olanzapine)
    - These are commonly used, due to their relatively favorable side-effect profiles.
    - They are most beneficial for patients with underlying agitation delirium.
  - **Phenobarbital**
    - Phenobarbital is occasionally useful, especially for patients with alcoholism or alcohol withdrawal.
  - **Oral alpha-2 agonists** (clonidine, guanfacine)
    - These may be considered in conjunction with propofol (if the patient is already on dexmedetomidine, then these will probably not add much).
    - Their greatest utility is in patients with tachycardia and hypertension (e.g., opioid withdrawal). Nocturnal administration may also promote sleep.
    - These agents aren’t particularly powerful – so don’t expect them to control refractory agitation.
  - **Sub-dissociative ketamine infusion**
    - For patients who are on a pain-dose ketamine infusion (e.g., at 0.1-0.2 mg/kg/hr), gently increasing the infusion rate into the sub-dissociative range may be trailed (e.g., towards 0.3-0.4 mg/kg/hr). This must be monitored carefully. If the patient responds favorably, higher doses of ketamine may be continued. Alternatively, if this is ineffective or causes agitation, then the dose must be reduced back to a pain-dose ketamine infusion.
  - **Valproate**
    - This is generally reserved for refractory agitated delirium.
    - Valproate has enhanced utility in patients with mood disorders, bipolar disorder.

#4) dissociative ketamine infusion
- If all else fails (steps #1-3), then another option is a dissociative-dose ketamine infusion (e.g., 1-5 mg/kg/hour) ([33068459](https://pubmed.ncbi.nlm.nih.gov/33068459)). This may be necessary for patients with profound hypotension, which limits the ability to give sedatives (e.g., propofol, alpha-2 agonists, or phenobarbital).
- After the patient is fully dissociated with ketamine, other sedatives and analgesics should be discontinued.

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**propofol**

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# benefits
- Rapid onset and offset, facilitating neurologic evaluation and extubation.
- Antiepileptic properties.
- Neuroprotective properties, including reduction of intracranial pressure.
- Does not seem to elicit tolerance or withdrawal.
- Suppresses respiration – which can be helpful among ventilated patients to reduce ventilator dysynchrony.

# drawbacks & contraindications
- Ongoing propofol infusions cannot be used in nonintubated patients (due to respiratory suppression).
  - (This is not referring to conscious sedation for procedures, where propofol can be used for short periods with intense monitoring.)
  - Propofol is potentially contraindicated in pancreatitis.
- **Hypertriglyceridemia**
  - Triglyceride levels should be monitored every 48 hours among patients on propofol infusions.
  - If triglyceride levels are gradually creeping up, try reducing the propofol dose.
  - If the triglyceride level is >500-800 mg/dl, propofol needs to be stopped ([32844730](https://pubmed.ncbi.nlm.nih.gov/32844730)). However, some institutions have recently started tolerating triglyceride levels up to 1,000 mg/dl, before stopping propofol ([33068459](https://pubmed.ncbi.nlm.nih.gov/33068459)).
  - (Note: Green urine due to propofol does not correlate with propofol infusion syndrome, nor is this an indication to stop the propofol.)
- Hypotension is a relative contraindication. This is generally managed by combining propofol with a low-dose vasopressor infusion (e.g., phenylephrine or norepinephrine), to counterbalance vasodilation due to the propofol.

# typical role in ICU sedation
- Propofol is a front-line sedative agent (alongside dexmedetomidine).
  - Especially useful for:
    - Patients who will require long-term intubation (since it doesn’t lead to tolerance or withdrawal).
    - Status epilepticus or seizure risk (e.g., alcohol withdrawal).

# dosing
- Long-term use of high doses may cause propofol infusion syndrome. This may be avoided by using doses <80 mcg/kg/min (<5 mg/kg/hr), by providing enteral nutrition, and by following serial triglyceride levels q48hr with discontinuation of propofol if the patient develops significant hypertriglyceridemia.
- Maintenance propofol infusions are ideally run at ~0.5-0.6 mg/kg/min (0.3 mg/kg/hr). Using higher doses increases the likelihood that propofol will increase the triglyceride level and need to be discontinued entirely.

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**dexmedetomidine**

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#1 benefits
- Doesn't suppress respiration:
  - Can be used in patients who aren't intubated (e.g., on BiPAP).
  - Can be used to bridge patients through the entire extubation process (i.e., dexmedetomidine doesn't need to be stopped prior to extubation).
- Titratable infusion, which can be discontinued easily.
- Patients often remain arousable while on dexmedetomidine (so this may be used in situations requiring frequent neurologic examinations).

#2 drawbacks & contraindications
- Hypotension & bradycardia (sympatholysis)
  - May cause bradycardia and hypotension (especially when bolused).
  - Dexmedetomidine is contraindicated in patients with heart block, bradycardia, or severe hypotension. (However, this property can occasionally be useful in patients with tachycardia.)
- Prolonged uninterrupted use (>3-5 days) may cause tolerance and subsequent withdrawal after dexmedetomidine is discontinued. There is little evidence regarding long-term use of dexmedetomidine, so it is hard to know exactly how common this is. Using lower doses of dexmedetomidine (e.g., 0.8 mcg/kg/hr or less) might help avoid withdrawal. ([32844730](https://pubmed.ncbi.nlm.nih.gov/32844730/))
- Dexmedetomidine is often unable to achieve very deep levels of sedation. Although deep sedation isn't usually preferred among ICU patients, it may be desirable in some situations (e.g., patients undergoing intubated prone ventilation).
- (Previously dexmedetomidine's popularity was limited by cost, but it is currently generic and this no longer seems to be an issue.)

#3 typical role in ICU sedation
- Front-line sedative agent (alongside propofol).
- Especially useful for:
  - Sedation during the extubation period.
  - Sedation of nonintubated patients (e.g., BiPAP).
  - Management of nocturnal agitation (may promote physiological sleep and reduce delirium). ([29498534](https://pubmed.ncbi.nlm.nih.gov/29498534/))

#4 dosing
- Boluses are not recommended, as they may cause severe bradycardia and hypotension. Rather than using a loading bolus, it may be safer to start at a relatively high infusion rate (e.g., 1-1.4 mcg/kg/hr), and then titrate the dose downward over 30-60 minutes as the medication takes effect.
- Infusion rate at 0-1.4 mcg/kg/hr.
- Ideally try to down-titrate (or stop) dexmedetomidine during the day, with subsequent up-titration at night:
  - Stopping dexmedetomidine during the day may help avoid tolerance and withdrawal.
  - Use of dexmedetomidine during the night may promote restorative sleep and help reset the circadian rhythm.
- Patients on dexmedetomidine continuously for >3-5 days may be transitioned to oral clonidine or guanfacine to avoid withdrawal symptoms (more on this below: [oral alpha-2 agonists](#oral_alpha-2_agonists)).

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### ketamine
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#4b dosing for partial dissociation

- Start at a low infusion of ~0.1 mg/kg. This should provide analgesia without any psychotomimetic side-effects.
- Gradually up-titrate ketamine with careful observation:
  - If up-titration causes agitation or anxiety, then decrease the infusion back to ~0.1-0.2 mg/kg.
  - If up-titration causes beneficial sedation, then continue the ketamine infusion.
- An infusion rate of ~0.3-0.5 mg/kg ketamine may provide useful analgesia and sedation in many patients.
- Co-administration of propofol or an alpha-1 agonist (e.g., dexmedetomidine, clonidine, or guanfacine) may tend to avoid ketamine-induced dysphoria, thereby increasing the utility of moderate ketamine infusions.
- An alternative strategy is to bolus the patient with 0.3 mg/kg ketamine. This will often push the patient slightly into the sub-dissociative range. This can be used as a test dose to determine how the patient responds to sub-dissociative ketamine. If the response is favorable (e.g., sedation and comfort), this suggests that the patient may respond well to an intermediate-dose ketamine infusion.

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**Butyrophenones, haloperidol & droperidol**

- Hemodynamically stable agents.
- Widely available and convenient for bolus dosing and rapid up-titration (especially haloperidol).
- Do not suppress respiration (allowing them to be used for nonintubated patients).

#2 drawbacks & contraindications

- QTc prolongation and Torsade de Pointes can occur (but this is exceedingly rare at the doses which are currently used).
- Extrapyramidal symptoms can occur:
  - These agents are contraindicated in patients with Parkinson’s disease.
  - Butyrophenones can cause dystonia or akathisia (disturbing restlessness). This generally isn’t a major concern, but is important to identify if it occurs. Akathisia must not be treated with escalating doses of antipsychotic agents.
  - Chronic, high-dose use may lead to tardive dyskinesia.
  - Neuroleptic malignant syndrome can occur (rarely).

#3 typical role in ICU sedation

- Front-line agent for acute management of agitated delirium.
- Generally used in an as-needed (PRN) fashion, for breakthrough agitation.

#4 dosing

**Haloperidol**

- Typically 2-5 mg IV, depending on level of arousal and agitation. Higher doses (e.g., 10 mg IV) may be used for dangerous agitation – but avoid these in elderly patients if possible.
- May be given IV or IM. In the ICU, it will typically be given intravenously, with an onset of action of 10-15 minutes.
- There is no clear “maximal dose” of haloperidol. Historically, massive doses were used with reasonable safety (e.g., >200 mg/day for up to two weeks). Given the potential for high doses of haloperidol to cause QT prolongation and extrapyramidal side effects, it’s probably ideal to use much lower doses than that. Addition of scheduled atypical antipsychotics may reduce the requirement for high doses of haloperidol.

**Droperidol**

- Droperidol is generally twice as potent as haloperidol – so half as much droperidol is needed when compared to the haloperidol doses listed above.

**Intravenous benzodiazepines – midazolam & lorazepam**

#1 benefits

- Hemodynamically stable.
- Antiepileptic properties.

#2 drawbacks & contraindications

- Perhaps the most deleterious sedative agent, acting as a risk factor for the development of post-traumatic stress disorder (PTSD).
- Tendency to increase the duration of mechanical ventilation (when compared to dexmedetomidine or propofol).
- May cause paradoxical agitation (potentially leading to a vicious spiral of increased benzodiazepine use, leading to obtundation).
- Continuous use may lead to tolerance, with subsequent withdrawal.
- Lorazepam infusions tend to cause propylene glycol intoxication.
- Midazolam may accumulate over time in adipose tissue, especially in patients with renal or hepatic dysfunction or due to various drug drug interactions.

#3 typical role in ICU sedation

- Usually benzodiazepines are a sedative of last resort.
- The practice of bolusing patients with PRN lorazepam at night should be avoided like the plague. This will often work in the short-term, but lorazepam will actually worsen delirium and agitation eventually.
- If a medication bolus is required to treat agitation, consider using haloperidol or up-titrating of other medications (e.g., propofol).
- Benzodiazepines are a trap.
- Benzodiazepines do have niche roles in a few situations:
  - Sedative of choice for intoxication, especially with sympathomimetics (due to muscle-relaxant and antiseizure properties).
  - Patients with profound hypotension (who are too unstable to receive propofol or dexmedetomidine). However, ketamine may be more useful in this situation.
- Benzodiazepines may be used for alcohol withdrawal (although phenobarbital is probably better).
#4 dosing

- It's generally best to use PRN lorazepam boluses, rather than a continuous infusion. Infusions tend to accumulate and lead to oversedation.
- Midazolam takes effect more rapidly, making it preferable for acute agitation.
- Typical dosing regimen:
  - Midazolam: 2-5 mg IV q15-30 min PRN
  - Lorazepam: 1-4 mg IV q30-60 min PRN

## Oral alpha-2 agonists

### #1 benefits

- Helps calm patients without causing delirium or obtundation (similar to dexmedetomidine).
- Doesn't suppress respiration.
- Clonidine provides some adjunctive analgesia.
- Facilitates withdrawal of opioids.

### #2 drawbacks & contraindications

- May cause bradycardia and hypotension (clonidine more so than guanfacine).
- Abrupt discontinuation can cause withdrawal (clonidine more so than guanfacine).
- Available only as oral agents in the United States.

### #3 typical role(s) in ICU sedation

1. Step-down agent, following a transition from IV dexmedetomidine.
2. May be used as an adjunctive agent for sedation (guanfacine) or analgesedation (clonidine).
3. May be used at night to promote sleep.
4. May be used to control hypertension and tachycardia (with sedation being a secondary bonus).

### #4 dosing

**Clonidine**

- **Sedation:** De novo: Start 0.1-0.2 mg q6hr, may up-titr the to 0.5 mg q6hr if needed. (https://pubmed.ncbi.nlm.nih.gov/25809176/)
  
  Transition from dexmedetomidine: Start 0.2-0.3 mg q6hr, may up-titr to 0.5 mg q6hr if needed. (https://pubmed.ncbi.nlm.nih.gov/25809176/)
  
- **Insomnia:** Start 0.1-0.2 mg QHS, may up-titr to 0.4 mg QHS.
  
- **Opioid withdrawal:** Most studies have used up to ~0.6-1.2 mg/day in divided doses, titrated against symptoms (27140827). However, with ICU-level monitoring higher doses may be reasonable (e.g. ~2 mg/day in divided doses) (18709354).

**Guanfacine**

- For continuous sedation, may start at a dose of 0.5 mg BID, with escalation to 1 mg TID.
- May be given once daily, four hours before sleep (1-2 mg). This will maximize sedation at night, while still providing some residual sedation during the day (29619866).
- One RCT involving quetiapine found benefit (infographic below).

More on alpha-2 agonists here (https://emcrit.org/pulmcrit/ketadex/).
QTc prolongation can occur with quetiapine to a slight extent. Alternatively, olanzapine does not cause Torsade de Pointes (more on this [here](https://emcrit.org/pulmcrit/intravenous-olanzapine-haloperidol/)).

**#3 typical role in ICU sedation**
- (1) Adjunctive sedation on the ventilator.
- (2) Quetiapine administration at night, to promote sleep.
- (3) Treatment of agitated delirium.

**#4 dosing**

**Quetiapine**
- For delirium, typically start at 50 mg BID and then titrate upwards. Starting at a higher dose could be reasonable for an intubated patient with severe agitation.
- For patients with nocturnal agitation and/or insomnia, may use QHS dose only.
- For adjunctive sedation on the ventilator, may use a higher dose at night (e.g., 100 mg before sleep plus 50 mg in the morning). This may help preserve circadian rhythms.
- Occasionally, for the impossible-to-sedate patient, very high doses may be used (e.g., 200-400 mg BID). This may be useful in patients with a history of substance abuse who fail to respond to standard sedative regimens.

**Olanzapine**
- 5-20 mg/day, ideally prior to sleep (to encourage a normal circadian rhythm). The half-life of olanzapine is long enough that it will continue to exert some sedative effect during the day as well, but this maximizes sedation at night.

More about atypical antipsychotics in the delirium section [here](https://emcrit.org/ibcc/delirium/#antipsychotics).

**melatonin**

**#1 benefits**
- May preserve sleep and circadian rhythms.
- May provide a very mild sedative effect (which reduces the required dose of other sedatives) ([25969139](https://pubmed.ncbi.nlm.nih.gov/25969139/)).
- Safe and inexpensive.

**#2 drawbacks & contraindications**
- Quality control of some over-the-counter melatonin formulations is dubious. (However, the therapeutic window is very wide, so if the patient receives slightly more or less than the intended dose it probably won’t really matter.)

**#3 typical role in ICU sedation**
- Adjunctive agent to prevent delirium and promote sleep.

**#4 dosing**
- 5-10 mg PO before sleep ([33048904](https://pubmed.ncbi.nlm.nih.gov/33048904/)).

**phenobarbital**

**#1 benefits**
- Treats alcohol or benzodiazepine withdrawal.
- It has anti-epileptic properties.
- Its pharmacology is predictable and drug levels can be measured (if necessary).
- It does not appear to cause paradoxical agitation (unlike benzodiazepines).
- Oral bioavailability is close to 100% among patients with a functional gastrointestinal tract.

**#2 drawbacks & contraindications**
- Long half-life (~3 days). Thus, if the patient is overly sedated with phenobarbital, resolution may be delayed.
- Contraindicated in advanced cirrhosis (patients with borderline hepatic encephalopathy are at increased risk of oversedation).
- Contraindicated in patients with active neurologic problems, who may experience waxing and waning mental status.

**#3 typical role in ICU sedation**
- (1) Useful for patients with a definite history of significant and active alcoholism.
  - i) Phenobarbital will help prevent alcohol withdrawal.
  - ii) Phenobarbital will provide useful basal sedation while on the ventilator.
- (2) Occasionally phenobarbital may be useful to provide basal sedation in a very difficult-to-sedate patient.

**#4 dosing**
- **Loading dose**
  - Typically, 10-15 mg/kg.
  - May be provided as a single dose among intubated, hemodynamically stable patients (although usually no more than 10 mg/kg).
  - May be provided in multiple divided doses if there are concerns regarding hypotension or oversedation.
- **Maintenance dose**
  - 1-2 mg/kg PO or IV daily may be considered among patients on prolonged mechanical ventilation.
  - For patients on shorter-term ventilation (e.g., <1 week), maintenance doses may not be needed.
  - Keep track of the amount of phenobarbital administered and avoid loading with >20 mg/kg. Phenobarbital will accumulate, so repeating PRN doses too often may lead to toxicity.
  - Therapeutic drug monitoring
    - For patients receiving maintenance doses of phenobarbital, occasionally measuring levels might enhance safety.
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- The optimal level isn't well defined. However, a level of roughly 15-25 μg/mL (64-107 μM/L) could be a reasonable initial target. In comparison, the therapeutic phenobarbital level for management of epilepsy is 15-40 μg/mL (64-172 μM/L).

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# Benefits

- Minimal cardiac or respiratory effects (allowing it to be used regardless of intubation status).
- No issues with tolerance or withdrawal.
- Anti-epileptic properties.
- Theoretical and case series evidence suggest that valproate might be helpful to reverse agitated delirium ([32273047](https://pubmed.ncbi.nlm.nih.gov/32273047)). Particularly, it may be effective in agitated delirium refractory to other therapies (e.g., antipsychotics).

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#2 Drawbacks & Contraindications

- Contraindications
  - Hepatic dysfunction
  - Urea cycle disorder or mitochondrial disorders that cause hyperammonemia.
  - Potential pregnancy
  - Pancreatitis
  - Thrombocytopenia (valproic acid may cause mild thrombocytopenia in ~1/3 of patients)
- Drawbacks
  - Valproate often takes a couple days to cause improvement.
  - Periodic monitoring of drug levels, liver function tests, and ammonia is advisable.

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#3 Typical Role in ICU Sedation

- Not generally used as a sedative agent. Indeed, valproic acid generally doesn't cause a substantial reduction in the level of consciousness, so it's not really a sedative ([32912027](https://pubmed.ncbi.nlm.nih.gov/32912027)).
- Valproic acid may be useful as a treatment for agitated delirium, especially:
  - Refractory agitation/delirium which has failed to respond well to other agents.
  - Patients with a history of borderline personality.
  - Patients with a history of traumatic brain injury ([28833346](https://pubmed.ncbi.nlm.nih.gov/28833346)).

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#4a Basic Pharmacology

- Valproate has a bioavailability of ~90%, so it may be given either enterally or intravenously.
- Extended-release formulations exist, but for the purpose of critical care the immediate-release formulations are more reliably and rapidly absorbed.
- At moderate blood levels (e.g., <75 mg/L or <525 μM/L), valproate is almost entirely bound to albumin (with a relatively low free valproic acid level). With increasing valproate levels, an increasing fraction of the drug is present in its free form – so the biologically effective level of valproate will increase markedly.
- Levels of free valproic acid may be increased in the following situations: ([28833346](https://pubmed.ncbi.nlm.nih.gov/28833346)).
  - Hypoalbuminemia
  - Uremia
  - Medications which displace valproate from albumin (e.g., aspirin, ibuprofen, propofol, clevidipine, and intravenous fat emulsion)
- Valproate is cleared by the liver, with a half-life of ~12 hours.

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#4b Dosing

- Consider loading with ~15 mg/kg q12h x 2 doses (for a total of 30 mg/kg loading dose) ([28833346](https://pubmed.ncbi.nlm.nih.gov/28833346)).
- The initial maintenance dose is ~10 mg/kg q12 hours (for a total of 20 mg/kg daily) ([28833346](https://pubmed.ncbi.nlm.nih.gov/28833346)).
- The maintenance dose may be gradually up-titrated to effect as needed, with a maximal dose of 30 mg/kg q12 hours (60 mg/kg daily).
- The half-life of valproic acid is ~12 hours, so drug levels won't reach steady state until a few days after a dose change. The dose can be escalated relatively rapidly (e.g., on a daily basis), but be aware that levels will continue to rise for a few days following dose escalation!
- After patients are improving and delirium has lifted, valproate may be gradually weaned off. Efforts should be made to avoid prolonged administration (especially discontinuation prior to discharge from the hospital).

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#4c Monitoring

- Valproic acid level monitoring
  - Periodic monitoring of valproic acid may be helpful if the dose is in question (e.g., patients on higher doses, obesity, questionable oral absorption, or drug-drug interactions) ([28833346](https://pubmed.ncbi.nlm.nih.gov/28833346)).
  - Valproate should always be measured as a trough level immediately before a dose.
  - The therapeutic valproic acid level for bipolar disorder is 50-125 mg/L (350-675 μM/L). However, the optimal dose range for critically ill patients remains unclear. Among critically ill patients with an increased fraction of free valproic acid, a somewhat lower total valproate level might be appropriate.
- Ammonia monitoring
  - Ammonia levels are often moderately elevated among patients on valproic acid (e.g., in the range of ~50-100 ug/dL). Mild ammonia elevation doesn't necessarily mandate discontinuation of valproate. Administration of oral L-carnitine may be considered for these patients, to prevent worsening hyperammonemia.
  - Ammonia levels don't need to be checked unless there is a concern for encephalopathy.
  - Elevation of transaminases may occur. Thus, periodic monitoring of liver function tests may be reasonable.

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# Benefits

- Hydroxyzine is an antihistamine sedative with a relatively benign side-effect profile (minimal cardiac or respiratory effects).
Hydroxyzine has weak anti-emetic properties. Its use has been validated in a RCT of critically ill patients.\(^1\) \(^2\)\(^3\)

### #2 drawbacks & contraindications

- Hydroxyzine may increase the risk of delirium (based on its anticholinergic effects).

### #3 typical role in ICU sedation

- Not commonly used.
- Could be considered for refractory agitation or in drug shortages.

### #4 dosing

- A dose of ~100 mg PO q8hr has been utilized as the primary sedative for intubated patients, up to a maximal dose of ~400 mg/day.\(^1\)\(^2\)\(^3\)\(^4\) However, when using hydroxyzine as an adjunctive sedative agent, a somewhat lower dose might be appropriate.

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**oral benzodiazepines**

### #1 benefits

- Hemodynamic stability.
- Reduce seizure threshold.

### #2 drawbacks & contraindications

- Perhaps the most deliriogenic sedative agent. It has a tendency to increase duration of mechanical ventilation.
- Continuous use may lead to tolerance and subsequent withdrawal.

### #3 typical role in ICU sedation

- Oral benzodiazepines are very rarely used (aside from a patient who prior to admission was chronically maintained on oral benzodiazepines).
- These might be considered in cases of medication shortage.

### #4 dosing

- Lorazepam 1-4 mg PO q6hr was validated in one RCT of oral sedation in the ICU.\(^1\)\(^2\)\(^3\)\(^4\)
- Benzodiazepines with longer half-lives could be more useful as basal sedatives among intubated patients, since they could be given once daily prior to sleep (leading to higher drug levels at night, which would support circadian rhythms). Commonly available options may include: Temazepam (half-life ~11 hours), ~15-60 mg QHS. Alprazolam (half-life ~12 hours), ~0.5-2 mg QHS. Clonazepam (half-life ~34 hours), ~0.5-2 mg QHS.

**Going further:**

- Related
  - Fentanyl infusions and the role of pain-dose ketamine
  - Safety of clonazepam re: QTc
  - Dexmedetomidine for extubating the agitated patient

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**summary**
The over-arching goal of sedation in the ICU is to render the patient comfortable with a minimal amount of medication exposure and toxicity. This involves continually titrating the medication regimen, with use of the lowest doses possible.

Avoid the use of high-dose, continuous dexmedetomidine infusions for more than ~3-5 days. Patients may develop tolerance and subsequent withdrawal.
Avoid using higher dose propofol infusions for prolonged periods of time (e.g., >50 mcg/kg/min or >3 mcg/kg/hr). Using high doses of propofol may lead to hypertriglyceridemia, necessitating its complete discontinuation.

Avoid benzodiazepines whenever possible. There isn’t a ton of Level-I evidence regarding ICU sedation, but all available evidence indicates that benzodiazepines are inferior to propofol or alpha-2 agonists (e.g., dexmedetomidine).

Going further:

- Sedation in the ICU
- Analgesia
- Delirium
- References

References:


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.