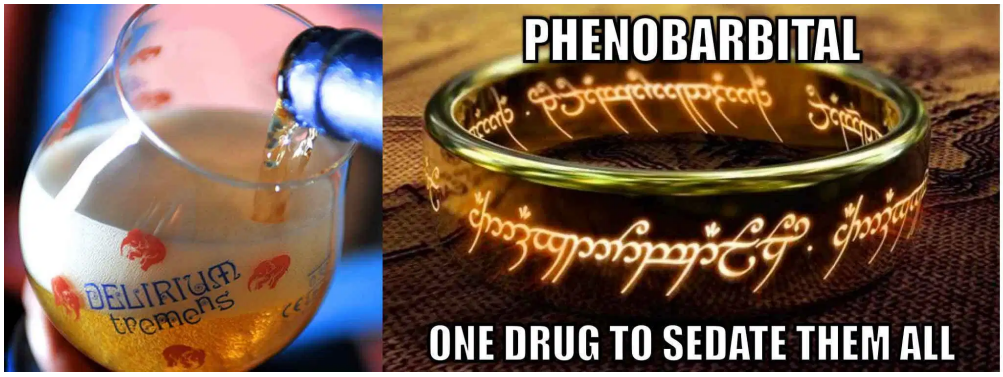
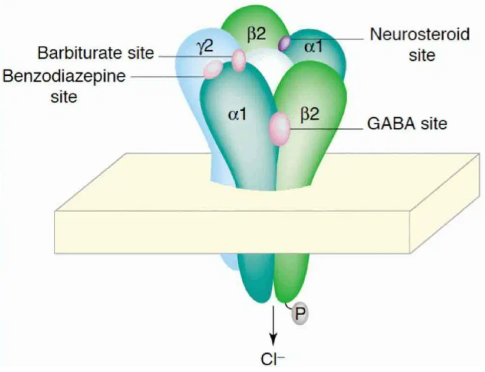
The Internet Book of Critical Care

Alcohol withdrawal

November 5, 2016 by **Josh Farkas**





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preamble & disclaimer

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There are numerous (perhaps *innumerable*) reasonable ways to treat alcohol withdrawal. Prior to the ~1970s, barbiturates were front-line agents. Following a push by pharma to market newly developed benzodiazepines, this shifted to benzodiazepines. This transition wasn't based upon any *evidence* that benzodiazepines deserved to be front-line agents, but rather perhaps the perception that benzodiazepines were newer and therefore *must* be better. Currently, the pendulum is swinging back to barbiturates. Those lacking a historical perspective will view benzodiazepines as conventional front-line therapy, but in the larger context of medical history the use of benzodiazepines for alcohol withdrawal may wind up having been a mistake.

This chapter presents a barbiturate-monotherapy strategy for most patients. There is no proof that this is superior to more complex strategies incorporating both benzodiazepines and barbiturates. Most patients could probably be treated just fine by a variety of different strategies. A barbiturate monotherapy approach is emphasized due to the power, simplicity, and versatility of this approach.

diagnosis

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EtOH history

- The most important component of the diagnosis.
- Many charts may list "alcoholism" years after the patient has quit drinking. Whenever possible, documentation in the electronic medical record should be verified.
  - It may be necessary to get collateral information from friends or family (even if this means calling them in the middle of the night).
- Does the patient withdraw when they stop drinking?
  - A history of alcohol withdrawal seizures or delirium tremens is concerning.
  - If the patient has a history of discontinuing alcohol without withdrawal, that's reassuring.

timing

- Second most important aspect of the diagnosis.
- Alcohol withdrawal seizures usually occur within 1-2 days of alcohol cessation. Delirium tremens usually occurs slightly later (beginning within a window of ~2-4 days after alcohol cessation).
- Delirium starting >4 days into the hospital course is more likely to have another etiology (e.g. sepsis, polypharmacy, sleep deprivation).
  - With increasing time since the last drink, it's increasingly unlikely that the patient has alcohol withdrawal.

clinical features of delirium tremens

- Typical features of delirium tremens are as follows:
  - Agitated delirium with hypertension, tachycardia, and diaphoresis.
  - Diffuse tremor
  - Hyperreflexia
  - Hallucinations
  - Low-grade fever
  - Nausea, vomiting

consider other possibilities

- Delirium tremens is a diagnosis of exclusion, so consider other causes of agitated delirium (hypoglycemia, infection, etc.).
  - For differential diagnosis & evaluation, see the chapter on ***delirium*** (https://emcrit.org/ibcc/delirium/) .
- Some clues that the patient *doesn't* have delirium tremens:

- Patient becomes somnolent following moderate-low doses of benzodiazepine (patients with real delirium tremens are benzodiazepine-resistant).
- Patient remains agitated despite >15 mg/kg phenobarbital (more on this below).
- Delerium without other features of delirium tremens (e.g. absence of hypertension, absence of tremors).

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understanding phenobarbital pharmacology

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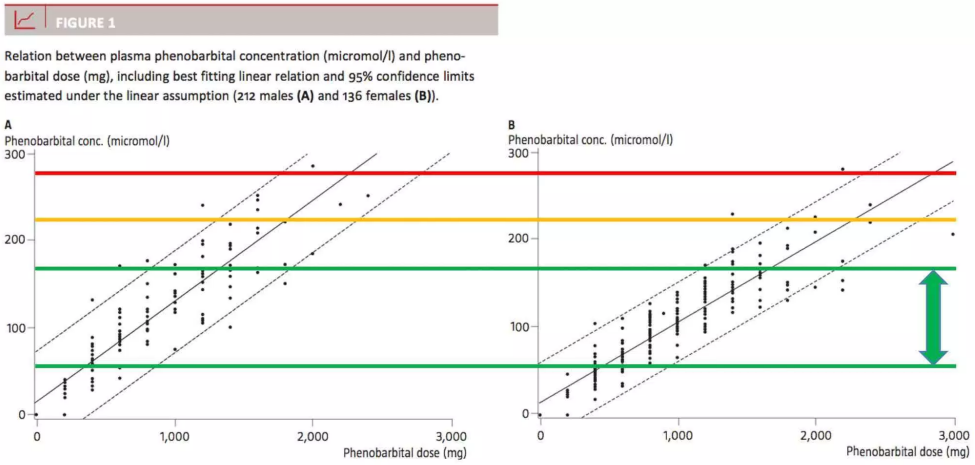
Phenobarbital has a uniquely simple pharmacology, which is well suited to treat alcohol withdrawal.

half-life

- Perhaps the most notable aspect of phenobarbital is its long half-life (~3-4 days).
- Doses that are administered over the course of 1-2 days will *accumulate*. The goal of giving additional doses is to gradually *increase* the total body phenobarbital level to a therapeutic concentration.
  - This is *different* from most drugs (e.g. lorazepam), where repeated doses are needed to maintain a stable drug level.

relationship of *dose* to *drug levels*



Relationship between cumulative phenobarbital dose and plasma phenobarbital concentration among patients treated for alcohol withdrawal. Green lines indicate the therapeutic range of phenobarbital concentration for *epilepsy* (**64-172 uM/L = 15-40 ug/ml**), the orange line indicates the level at which mild signs of toxicity are usually noted such as atatxia and nystagmus (**215 uM/L = 50 ug/ml**) and the red line indicates the lowest level which has been associated with stupor or coma (**>280 uM/L = 65 ug/ml**). Please note however that the ideal phenobarbital concentration for the treatment of alcohol withdrawal remains unclear. If the patient's weights were taken into account, these relationships would be even more tightly linear. Note that based on this data, one gram of phenobarbital would achieve a reasonable phenobarbital level in nearly all patients.

Tangmose et al 2010 PMID 20682131

- The drug level is a *linear* function of the amount of phenobarbital administered.
- A predictable linear relationship allows weight-based doses to reproducibly achieve therapeutic drug levels.
- The volume of distribution is ~0.65 L/kg (7068937 (https://www.ncbi.nlm.nih.gov/pubmed/7068937), 3973064 (https://www.ncbi.nlm.nih.gov/pubmed/3973064)). This allows the serum level to be estimated from the administered dose using the formula below. Some limitations of this formula:
  - The cumulative dose should be administered within <48 hours (if administered over a longer time, then significant metabolism may occur).
  - The impact of severe obesity remains unclear.

Prediction of phenobarbital level from cumulative dose

Conventional units (USA):

Phenobarbital level in ug/ml = 1.5(Dose in mg/kg)

SI units:

Phenobarbital level in uM/L = 6.6(Dose in mg/kg)

-Internet Book of Critical Care, by @PulmCrit

(https://emcrit.org/wp-content/uploads/2016/11/phenopk33.svg) **interpretation of drug levels**

interpretation of phenobarbital levels

	Conventional Units (ug/ml)	SI units (uM/L)
Therapeutic Range, Epilepsy	15-40 ug/mL	64-172 uM/L
Mild signs of toxicity usually noted (e.g. ataxia, nystagmus)	>50 ug/mL	>215 uM/L
Severe toxicity can occur (e.g. stupor/coma)	>65 ug/mL	>280 uM/L
Therapeutic range, Monotherapy for EtOH withdrawal	~10-40 ug/mL (??)	~43-172 uM/L (??)

This table is only intended to provide a rough concept of phenobarbital levels. The optimal phenobarbital levels in treatment of alcohol withdrawal remains unclear. Ultimately, doses need to be titrated based on clinical response. For example, patients with alcohol withdrawal will often have an excellent clinical response at phenobarbital levels which are *below* the traditional therapeutic range for epilepsy.

-The Internet Book of Critical Care, by @PulmCrit

(https://emcrit.org/wp-content/uploads/2016/11/phenolevels.svg)

- Phenobarbital levels may be roughly interpreted as shown above.
- One important caveat is that phenobarbital is synergistic with benzodiazepine, so toxicity could occur at *lower* phenobarbital levels in the presence of benzodiazepine.
- These pharmacokinetics demonstrate why *it is impossible for a dose of 10 mg/kg phenobarbital to cause a toxic phenobarbital level*.
  - 10 mg/kg will yield a drug level of ~15 ug/mL, which is more than *four times lower* than levels which will cause severe toxicity.
  - Please note that 10 mg/kg phenobarbital could tip over a patient who is on the borderline of obtundation due to *other* causes (e.g. benzodiazepines, head trauma, etc.). However, 10 mg/kg phenobarbital *alone* given in a patient with uncomplicated alcohol withdrawal should be very safe.

routes of administration

- Phenobarbital can be given intravenously, intramuscularly, or orally. All routes achieve ~100% bioavailability.
- IV administration is preferred in the critical care arena, because this allows for more rapid achievement of peak drug levels. Rapid absorption decreases the risk of *dose stacking* (administering multiple doses before the first dose has had time to act fully, leading to excessive dosing). When given intravenously, the drug distributes within <30 minutes. This allows for PRN doses to be given q30 minutes.
- Oral administration works fine, but absorption is slower. In order to avoid dose stacking, PRN doses must be administered more slowly (q60 minutes).
  - Theoretically a risk of dose stacking could exist in patients with gastroparesis or related gastrointestinal pathologies.
- Intramuscular administration is another effective option.

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advantages of phenobarbital over benzodiazepines

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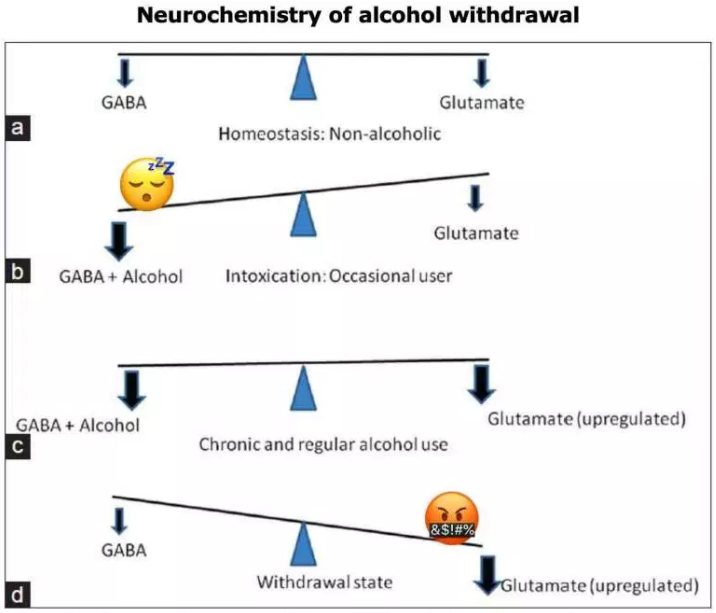
There are numerous reasons why phenobarbital is a safer and more reliable therapy than benzodiazepines:

1) Barbiturates have uniform efficacy, whereas benzodiazepines may fail to work.



Alcohol withdrawal involves *deficient* GABA activity and *excessive* glutamate activity. Benzodiazepines augment GABA activity, but this is only part of the problem. Phenobarbital augments GABA activity and *also* inhibits glutamate signaling (via the AMPA-type glutamate receptor).
Kattimani S 2013 PMID 25013309

- It's well established that a subset of patients will *fail* to respond to benzodiazepines, yet subsequently will be treated successfully with barbiturates. This occurs for the following reasons:
  - (1) Benzodiazepines depend on the presence of endogenous presynaptic GABA molecules (so benzodiazepines won't work alone). Alternatively, phenobarbital is able to *directly* open GABA receptors (without any help from presynaptic GABA).
  - (2) Benzodiazepines work only on GABA receptors, which is only *part* of the problem in alcohol withdrawal. In contrast, barbiturates also work on the glutamate system (down-regulating excitatory glutamate signaling by acting on the AMPA- and kainate-type glutamate receptors)(30876654 (https://www.ncbi.nlm.nih.gov/pubmed/30876654)).
- There don't appear to be patients who fail to respond to barbiturates which are dosed appropriately.

2) Benzodiazepines may cause paradoxical agitation and delirium. Barbiturates don't cause paradoxical reactions and seem to cause less delirium.

- Paradoxical agitation
  - Benzodiazepines can occasionally cause *paradoxical agitation*. This is uncommon, but it is more frequently seen in patients with alcoholism. Paradoxical agitation can be enormously problematic when treating alcohol withdrawal, because this will *amplify* the

agitation. If further benzodiazepines are given, this may lead rapidly to a vicious spiral of escalating benzodiazepine doses which precipitates intubation. More on paradoxical agitation here (*link* (https://emcrit.org/pulmcrit/recognizing-and-managing-paradoxical-reactions-from-benzodiazepines-propofol/)).

- Barbiturates don't appear to cause paradoxical agitation. This might reflect a more diffuse and *balanced* action of barbiturates on the brain, which doesn't leave some parts of the brain disinhibited.

- Delirium
  - Benzodiazepines are notorious for causing delirium among critically ill patients. The fact that high-dose benzodiazepines can *cause* delirium in patients with alcohol has been shown (e.g. one study used *flumazenil* to combat benzodiazepine-induced delirium!) (24619543 (https://www.ncbi.nlm.nih.gov/pubmed/24619543)).
  - Any psychoactive drug can cause delirium, so barbiturates may potentially do this as well. However, delirium seems to be less of an issue with barbiturates (this could also relate to the *dosage* of phenobarbital used, with judicious avoidance of toxic doses).

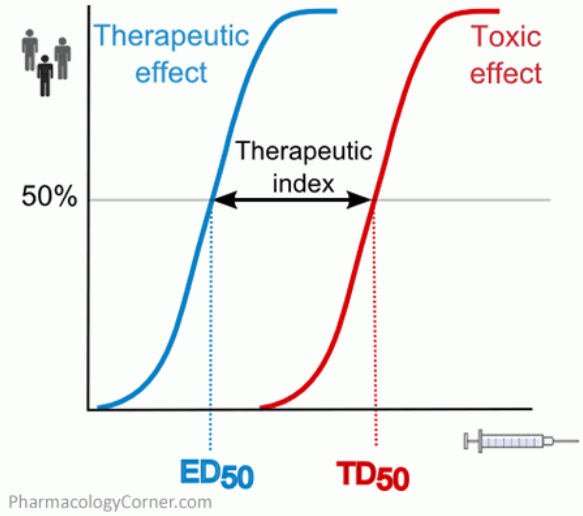
3) Phenobarbital has more predictable *pharmacokinetics* than benzodiazepines

- Once the pharmacokinetics of phenobarbital are understood, it's easy to estimate the phenobarbital level and efficacy within a specific patient. Alternatively, benzodiazepine pharmacokinetics are much more complex. This can make it difficult to determine whether a patient is experiencing excessive or deficient doses of benzodiazepine.
- For example: If a patient received 10 mg of lorazepam in divided doses over the last 12 hours, it's impossible to know how much lorazepam remains in their body. Alternatively, if a patient received 10 mg/kg phenobarbital over the last 12 hours, their phenobarbital level is extremely predictable (~15 ug/ml).

4) Phenobarbital has more predictable *pharmacodynamics* than do benzodiazepines

- The clinical response to benzodiazepines is variable:
  - Most patients will respond well to relatively low doses (e.g. 50-100 mg diazepam).
  - Some patients will require massive doses (e.g. 500 mg diazepam).
  - Some patients will be entirely benzodiazepine-refractory.
- The clinical responsiveness to phenobarbital is more predictable (with a total dose range of roughly 5-25 mg/kg). This dose range is *narrower* than the effective dose range of benzodiazepines (perhaps 50-infinity mg of diazepam).
- Pharmacodynamic predictability can be helpful clinically to determine when alcohol withdrawal has been treated effectively (and thus when it's time to *stop* giving GABAergic medications). More on this below.

5) Phenobarbital has a greater therapeutic index than do benzodiazepines



- When given as monotherapy to a patient who isn't on benzodiazepine and has no other neurologic problems:
  - The *therapeutic* dose of phenobarbital is ~5-25 mg/kg total body weight to achieve a serum level of ~10-40 ug/ml.
  - The *toxic* dose of phenobarbital (the dose required to cause stupor/coma requiring intubation) is >40 mg/kg to achieve a serum level of >65 ug/ml.

- Thus, the dose of phenobarbital required to cause severe harm is really quite high (e.g. >2.5 grams). If phenobarbital is gradually up-titrated and capped at 30 mg/kg, it should be nearly impossible to cause stupor/coma from the phenobarbital itself.
- In contrast, benzodiazepine may have a smaller therapeutic index. The range of therapeutic doses is very broad (see #4), *overlapping* with the toxic dose range.
  - Experience with procedural sedation teaches us that the dose of benzodiazepine required to sedate one person may equal the dose that would push another person into a coma.

6) The prolonged half-life of phenobarbital allows for precise dose-titration and gentle auto-tapering

- The long half-life of phenobarbital is one of its greatest strengths here. It allows for two therapeutic modalities which are largely impossible with benzodiazepines:
  - (a) The total phenobarbital level can be gradually up-titrated over a period of 24-48 hours (with successive PRN doses). This allows for *precise* titration to achieve a patient-specific dose.
  - (b) Once a therapeutic phenobarbital level is reached, this will very gradually *auto-taper* over several days (providing ongoing protection against rebound symptoms).
- This pharmacology stands in stark contrast with that of lorazepam (for example), which is difficult to maintain within a steady therapeutic level. Even if a patient can be rendered perfectly controlled with lorazepam, levels are likely to fall within the next several hours, leading to recrudescent symptoms. As such, patients may be left riding a lorazepam roller-coaster for days.

7) Phenobarbital may be superior for prevention of seizure

- Both benzodiazepines and barbiturates have anti-seizure activity. However, barbiturates may have some advantages over benzodiazepines:
  - (a) Barbiturates in general have more potent anti-epileptic activity than do benzodiazepines (due to a broader range of neurotransmitter effects, as discussed above).
  - (b) Some very weak data suggests that barbiturates may be superior in alcohol withdrawal seizure (18975).
  - (c) For patients who have had a seizure, dosing of phenobarbital is more straight-forward than dosing of a benzodiazepine. As discussed further below (#prevention_of_alcohol_withdrawal), phenobarbital can generally be raised to a therapeutic level for epilepsy (>15 ug/mL). In contrast, the appropriate dose of benzodiazepine to prevent recurrence of an alcohol-withdrawal seizure is largely guesswork.

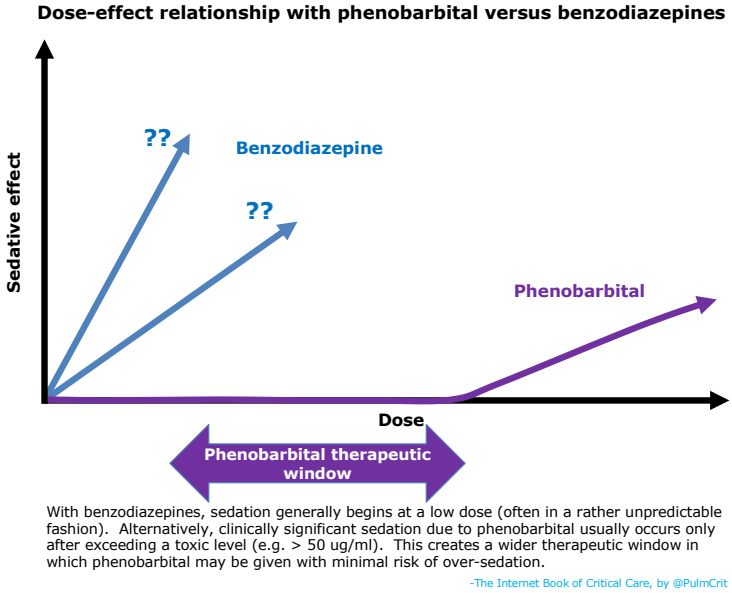
8) Phenobarbital levels can be measured & levels have meaning

- Occasionally, we all encounter a patient where we get a bit lost. Perhaps the patient has been transferred between multiple hospitals or multiple units. It's unclear how much drug they received. They remain agitated – but are they *under*-medicated or *over*-medicated?
- If this occurs with phenobarbital monotherapy, the solution is simple – check a phenobarbital level.
- If this occurs with benzodiazepines, it may be impossible to sort out where you are.

9) Phenobarbital can be administered via all routes

- Phenobarbital can be given intravenously, orally, or intramuscularly. This facilitates seamless transition between different units which may administer phenobarbital via different routes (e.g. a patient might receive IV phenobarbital in the emergency department and later oral phenobarbital on the ward).
- This isn't *unique* (lorazepam or diazepam can also be given by multiple routes). However, it does represent an advantage over some benzodiazepines which are available only orally (e.g. oxazepam or chlordiazepoxide).

10) Phenobarbital has little sedating effect at moderate doses, allowing it to be given prophylactically



(https://emcrit.org/wp-content/uploads/2016/11/phenowindow.svg)

- A dose of 10 mg/kg phenobarbital will achieve a drug level of ~15 ug/ml. This drug level should have little to no sedating effect, allowing it to be given safely to a patient who is *asymptomatic*. This allows a meaningful dose of phenobarbital to be given in a preventative fashion, to prophylax against the development of alcohol withdrawal (more on this below (#prevention_of_alcohol_withdrawal)).
- A similar strategy is much harder to employ with benzodiazepines, because in an asymptomatic patient benzodiazpines may have a sedating effect (figure above).

11) Phenobarbital has no real risk of propylene glycol intoxication

- Phenobarbital, lorazepam, and diazepam are all formulated in propylene glycol. Administration of large quantities of propylene glycol may lead to intoxication (with symptoms including delirium and metabolic acidosis).
- Lorazepam: This has the greatest risk of propylene glycol intoxication, because it wears off over hours and needs to be re-dosed frequently. In particular, giving lorazepam as a continuous infusion very often leads to propylene glycol accumulation.
- Diazepam: Propylene glycol is less common with diazepam, because diazepam's half-life is longer and less re-dosing is required.
- Phenobarbital: This carries no real risk of propylene glycol toxicity, because the total volume of drug required is relatively low (due to its half-life, phenobarbital never needs to be re-dosed).

12) Phenobarbital is widely available and potentially inexpensive

- Phenobarbital is part of the World Health Organization list of *essential medications*. It should be widely available at nearly any hospital.
- Intravenous phenobarbital is *preferred* for critically ill patients (due to faster onset and lower risk of dose-stacking). However, oral phenobarbital will work fine for the vast majority of patients. Oral phenobarbital is extremely inexpensive (e.g. a bottle containing 3.8 grams of phenobarbital costs under $20).

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contraindications to phenobarbital

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contraindications

- (1) Allergy to phenobarbital (seems rare to nonexistent).
- (2) Diagnosis of alcohol withdrawal is unclear.
  - If you're wrong with phenobarbital, it will stick around for a while.
  - The more complex and dynamic the patient is, the greater amount of caution should be exercised with phenobarbital.
  - In situations of diagnostic confusion, it may be safer to wade in gingerly with small doses of IV diazepam (more on this *here* (#benzodiazepines)).
- (3) Drug interactions

- Phenobarbital interacts with a *lot* of medications.
- This is rarely a problem. However, if your patient is on unusual medications (e.g. HIV medications), this may become a consideration.

- (4) Advanced cirrhosis with hepatic encephalopathy
  - These patients can become somnolent and difficult to awaken *solely* due to their underlying hepatic encephalopathy.
  - Perhaps the greatest risk for persistent coma following phenobarbital administration.
  - Would consider this to be nearly an absolute contraindication to phenobarbital.
- (5) Acute intermittent porphyria
- (6) Chronic use of phenobarbital as an antiepileptic agent (such patients may *already* have a therapeutic phenobarbital level)

cautions:

- (1) Patients who have received a considerable dose of benzodiazepine.
  - Phenobarbital will function *synergistically* with benzodiazepines.
  - Phenobarbital can be used here, but start low and go slowly (e.g. 130 mg IV PRN q30-60 minutes).
- (2) Patients on other medications which may suppress respiration (e.g. opioids). Phenobarbital can be used with the following cautions:
  - (a) Start low and go slowly (with small PRN doses).
  - (b) Don't give additional doses of opioids while you are simultaneously giving phenobarbital.
  - (c) Minimize all other sedating drugs as much as possible.
- (3) Patients with a belligerent personality
  - This may encourage aggressive use of PRN medications.

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phenobarbital guideline

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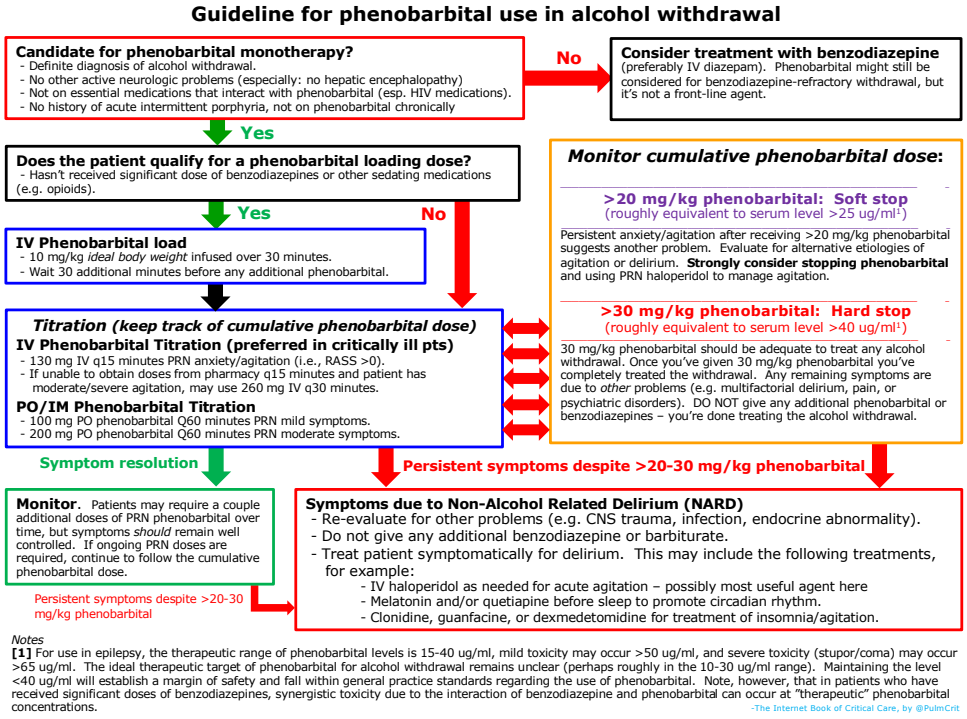
This guideline summarizes key information about phenobarbital:



(https://emcrit.org/ibcc/etoh/) phenobarbital loading dose

- A dose of 10 mg/kg IV has been proven to be safe and to reduce the likelihood of ICU admission (22999778 (https://www.ncbi.nlm.nih.gov/pubmed/22999778)).
- 10 mg/kg will achieve a serum phenobarbital level of ~15 ug/ml.
  - This shouldn't cause significant somnolence *on its own.*

- Phenobarbital can cause synergistic sedation in combination with other drugs (especially benzodiazepines). Therefore, a loading dose *could* theoretically cause excessive sedation in a patient who has received a substantial dose of benzodiazepine.
- Beginning treatment of alcohol withdrawal with a loading dose of phenobarbital *accelerates* the achievement of an adequate serum drug level.
  - You can achieve the same thing with numerous doses of 130-260 mg IV phenobarbital as needed, but it will take longer.

Patients who have received a significant dose of benzodiazepines can be easily transitioned to a phenobarbital monotherapy pathway (without a loading bolus of phenobarbital). Thus, the administration of benzodiazepines doesn't commit the patient to continue benzodiazepine treatment indefinitely. However, this isn't ideal because omission of the loading bolus may delay achievement of therapeutic phenobarbital levels.

-The Internet Book of Critical Care, by @PulmCrit

phenobarbital titration

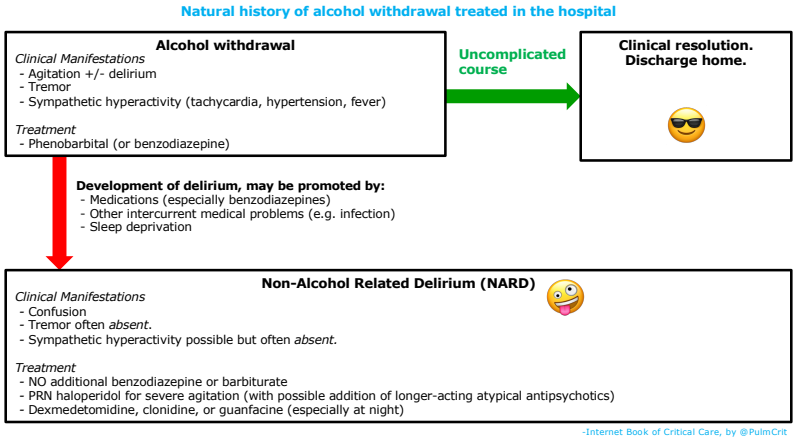
- Successive additional doses of phenobarbital may be given in a PRN fashion.
- The best validated strategy here is to use 130 mg IV q30 minutes to target a RASS score of 0-1 (29925291 (https://www.ncbi.nlm.nih.gov/pubmed/29925291)).
- Safety of the phenobarbital titration is generated by two factors:
  - (1) Doses are provided in a small and incremental fashion – making it very unlikely that the patient would *suddenly* be pushed into a stuporous/comatose state.
  - (2) The total cumulative dose of phenobarbital is limited to 20-30 mg/kg (which, by itself, shouldn't be a large enough dose to cause stupor/coma).

limit phenobarbital dose to 20-30 mg/kg

- The maximal dose of phenobarbital required to treat alcohol is *unclear*.
  - Some authors have suggested that <20 mg/kg should be adequate for all patients (1986421 (https://www.ncbi.nlm.nih.gov/pubmed/1986421) , 30876654 (https://www.ncbi.nlm.nih.gov/pubmed/30876654)).
  - Other studies have reported the use of considerably larger doses (e.g. 29925291 (https://www.ncbi.nlm.nih.gov/pubmed/29925291) , 20682131 (https://www.ncbi.nlm.nih.gov/pubmed/20682131)).
- Currently, 20-30 mg/kg phenobarbital seems like a reasonable stopping point, for the following reasons:
  - A phenobarbital protocol at Massachusetts General Hospital was uniformly effective *without* requiring cumulative doses >20 mg/kg (30876654 (https://www.ncbi.nlm.nih.gov/pubmed/30876654)). This study demonstrated that any residual symptoms unresponsive to such doses of phenobarbital could be safely treated by non-GABA-ergic medications (e.g. haloperidol).
  - 30 mg/kg phenobarbital correlates roughly with ~40 ug/ml serum level, which is the upper limit of the therapeutic range for epilepsy. A limit of 30 mg/kg phenobarbital should keep levels within a range which is established to be generally safe.
- 20 mg/kg phenobarbital is proposed as a "**soft stop**."
  - The *vast majority* of patients with alcohol *should* be treatable with 20 mg/kg phenobarbital (plus other drug classes such as antipsychotics and alpha-agonists PRN).
  - Before exceeding 20 mg/kg, carefully re-evaluate the patient and ensure that symptoms are definitely due to alcohol withdrawal.
  - For patients with a history of severe delirium tremens and refractory seizure, doses of 20-30 mg/kg might be reasonable to maximize the anti-epileptic effects of phenobarbital.
- 30 mg/kg phenobarbital is proposed as a "**hard stop**"

- Essentially all patients with alcohol withdrawal should be treatable with 30 mg/kg phenobarbital (plus other drug classes such as antipsychotics and alpha-agonists PRN).
- Symptoms persisting beyond 30 mg/kg phenobarbital are unlikely due to alcohol withdrawal (they're increasingly likely to be due to non-alcohol-related delirium).

recognize the transition from alcohol withdrawal to Non-Alcohol-Related Delirium (NARD)



(https://emcrit.org/wp-content/uploads/2016/11/nard2.svg)

- Some patients with alcohol withdrawal may evolve into a *non-alcohol-related* delirium state (NARD, figure above).
  - This is well-described among patients treated with benzodiazepine, who will often develop a benzodiazepine-induced delirium. One case series describes treatment of this condition with flumazenil! (24619543 (https://www.ncbi.nlm.nih.gov/pubmed/24619543))
  - NARD is less common among patients treated with phenobarbital, but may still occur (especially in patients with multiple medical problems).
- Timely recognition of NARD is critical, because ongoing treatment with GABAergic medications (benzodiazepines or barbiturates) will *exacerbate* this condition.
  - Failure to diagnose NARD may lead to a vicious cycle of over-medication, which eventually precipitates stupor and coma.
- Clues to the development of NARD are the following:
  - Patient remains agitated or belligerent but is showing no other signs of alcohol withdrawal (e.g. no tremor, hypertension, or tachycardia).
  - Symptoms persist longer than is typical for alcohol withdrawal treated with phenobarbital (e.g. >2-3 days). With ongoing time after admission, it's *increasingly* likely that the patient has nonspecific delirium and *less* likely that the patient has alcohol withdrawal.
  - Patient has already received a dose of phenobarbital which would be expected to be adequate for alcohol withdrawal (e.g. >20 mg/kg).
- NARD should be treated similarly to other agitated delirium states (more on this in the *delirium chapter* (https://emcrit.org/ibcc/delirium/)):
  - The etiology should be evaluated (to exclude a serious underlying problem).
  - Contributing factors should be eliminated if possible.
  - Symptoms may be controlled (e.g. using haloperidol, dexmedetomidine, clonidine, or guanfacine).

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therapeutic target (CIWA vs. RASS)

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CIWA is a complex score which can be used to monitor and titrate therapy for alcohol withdrawal. CIWA scoring has several drawbacks, and generally isn't very useful (especially within a critical care arena, which is staffed by experienced nurses).

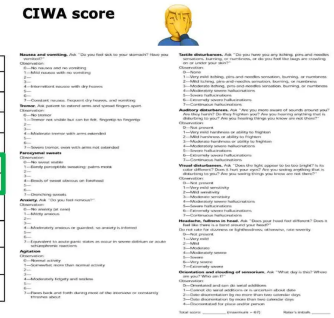
- CIWA is extremely effort-intensive.
- CIWA can be affected by a wide variety of abnormalities which may be impacted by other physiologic derangement (e.g. tachycardia due to atrial fibrillation).
- Due to the multitude of factors composing a CIWA scale, it can be difficult to determine precisely what a specific CIWA score means (similar to the total Glasgow Coma Scale).

The preferred therapeutic target for medication titration in the Richmond Agitation and Sedation Scale (RASS) as shown below. This is simpler and more reproducible. The use of a RASS score as the therapeutic target for dosing phenobarbital was validated by Oks et al (29925291 (https://www.ncbi.nlm.nih.gov/pubmed/29925291)).

Richmond Agitation and Sedation Score (RASS)
- green box = therapeutic target in EtOH withdrawal

Target RASS	RASS Description
+ 4	Combative, violent, danger to staff
+ 3	Pulls or removes tube(s) or catheters; aggressive
+ 2	Frequent nonpurposeful movement, fights ventilator
+ 1	Anxious, apprehensive , but not aggressive
0	Alert and calm
- 1	awakens to voice (eye opening/contact) >10 sec
- 2	light sedation, briefly awakens to voice (eye opening/contact) <10 sec
- 3	moderate sedation, movement or eye opening. No eye contact
- 4	deep sedation, no response to voice, but movement or eye opening to physical stimulation
- 5	Unarousable, no response to voice or physical stimulation

CIWA score



RASS scoring is simple, easy to understand, and validated to guide administration of phenobarbital in the ICU. Alternatively, CIWA scoring is excessively labor-intensive, complex, and overall unhelpful.

Although RASS score is better than CIWA, no tool can replace bedside assessment by an experienced clinician. When in doubt about whether the patient truly has alcohol withdrawal symptoms, the patient should be thoughtfully re-assessed.

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checking phenobarbital levels?

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Phenobarbital levels usually don't need to be checked. Instead, it's generally adequate to keep track of the total cumulative dose of phenobarbital which has been administered (because the level will vary in a predictable and linear fashion, in relationship to the total dose of phenobarbital administered). However, phenobarbital levels may (rarely) be advisable in a few situations:

1) amount of phenobarbital which has been received is unclear

- Sometimes records may be unclear regarding how much phenobarbital the patient has truly received (e.g. patients undergoing inter-hospital transfer).
- A phenobarbital level will definitively resolve this question.

2) severe obesity

- The dosing of phenobarbital isn't 100% clear for patients with severe obesity (e.g. body mass index > 40).
- One study suggests that the phenobarbital may be dosed based on the patient's *actual* body weight (1587059 (https://www.ncbi.nlm.nih.gov/pubmed/1587059)). However, this *isn't* well validated.
- To err on the side of caution, a reasonable approach may be to use the ideal body weight initially. If symptoms persist despite administering a dose of >15-20 mg/kg ideal body weight, then check a phenobarbital level. Additional phenobarbital may be given based on symptoms (while keeping the phenobarbital level well below 40 ug/ml).
    - All you really need is a *single* phenobarbital dose to determine the volume of distribution. The relationship between phenobarbital dose and concentration is *linear*, so a single point will allow prediction of subsequent levels.

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pitfalls of phenobarbital

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The errors which occur with phenobarbital are generally no different from errors which may be made with any drug when treating alcohol withdrawal.

1) wrong diagnosis / premature diagnostic closure

- Since phenobarbital is long-acting, any side-effects will also be long-acting.
- Prior to using phenobarbital, try to be fairly certain about the correct diagnosis.
- In cases of diagnostic uncertainty, titrated benzodiazepine might be a better option.

2) failure to keep track of the total phenobarbital dose

- The total cumulative phenobarbital dose must be monitored and limited to below 20-30 mg/kg.
- If there is uncertainty about the total phenobarbital dose, then checking a level may be useful.

3) use of phenobarbital to suppress a personality disorder

- Make sure that phenobarbital is being used to treat true symptoms of *alcohol withdrawal*.
- Never use phenobarbital to suppress a belligerent personality (without other signs/symptoms of alcohol withdrawal).
    - Note: Practitioners aren't doing this at a conscious level. However, patients who are aggressive will encourage a more heavy-handed approach to medication administration.

4) avoid combining phenobarbital and benzodiazepines

- Phenobarbital and benzodiazepines function synergistically. Therefore, a dose of phenobarbital which is safe by itself (say, 18 mg/kg) could cause respiratory suppression if paired with a large dose of benzodiazepines.
- Phenobarbital and benzodiazepines should never be titrated up simultaneously. Ideally once a decision has been made to use phenobarbital, no further benzodiazepines should be used.
- Once the patient has been titrated to a large cumulative dose of phenobarbital (e.g. >15 mg/kg), the risk of over-sedation with benzodiazepines increases.

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benzodiazepines

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candidates for benzodiazepine therapy

- Not usually preferred for patients with definite alcohol withdrawal (especially if severe).
- Benzodiazepines may be useful for patients admitted for another reason (e.g. pneumonia), who are experiencing mild withdrawal symptoms.
- Benzodiazepines are most useful when you're not entirely sure that the patient has alcohol withdrawal:
    - Small doses of diazepam may be given to determine the patient's response.
    - If the patient becomes sedated after a low dose of benzodiazepine, they probably *don't* have delirium tremens (true delirium tremens causes at least a moderate tolerance of benzodiazepines).

IV diazepam is vastly superior to IV lorazepam

- Advantages of diazepam over lorazepam:
    - Faster onset (within 2-5 minutes) prevents dose stacking. In contrast, lorazepam can take a while to work, which creates a risk of giving multiple doses before the initial doses have had a full effect (eventually leading to over-sedation which requires intubation).
    - Diazepam has a longer duration of action (slow terminal half-life), which diminishes rebound symptoms.
- Diazepam metabolism will be slower in patients with cirrhosis, but diazepam is still probably preferable there (if the patient truly has alcohol withdrawal, then a long half-life is beneficial).
- The choice of phenobarbital versus benzodiazepines remains controversial, with some practitioners continuing to prefer benzodiazepine therapy initially. However, there is no real controversy about the superiority of IV diazepam over IV lorazepam.

how to use IV diazepam

- Diazepam is typically dosed with escalating doses as needed Q5-10 minutes (e.g. 10 mg, 10 mg, 20 mg, 20 mg, 20 mg, 40 mg, 40 mg, 40 mg).
- A subset of patients has *benzodiazepine-resistant* DTs. If your patient isn't responding well to benzodiazepines, consider transitioning to phenobarbital.

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ketamine

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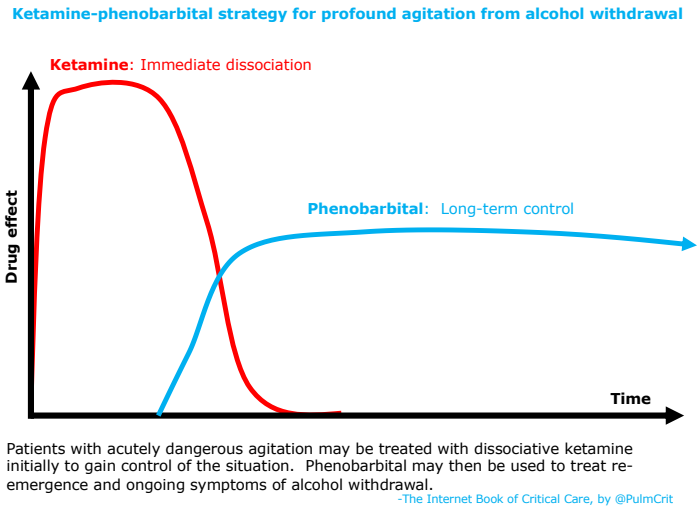
ketamine has many desirable properties

- Doesn't suppress respiration (so unlikely to precipitate a requirement to intubate the patient).
- Effective analgesic.

- Effective anti-epileptic (may help avoid alcohol-withdrawal seizures).
- Immediately available in most critical care settings, may be given rapidly if need be.

dissociative ketamine



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- Rarely, a dissociative dose of ketamine (e.g. 1.5-2 mg/kg) may be useful for a patient with alcohol withdrawal who is profoundly and dangerously agitated.
  - In practice, this should only *rarely* be encountered.
  - Most patients with isolated alcohol withdrawal who are treated up-front with barbiturates *won't* progress to a state of severe agitation.
- Dissociative ketamine will achieve behavioral control for ~30 minutes. This is enough time to order phenobarbital and start it running in (e.g. 5-10 mg/kg depending on the context).
- As the patient is waking up from the ketamine, *phenobarbital* may be used to prevent re-emergence.
  - Phenobarbital is used here in a fashion similar to a benzodiazepine to prevent re-emergent agitation.
- Dissociative ketamine (like dexmedetomidine) isn't a destination therapy – this simply buys time to facilitate transition to phenobarbital.

pain-dose ketamine

- Untreated pain can be a problem for patients with alcohol withdrawal. Pain can be a driver of *agitation*, which may potentially lead to excessive use of sedatives.
- A pain-dose ketamine infusion is a great option for the patient with alcohol withdrawal and active pain. The management here is identical to the use of low-dose ketamine infusion for pain in other contexts (described further *here* (https://emcrit.org/pulmcrit/analgesic-ladder/)).
- In this situation, the ketamine infusion is primarily intended to treat *pain*. It is possible (likely) that the ketamine may also exert some mild beneficial effects on alcohol withdrawal – which is a fringe *bonus*.

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dexmedetomidine

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general description

- Dexmedetomidine treats symptoms, but doesn't address the underlying physiological problems (inadequate GABA signaling and excess NMDA activity).
  - Doesn't protect against seizure.
  - Should never be used as a sole agent for treatment of DTs or alcohol withdrawal seizure.
- Advantages
  - (1) Titratable agent – may be adjusted up/down as needed.
  - (2) Doesn't suppress respiration.
  - (3) Arguably the *safest* agent to use (least likely to precipitate over-sedation and require intubation).

niche role of dexmedetomidine

- Uses
  - (1) Achieve behavioral control *while* you're working on gradual up-titration of phenobarbital or performing other tests (e.g. lumbar puncture). In complex patients this can be helpful to for buying time that allows you to sort out exactly what is going on (e.g. a patient has received a potpourri of medications and it's unclear if they have untreated alcohol withdrawal or benzodiazepine-induced delirium).
  - (2) Patient has already received a moderate amount of phenobarbital (e.g. >10-15 mg/kg) and is getting increasingly agitated overnight. Dexmedetomidine is a great drug for nocturnal delirium, so this can help get the patient some sleep overnight. Stop the dexmedetomidine the next morning and re-assess whether more phenobarbital is required. A patient who is suffering from nocturnal agitation (rather than alcohol withdrawal) may be perfectly fine the next morning with the dexmedetomidine discontinued – without requiring additional phenobarbital.
  - (3) Treatment of non-alcohol-related delirium (NARD; more on this below).
- Dexmedetomidine is never a destination – it's a short-term *bridge* to control symptoms while the situation clarifies itself.
- Ideally, dexmedetomidine should be used only infrequently, for the following reasons:
  - It delays disposition out of the ICU (a patient still on dexmedetomidine must stay in the ICU).
  - It delays up-titration of phenobarbital (definitive therapy).

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antipsychotics & clonidine

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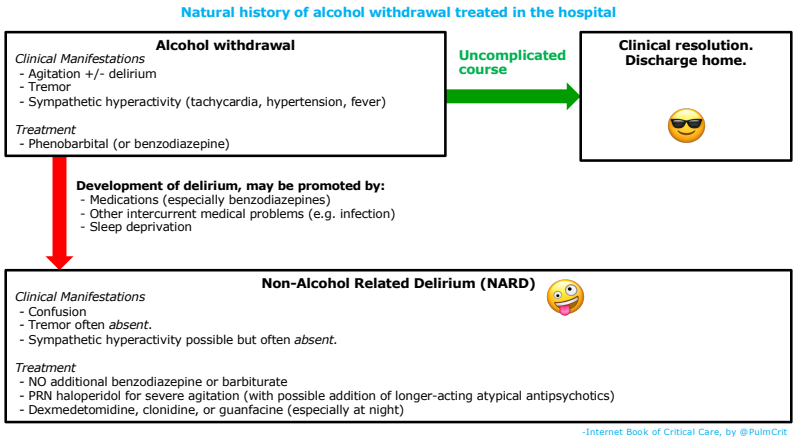
these agents should generally be *avoided* during initial treatment:

- They don't treat the underlying problem (inadequate GABA signaling and excessive glutamate activity).
- They don't have anti-seizure properties.
- They may mask the symptoms of alcohol withdrawal, without addressing the real problem.

anti-psychotics and oral alpha-agonists may be useful for treating non-alcohol related delirium (NARD)

- Some patients will develop a nonspecific, mixed delirium state following treatment for alcohol withdrawal (NARD, see figure below).
- Antipsychotics (preferably small doses of PRN IV haloperidol) and oral alpha-agonists (e.g. clonidine) may be helpful for symptomatic therapy of NARD.
  - The smallest possible dose which will achieve symptomatic control should be used.



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alcohol continuation to prevent withdrawal

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Alcohol may rarely be used to *prevent* withdrawal. This could be sensible in the following situation:

- Patient has decisional capacity and clearly wishes to continue drinking.

- Absence of significant cirrhosis.
- Patient isn't NPO.
- Alcohol is on hospital's formulary (or the patient's family can provide this).

Alcohol is the ideal substance to prevent withdrawal because – by definition – it hits the same exact receptors as alcohol. A large amount of alcohol may not be required to prevent withdrawal: often 1-2 drinks per night will be sufficient.

Continuation of alcohol is a sensible approach to the patient with no intention of quitting. The main limitation is that most hospitals don't have alcohol on formulary any more. Overall the use of alcohol has largely been replaced by *prophylactic phenobarbital* (discussed below (#prevention_of_alcohol_withdrawal)).

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supportive care

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electrolytic repletion

- Patients are often deficient in multiple electrolytes (especially potassium, magnesium, and phosphate). Specifically:
- (1) Severe alcoholism often causes a severe total-body magnesium deficit, which may require *numerous* doses of intravenous magnesium to correct (or a magnesium infusion).
- (2) Patients with alcoholism are at increased risk for re-feeding syndrome – which may require substantial quantities of phosphate repletion.

glucose monitoring

- Follow glucose levels intermittently in patients who are NPO. Patients with alcoholism and cirrhosis may have impaired liver glycogen reserves, which puts them at risk for hypoglycemia.

vitamin B1 (IV thiamine)

- Alcoholic patients are often thiamine deficient. These patients may develop Wernicke's encephalopathy, which can mimic alcohol withdrawal. It's often impossible to clinically exclude Wernicke's encephalopathy (because patients with alcohol withdrawal may not cooperate with a full neurologic examination).
- When in doubt, the safest thing is to administer high-dose thiamine (500 mg IV q8hr). This will treat Wernicke's encephalopathy if it is present (and it extremely safe regardless).
    - Banana Bags aren't useful because they contain only 100 mg thiamine in a liter of normal saline. It would take fifteen liters of banana bag fluid per day to treat Wernicke's Encephalopathy.

refeeding syndrome

- Severe alcoholics with poor nutrition may be at risk for re-feeding syndrome.
- Start nutrition gradually and monitor electrolytes carefully.

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alcohol withdrawal seizures

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general

- Alcohol withdrawal seizures are usually self-limiting, but patients can progress into status epilepticus. Therefore, treatment should be given promptly.
- The usual pattern is 2-6 seizures, each of which is brief and self-limiting.

evaluation

- Consider alternative causes of seizure, especially if the patient doesn't respond well to therapy.
- Patients with alcoholism have high rates of trauma and may have intracranial hemorrhage.

treatment

- Ongoing convulsive seizures should be treated as per a standard status epilepticus algorithm. However, alcohol withdrawal usually doesn't cause this – there is generally a break between seizures which allows anti-epileptic therapy to be administered (thereby preventing recurrent seizures).
- Traditional anti-epileptic drugs may not work (especially *phenytoin,* which lacks activity against this seizure type).
- Phenobarbital seems like a rational choice here (given the ability of phenobarbital to treat alcohol withdrawal and treat seizure).
  - There isn't any data directly regarding the ideal dose in this situation.
  - A usual loading dose of phenobarbital for the treatment of seizure is ~15-20 mg/kg. If the patient's mental status is reasonably normal, then phenobarbital may be given in divided doses with a goal of titrating up to a total dose of ~15-20 mg/kg.
- Scheduled benzodiazepine is an alternative treatment (with perhaps even *less* clarity regarding the optimal dosage).

vitamin B6 (pyridoxine) may be considered for seizure

- Pyridoxine deficiency is well known to promote seizures in various clinical scenarios (e.g. isoniazid use and pregnancy).
- Alcoholism is one cause of pyridoxine deficiency. Some emerging literature suggests that occasional patients with alcoholism may develop seizures due to pyridoxine deficiency (25343127 (https://www.ncbi.nlm.nih.gov/pubmed/25343127), 26157671 (https://www.ncbi.nlm.nih.gov/pubmed/26157671)).
- Testing for pyridoxine deficiency is possible (e.g. measurement of homocysteine levels). However, it may be easier to simply empirically administer pyridoxine to alcoholic patients with who have seizures. Oral pyridoxine is widely available and inexpensive (28789699 (https://www.ncbi.nlm.nih.gov/pubmed/28789699)).

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prevention of alcohol withdrawal

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criteria for prophylactic phenobarbital:

- (1) Must have a definite history of severe, steady alcohol intake *up until the time of admission*.
  - Verify with the patient/family that there is *ongoing* alcohol use.
- (2) Felt to be at significant risk from alcohol withdrawal, for example:
  - (a) History of alcohol withdrawal (especially prior seizures or delirium tremens)
  - (b) Co-existent medical problem which could be *exacerbated* by withdrawal (e.g. unstable angina)
- (3) No active neurologic problems
  - Normal baseline mental status
- (4) No risk factors for over-sedation due to phenobarbital
  - Not on benzodiazepines, high-dose opioids, or multiple drugs that may cause respiratory suppression
  - No history of hepatic encephalopathy

evidence-based prediction of the risk of alcohol withdrawal

Predictors of severe alcohol withdrawal syndrome

Risk factor	+LR	-LR
History of delirium tremens	3	0.8
Systolic Blood pressure >140	1.7	0.8
History of mood disorder	3	0.6
Substance use disorder, other than alcohol	6	0.94
BAC > 200 mg/dL on admission	3.5	0.6
PAWSS score of 4 or greater (more on this below)	174	0.07

Data obtained from JAMA Rational Clinical Exam: Will this hospitalized patient develop severe alcohol withdrawal syndrome? Wood E. et al. 2018 PMID 30167704

(https://emcrit.org/wp-content/uploads/2016/11/jamapaws3.svg)

- In situations where the risk of alcohol is unclear, the above factors may be considered.

- The best predictor of severe alcohol withdrawal seems to be the *PAWSS score* 😺(may be calculated using MDCalc here (https://www.mdcalc.com/prediction-alcohol-withdrawal-severity-scale)).

procedure for prophylactic phenobarbital

- Try to get the patient a total of 10 mg/kg phenobarbital (cumulative dose).
- Phenobarbital may be given as a single dose, or in divided doses (if there is concern that it could lead to somnolence). Intravenous or oral phenobarbital may be used.
- Generally best to give the phenobarbital in the evening, as it may cause patients to be sleepy.

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ventilator sedation for the intubated alcoholic

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the clinical scenario:

- An alcoholic patient is intubated for some other reason (usually respiratory failure due to pneumonia)
- The patient is difficult to sedate on the ventilator with persistent agitation.

initial management on the ventilator:

- (1) Propofol is the first-line sedative here, with excellent effectiveness for delirium tremens. Like phenobarbital, propofol will affect both the GABA and glutamate receptors (making it more effective than benzodiazepines).
- (2) For patients who are requiring a fair amount of propofol (~>40 mcg/kg/min), consider loading with 10 mg/kg phenobarbital. This may have some advantages:
  - (a) Reduced requirement for propofol (may decrease the risk of propofol infusion syndrome)
  - (b) May facilitate weaning off propofol and being extubated (without unmasking underlying alcohol withdrawal).
- Administration of 10 mg/kg phenobarbital shouldn't cause excessive somnolence which could interfere with extubation, unless the patient has received a significant dose of benzodiazepine, or the patient has other active neurologic problems.
  - If the patient is requiring a moderate to high dose of propofol for sedation, this generally indicates that they will be able to tolerate phenobarbital without its causing excessive somnolence. (On the contrary, if the patient is perfectly comfortable on low-dose propofol, then they probably don't need phenobarbital.)

weaning from mechanical ventilation:

- (1) If the patient remains difficult to sedate, it may be useful to transition from propofol to dexmedetomidine prior to extubation. Dexmedetomidine may be continued throughout the entire extubation period.
- (2) If agitation remains problematic *despite* the use of dexmedetomidine and 10 mg/kg phenobarbital, additional PRN doses of phenobarbital may be provided up to a cumulative dose of ~15 mg/kg.
  - Be careful, because part of the agitation may be driven by stimulation from the endotracheal tube. Therefore, if you render the patient completely comfortable on the ventilator there may be a risk that once the *stimulation* of the endotracheal tube is removed the patient will be *too* sedated.
  - When in doubt, it may be useful to extubate the patient on high-dose dexmedetomidine with careful observation. Removal of the endotracheal tube alone may be sufficient to render the patient comfortable. If there are ongoing signs and symptoms of alcohol withdrawal (or an ongoing requirement for high-dose dexmedetomidine), these may be indications for careful addition of PRN doses of phenobarbital.

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the future of phenobarbital

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Disclaimer: This section is hypothetical regarding possible future therapies.

(1) higher loading doses

Current protocols often involve an initial loading dose of 10 mg/kg phenobarbital, based on pharmacokinetic modeling which shows that this is a safe dose for patients who haven't received other sedatives. A dose of 10 mg/kg phenobarbital typically achieves a drug level of ~15 ug/mL,

which is far below the toxic dose range. This dose was selected in a somewhat arbitrary fashion, within the context of a medical system which may not have been well-versed in the use of phenobarbital (and thus afraid to use higher doses).

Using an initial loading dose of 15-20 mg/kg phenobarbital would still achieve a phenobarbital level *well* below the toxic level. It's not hard to imagine *increasing* the initial dose to 15-20 mg/kg, or perhaps using a multi-dose loading approach to achieve a higher cumulative dose up-front (e.g. 10 mg/kg, followed by two 5 mg/kg doses over a few hours if tolerated). If patients could be loaded with 20 mg/kg within hours of admission, *most patients would require no additional therapy at all*. This could reduce the requirement for subsequent ICU or hospital admission.

(2) expedited transition from emergency department to outpatient treatment pathways

The traditional approach to alcohol withdrawal has involved lengthy hospital admission for *complex* titration of *numerous* medications (often primarily benzodiazepines). Appropriately dosed phenobarbital may obviate the need for all of this, in many cases (e.g. patients without other co-morbid issues who haven't yet developed frank delirium tremens).

Phenobarbital has already been demonstrated to reduce the need for ICU admission. The next step in this progression is to adopt accelerated phenobarbital dosing schedules (#1 above), which may allow treatment to occur fully within the emergency department. Subsequently, patients could be dispositioned to a rehab facility or home (depending on the level of support at home).

There is already some literature supporting the ability to treat patients with phenobarbital and subsequently discharge them home (20825805 (https://www.ncbi.nlm.nih.gov/pubmed/20825805)). Phenobarbital is ideal in this regard because the patient can receive all necessary medication in the emergency department *under supervision*. This is probably much safer than sending patients home with benzodiazepines (e.g. an oral chlordiazepoxide taper) – which could potentially be used incorrectly.

(3) fully outpatient treatment pathway

Another treatment pathway could be envisioned as well, for outpatients who are wishing to detoxify themselves from alcohol (without the cost of admission to a hospital). The patient could present to an outpatient clinic in the morning and be treated with titrated doses of phenobarbital (possibly oral, IV, or IM depending on local resources and expertise). The patient could be treated with successive dosing to achieve ~10-15 mg/kg cumulative dose under medical supervision. If this was tolerated, the patient could be sent home with instructions to take additional oral doses as needed (possibly 130 mg q1hr PRN with a limit of 20 mg/kg cumulative dose).

conclusion

Phenobarbital is an extremely powerful and versatile medication for the treatment of alcohol withdrawal. We are only beginning to scrape the surface of how this medication may be used to treat and prevent alcohol withdrawal. Currently expertise using phenobarbital is concentrated largely in the critical care arena, but this needs to be translated into other contexts as well (e.g. hospital wards and outpatient settings). Wider use of phenobarbital could potentially improve patient care considerably, while simultaneously dramatically cutting costs and mobilizing limited hospital resources.

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checklist

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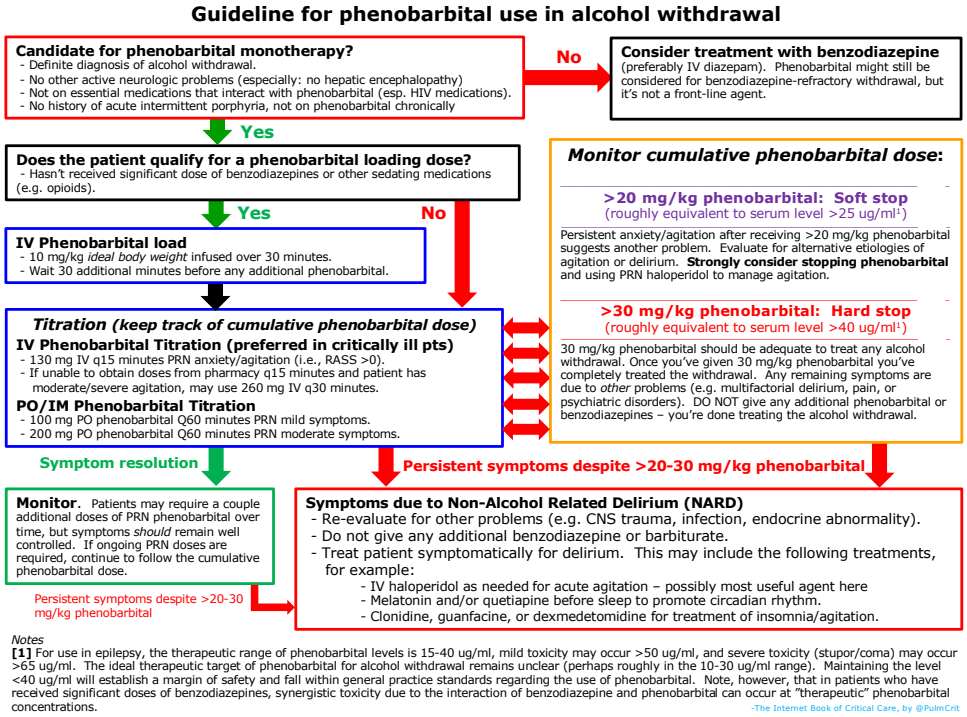
checklist for management of alcohol withdrawal

- Diagnosis
  - Verify alcoholism history (if possible).
  - Consider the possibility of *concurrent* diagnoses (e.g. withdrawal *plus* sepsis).
- Evaluation for ICU-level alcohol withdrawal: *Consider*-
  - STAT fingerstick glucose
  - Electrolytes, including Ca/Mg/Phos
  - CBC with differential, Coags, Liver function tests
  - Chest X-ray
  - Consider CT head to exclude subdural hematoma
  - Follow serially: Glucose, electrolytes (esp. phosphorous)
- Treatment

- Empiric IV thiamine (consider 500 mg IV q8hr if possible Wernicke's)
- Repletion of electrolytes as needed
- Phenobarbital as below



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podcast

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questions & discussion

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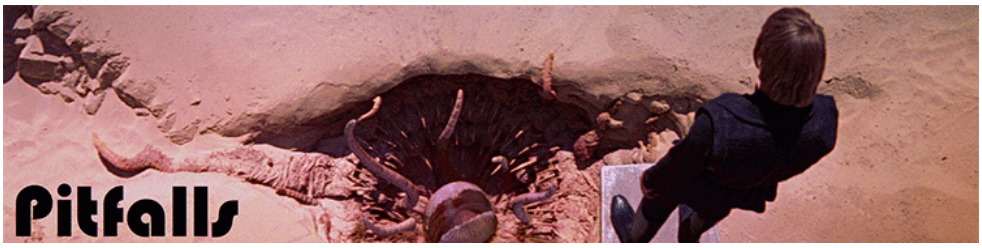
To keep this page small and fast, questions & discussion about this post can be found on another page ***here*** (https://emcrit.org/pulmcrit/etoh/) .



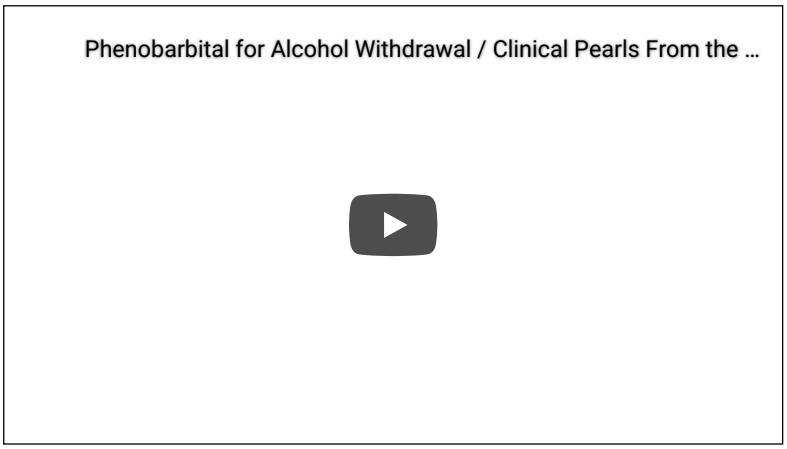
(https://i1.wp.com/emcrit.org/wp-content/uploads/2016/11/pitfalls2.gif)

- Failure to take an accurate history of alcohol use.
- Failure to keep track of the cumulative phenobarbital dose (and stop after reaching a dose >20-30 mg/kg).
- Concluding that phenobarbital isn't working (and therefore the patient must be intubated) prior to using an adequate phenobarbital dose.
- More pitfalls: *Pitfalls of phenobarbital (above) (#pitfalls_of_phenobarbital)*

Going further:

- Phenobarbital for EtOH w/d #1 (12/14) (https://emcrit.org/pulmcrit/treating-delirium-tremens-pharmacokinetic-engineering-with-diazepam-and-phenobarbital/)
- Phenobarbital for EtOH w/d #2 (monotherapy, 10/15) (https://emcrit.org/pulmcrit/phenobarbital-monotherapy-for-alcohol-withdrawal-simplicity-and-power/)
- Phenobarbital for EtOH w/d #3 (monotherapy reloaded, 12/17) (https://emcrit.org/pulmcrit/phenobarbital-reloaded/)
- Phenobarbital for EtOH w/d #4 (one order to sedate them all, 10/18) (https://emcrit.org/pulmcrit/phenobarbital-oks/)
- Phenobarbital for EtOH w/d #5 (evidence update 2018-2019) (https://emcrit.org/pulmcrit/phenobarb-sampler/)
- Ketamine for alcohol withdrawal? (https://emcrit.org/pulmcrit/ketamine-alcohol-withdrawal/)
- Paradoxical reactions due to BZDs & propofol (https://emcrit.org/pulmcrit/recognizing-and-managing-paradoxical-reactions-from-benzodiazepines-propofol/)

This talk is from 1/30/18 so the general principles are accurate but the exact algorithm has evolved a bit since then:



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.