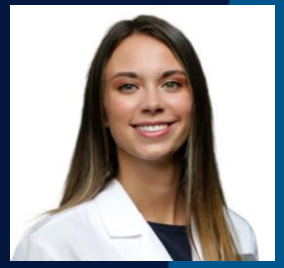
Barbiturates are Back: An Update on the Inpatient Management of Acute Alcohol Withdrawal

A presentation for HealthTrust Members
May 15, 2024



Ali Goforth, PharmD
PGY1 Pharmacy Resident
TriStar Medical Center

Preceptor: Erica Roman, PharmD, BCPS
Cardiovascular/Critical Care Clinical Pharmacist
TriStar Centennial Medical Center

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Objectives for Pharmacists & Nurses

- Recall the pathophysiology of acute alcohol withdrawal and associated complications
- Identify the preferred therapeutic target for the management of a patient in acute alcohol withdrawal
- Recognize literature-based recommendations for pharmacologic agents in the treatment of acute alcohol withdrawal

Alcohol Withdrawal Syndrome

Acute Alcohol Withdrawal

- Intentional or unintentional abrupt reduction or cessation of long-term alcohol consumption
  - Impacts 8% of patient hospitalized with alcohol use disorder
    - Up to 15% of those patients will progress to severe alcohol withdrawal
- Associated with increased morbidity, mortality, length-of-stay, and cost

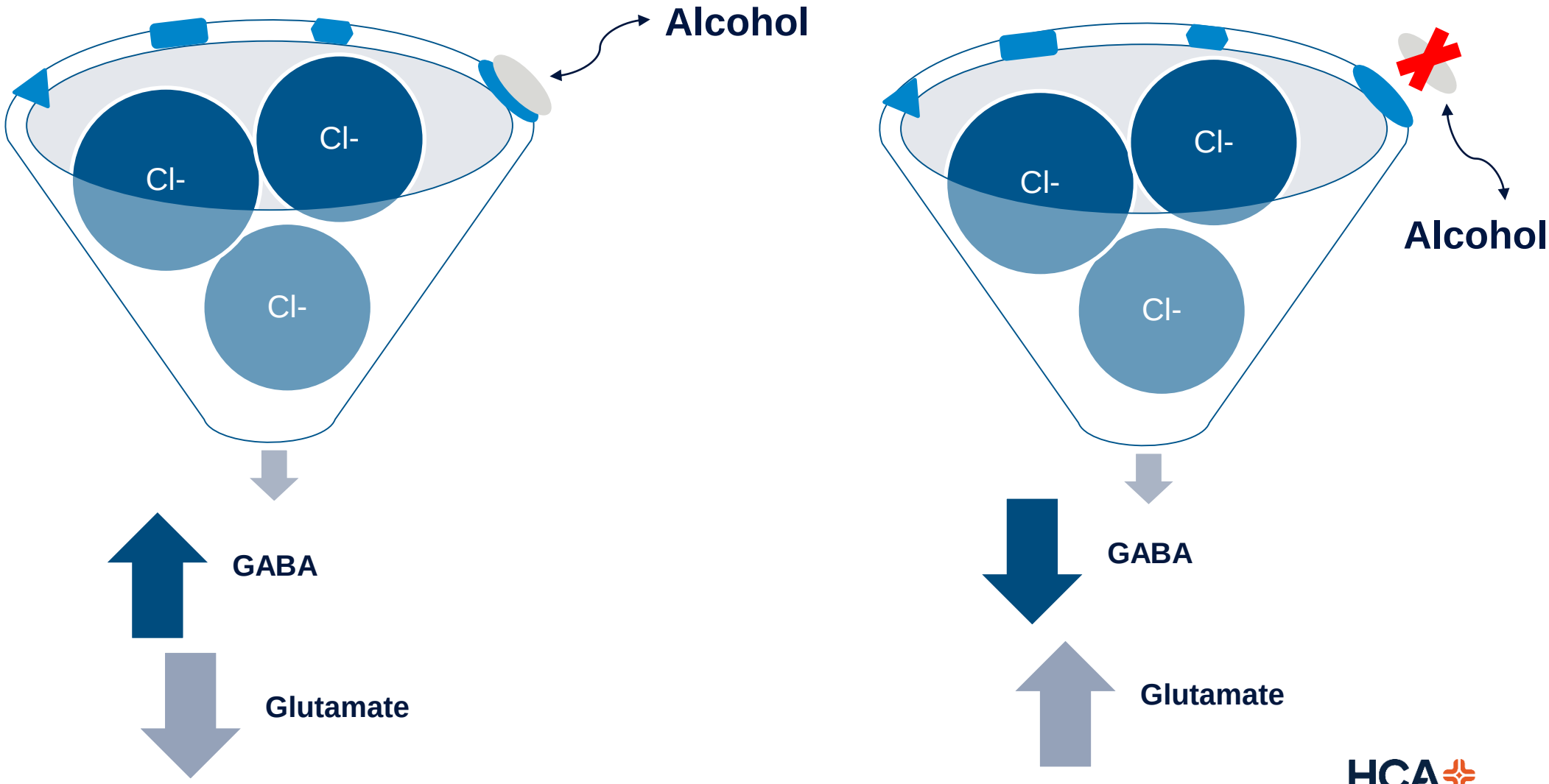
Source: Jesse S, et al. *Acta Neurol Scand*. 2017.

Risk Factors for Alcohol Withdrawal Syndrome

- Associated with increased risk:
  - Consuming more alcohol
  - Combing with medications such as barbiturates or benzodiazepines
  - Prior withdrawal
- Screening Tool to Determine Risk:
  - Prediction of Alcohol Withdrawal Severity Scale (PAWSS)

Sources: Maldonado, et al. Alcohol. 2014.
Jesse S, et al. *Acta Neurol Scand*. 2017.

Pathophysiology of Acute Alcohol Withdrawal



Source: Jesse S, et al. *Acta Neurol Scand*. 2017.

Assessment Question #1

Which two neurotransmitters are primarily involved in alcohol withdrawal syndrome?

A. Glutamate

B. Acetylcholine

C. Gamma-aminobutyric acid (GABA)

D. Serotonin

Assessment Question #1 – Correct Response

Which two neurotransmitters are primarily involved in alcohol withdrawal syndrome?

A. Glutamate

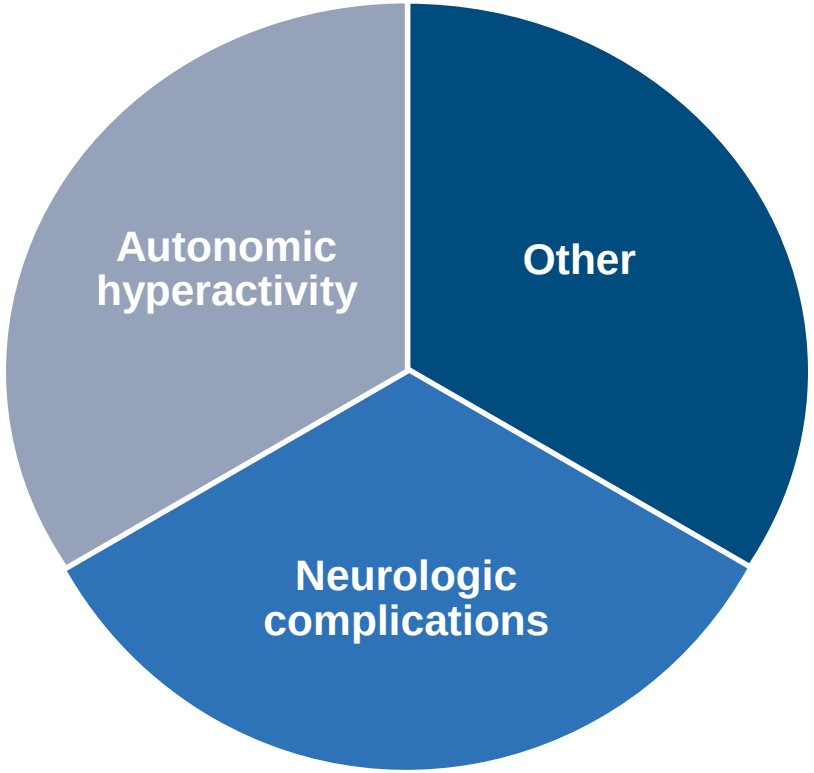
B. Acetylcholine

C. Gamma-aminobutyric acid (GABA)

D. Serotonin

Clinical Presentation of Acute Alcohol Withdrawal

- Signs and symptoms occur ~6-48 hours after last alcohol consumption



Source: Farrokh S, et al. *Neurocrit Care.* 2021 Apr;34(2):593-607.

Development of Alcohol Withdrawal Complications

Minor Withdrawal (~6 hours)

- Anxiety, agitation
- Tremors, restlessness, insomnia
- Diaphoresis, palpitations

Alcoholic Hallucinations (~8 to 12 hours)

- Visual
- Auditory
- Tactile

Alcohol Withdrawal Seizures (~12 to 48 hours)

- Risk increases with each withdrawal episode
- Generalized tonic-clonic

Delirium tremens (~2 to 4 days)

- Severe agitation
- Disorientation, hallucinations
- Fever, tachycardia, hypertension, sweats

Source: Farrokh S, et al. *Neurocrit Care.* 2021 Apr;34(2):593-607.

Therapeutic Targets in Acute Alcohol Withdrawal

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Clinical Institute Withdrawal Assessment – Alcohol Revised (CIWA-Ar)

- 10-item assessment tool that quantifies the severity of alcohol withdrawal

Pros	Cons
• Symptom-driven • Guides treatment for many AWS protocols	• Cannot be utilized if history of AWS seizures/DT • Cannot predict patients at-risk • Labor intensive on nursing • Impacted by comorbidities

AWS: alcohol withdrawal syndrome; DT: delirium tremens

Source: J Addict Med. 2020;14(3S, suppl 1):1-72.

Richmond Agitation Sedation Scale (RASS)

- Assessment tool that measures agitation and sedation in ICU patients

Pros	Cons
• Can utilize if unable to assess symptoms • Less labor intensive	• Limited to ICU patients

ICU: intensive care unit

Source: Oks M, et al. *J Intensive Care Med*. 2020 Sep;35(9):844-850.

Assessment Question #2

What is the preferred therapeutic target for managing acute alcohol withdrawal?

A. CIWA-Ar

B. RASS

C. Glascow-Coma Scale

D. A & B

Assessment Question #2 – Correct Response

What is the preferred therapeutic target for managing acute alcohol withdrawal?

A. CIWA-Ar

B. RASS

C. Glascow-Coma Scale

D. A & B

Treatment of Acute Alcohol Withdrawal

2020 ASAM Clinical Practice Guidelines

Active withdrawal:

- **First-Line:** Benzodiazepines
  - Mechanism of action: Bind to the benzodiazepine specific site on the GABA-A receptor, which increases the influx of chloride ions and subsequently leads to an inhibitory effect (similar to alcohol)
    - Increases the frequency that the channel is opening
    - Requires presence of pre-synaptic GABA
  - Long-acting preferred (diazepam, chlordiazepoxide, lorazepam)

Source: J Addict Med. 2020;14(3S, suppl 1):1-72.

Front Loading Strategy

- High doses of longer-acting benzodiazepines
  - Achieve initial sedation quickly
  - Self-tapering effect
  - Recommended for those in severe withdrawal

Pros	Cons
• Reduces risk of complications • Reduces total benzodiazepine dose • Shortens duration of withdrawal symptoms	• Increased risk of sedation and respiratory depression

Sources: J Addict Med. 2020;14(3S, suppl 1):1-72.
Jesse S, et al. *Acta Neurol Scand*. 2017.

Front Loading Example Regimens

Medication	Dosing Strategy
Diazepam	• 10-20 mg every 1-2 hr until patient reaches adequate sedation • 5-10 mg IV every 5-10 minutes until patient reaches adequate sedation
Lorazepam	• 2-4 mg IV every 15-20 minutes until patient reaches adequate sedation
Chlordiazepoxide	• 100 mg every 1-2 hr until patient reaches adequate sedation

Source: Jesse S, et al. *Acta Neurol Scand*. 2017.

Fixed Dosing Strategy

- Specific amount of benzodiazepines are administered at “fixed” intervals
  - Can give additional doses if patients symptoms warrant it

Pros	Cons
• Beneficial for patients with history of seizures or delirium tremens • Beneficial in patients in whom you cannot assess symptoms • Less demand on nursing	• Increased utilization of benzodiazepines

Sources: J Addict Med. 2020;14(3S, suppl 1):1-72.
Jesse S, et al. *Acta Neurol Scand*. 2017.

Fixed Dosing Example Regimens

Medication	Dosing Strategy
Diazepam	• 10 mg every 6 hours x 4 doses • 5 mg every 6 hours x 8 doses
Lorazepam	• 2 mg every 6 hours x 4 doses • 1 mg every 6 hours x 8 doses
Chlordiazepoxide	• 50 mg every 6 hours x 4 doses • 25 mg every 6 hours x 8 doses
*tapered every 2-3 days once stabilized (last 7-10 days) *additional doses can be given if symptoms not controlled	

Sources: Jesse S, et al. *Acta Neurol Scand*. 2017.
Mayo-Smith MF. JAMA. 1997 Jul 9;278(2):144-51.

Symptom-Triggered Strategy

- Benzodiazepines given in response to patient symptoms

Pros	Cons
• Decreased total amount of benzodiazepines administered • Decreased risk of adverse effects (sedation, respiratory depression)	• Requires close monitoring (CIWA-Ar to assess need for treatment) • Requires additional training of staff • Cannot be used in patients with history of seizures or delirium tremens

Sources: J Addict Med. 2020;14(3S, suppl 1):1-72.
Jesse S, et al. *Acta Neurol Scand*. 2017.

Symptom-Triggered Example Regimens

Medication	Dosing Strategy
Diazepam	• 5-10 mg once
Lorazepam	• 1-2 mg once
Chlordiazepoxide	• 25-100 mg once
*If CIWA ≥ 8 *Reassessed every hour and re-dosed until CIWA <8	

Source: Jesse S, et al. *Acta Neurol Scand*. 2017.

Concerns with Benzodiazepines

- Paradoxical agitation
- Delirium
- Respiratory depression
- Benzodiazepine-resistance

Source: J Med Toxicol. 2022 Jul; 18 (3): 198-204.

Benzodiazepine Resistance

- Benzodiazepines are dependent on endogenous GABA
  - GABA deficiency
  - Down-regulation, conformational changes of GABA receptors
- Dosing thresholds to classify:
  - First hour of treatment
    - Diazepam: 50 mg
    - Lorazepam: 10 mg
  - Three to four hours into treatment
    - Diazepam: 200 mg
    - Lorazepam: 40 mg
- Leads to increased ICU admission/mechanical ventilation

Sources: Hack JB, et al. J Med Toxicol. 2006 Jun;2(2):55-60.
Shah P, et al. J Med Toxicol. 2022 Jul; 18 (3): 198-204.

Common Adjunctive Therapies

Control alcohol withdrawal	• Carbamazepine • Gabapentin • Valproic acid • Phenobarbital • Continuous IV sedation (ie. propofol)
Control autonomic hyperactivity	• Alpha-2 adrenergic agonist (dexmedetomidine, clonidine) • Beta-blockers
Supportive care	• Thiamine (prevent Wernicke encephalopathy) • Folate (hyperhomocysteinemia) • Fluid and electrolyte replacement • Caloric support

Source: J Addict Med. 2020;14(3S, suppl 1):1-72.

Phenobarbital in Acute Alcohol Withdrawal

Phenobarbital

- Barbiturate
  - Mechanism of action: Binds to an allosteric site on the GABA-A receptor, which prolongs the duration that the Cl- channels are open and potentiates the GABA-mediated inhibitory effects. It also antagonizes glutamate activity
    - Increases the duration that the channel is open
  - Pharmacokinetics:
    - Onset of action: 5 minutes
    - Duration: >6 hours
    - Half-life elimination: ~3-4 days
- Recommendations from the guidelines:
  - “Phenobarbital should only be used by clinicians experienced with its use due to narrow therapeutic index and side effects”
    - Monotherapy or adjunctive therapy

Sources: J Addict Med. 2020;14(3S, suppl 1):1-72.
Phenobarbital. Lexicomp.

Phenobarbital Side Effect Profile/Considerations

- Hypotension
- Medication-induced respiratory failure
  - Cross-tolerance in patients with alcohol abuse
    - Tolerate much higher doses
- Oversedation
- Drug-drug interactions
  - Strong CYP3A4 inducer
  - Weak inducer (CYP1A2, CYP2A6, CYP2B6, CYP2C9)
- Contraindications
  - Pregnancy
  - Marked hepatic impairment

Sources: Shah P, et al. J Med Toxicol. 2022 Jul; 18 (3): 198-204.
Kessel KM, et al. Annals of Pharmacotherapy; 2024: 1-9.

Proposed Benefits of Phenobarbital

- Rapid onset of action
- Long half-life
  - Uptitration to therapeutic dose
  - Auto-taper off
- Works synergistically with benzodiazepines
- Impacts both GABA and glutamate
- Can obtain levels if concerned about toxicity
- Available by mouth/per tube, intravenously, intramuscularly
- Low cost

Sources: Shah P, et al. J Med Toxicol. 2022 Jul; 18 (3): 198-204.
Kessel KM, et al. Annals of Pharmacotherapy; 2024: 1-9.
Tidwell WP, et al. Am J Crit Care. 2018 Nov; 27(6): 454-460.

Phenobarbital Dosing Strategies

- Low-intermittent dosing
- Front-loaded dosing
  - Rapidly increases serum phenobarbital concentration
  - Provides longer duration of action

Source: J Addict Med. 2020;14(3S, suppl 1):1-72.

Rosenson J, Clements C, Simon B, et al. Phenobarbital for acute alcohol withdrawal: a prospective randomized double-blind placebo-controlled study. *J Emerg Med.* 2013 Mar; 44 (3):592-598.e2. doi:10.1016/j.jemermed.2012.07.056	
Population	• Patients with acute AWS presenting to the ED

Interventions	Institutional-symptom triggered lorazepam protocol PLUS
	• Single-dose IV phenobarbital (n=51)
	  • 10 mg/kg in 100 mL normal saline
	• Placebo (n=51)
	  • 100 mL normal saline

Endpoints	Primary: Initial level of hospital admission Secondary: • Use of continuous lorazepam infusion • Time from hospital admission to discharge • Total amount of lorazepam used • Adverse effects
Results	Primary: • ICU admission: 8% versus 25% (95% CI 4-32) Secondary: • Decreased use of continuous lorazepam infusion • Decreased total lorazepam required • No differences in adverse effects
Conclusion	Single-dose of IV phenobarbital **led to decreased ICU admission rates** and **decreased use of continuous lorazepam infusions** and was not associated with increased adverse effects

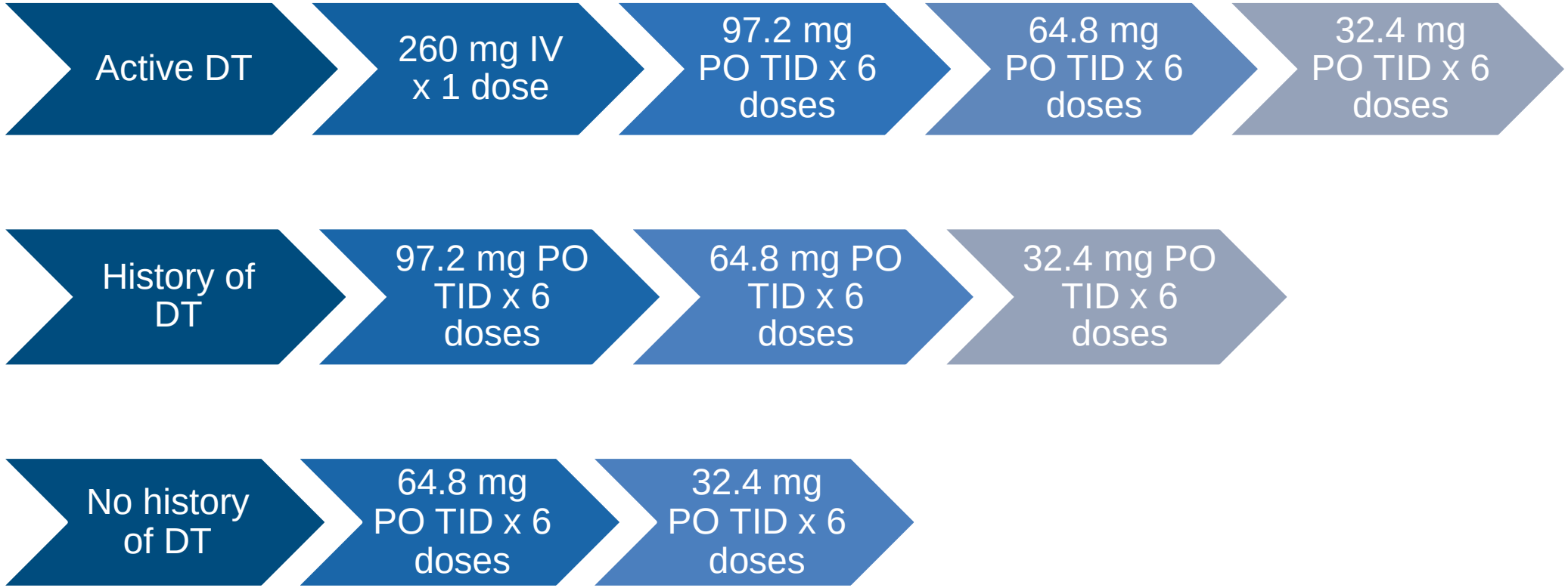
Tidwell WP, Thomas TL, Pouliot JD, et al. Treatment of Alcohol Withdrawal Syndrome: Phenobarbital vs CIWA-Ar Protocol. *Am J Crit Care.* 2018 Nov; 27(6): 454-460. DOI: 10.4037/ajcc2018745.

Population	• Medical ICU patients treated for the onset or prevention of AWS
Interventions	• Symptom-triggered benzodiazepine protocol (n=60) • Phenobarbital protocol (n=60)

Endpoints	• Primary: ICU length of stay
	• Secondary:
	  • Hospital length of stay
	  • Incidence of invasive mechanical ventilation
	  • Use of adjunctive pharmacotherapy

Results	• **Decreased ICU length of stay** (2.4 vs 4.4 days; p<0.001) • Decreased hospital length of stay (4.3 vs 6.9 days; p=0.004) • **Decreased incidence of mechanical ventilation** (2% vs 23%; p=<0.001) • Decreased use of adjunctive agents (dexmedetomidine) • **Decreased total lorazepam equivalents** (11.3 vs 35.2, p<0.001)
Conclusion	Phenobarbital protocol for the treatment of alcohol withdrawal was an effective alternative to the symptom-triggered benzodiazepine protocol

Treatment of Alcohol Withdrawal Syndrome: Phenobarbital vs CIWA-Ar Protocol



DT: delirium tremens; PO: by mouth; TID: three times a day; PRN: as needed

Lorazepam 1 mg IV q4hr PRN agitation

Source: Tidwell WP, et al. Am J Crit Care. 2018 Nov; 27(6): 454-460.

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Shah P, Stegner-Smith KL, Rachid M, et al. Front-Loaded versus Low-Intermittent Phenobarbital Dosing for Benzodiazepine-Resistant Severe Alcohol Withdrawal. *J Med Toxicol.* 2022 Jul; 18 (3): 198-204. DOI: 10.1007/s13181-022-00900-8.DOI: 10.1007/s13181-022-00900-8.

Population	• Adult patients in the medical ICU with severe benzodiazepine-resistant AWS

Interventions	Lorazepam 8 mg IV push every 5 minutes x 3 doses
	• CIWA >20
	  • Low-intermittent phenobarbital doses (n=41)
	  • Front-loaded phenobarbital doses (n=46)

Endpoints	• Primary: Incidence of mechanical ventilation
	• Secondary:
	  • ICU length of stay
	  • Time to control of AWS post phenobarbital administration
	  • Duration of mechanical ventilation
	  • Lorazepam requirements in the 24 h pre- and post-phenobarbital administration
	  • Need for adjunctive sedative infusions

Results	• Decreased incidence of mechanical ventilation (28% vs 63%; OR 4.4 (95% CI 1.8-10.9) • Decreased benzodiazepine requirements (median 86 mg [IQR 24-197] vs 228 mg [IQR 115-298]; p<0.01) • Decreased need for any continuous sedative infusion (OR 7.7 [95% CI 1.6-27], p<0.01) • Decreased transient hypotension (22% vs 56%, p=0.001) • No difference in respiratory failure or ICU LOS
Conclusion	• **Front-loaded phenobarbital** dosing was associated with **significantly lower mechanical ventilation incidence, lower benzodiazepine requirements, and less continuous sedative use**

Front-Loaded versus Low-Intermittent Phenobarbital Dosing for Benzodiazepine-Resistant Severe Alcohol Withdrawal

- Used as adjunct if CIWA-Ar score > 20 despite 3 doses of IV lorazepam
  - Front-loaded
    - 10 mg/kg (actual body weight) IV infusion over 30 minutes
    - Could receive additional doses (physician and pharmacist judgement)
  - Low-intermittent
    - 260 mg IV push x 1
    - 130 mg IV push every 15 minutes PRN (Maximum of 8 doses)
    - Maximum cumulative dose: 1300 mg
- CIWA-guided lorazepam protocol resumed after completion of phenobarbital protocol

Source: Shah P, et al. J Med Toxicol. 2022 Jul; 18 (3): 198-204.

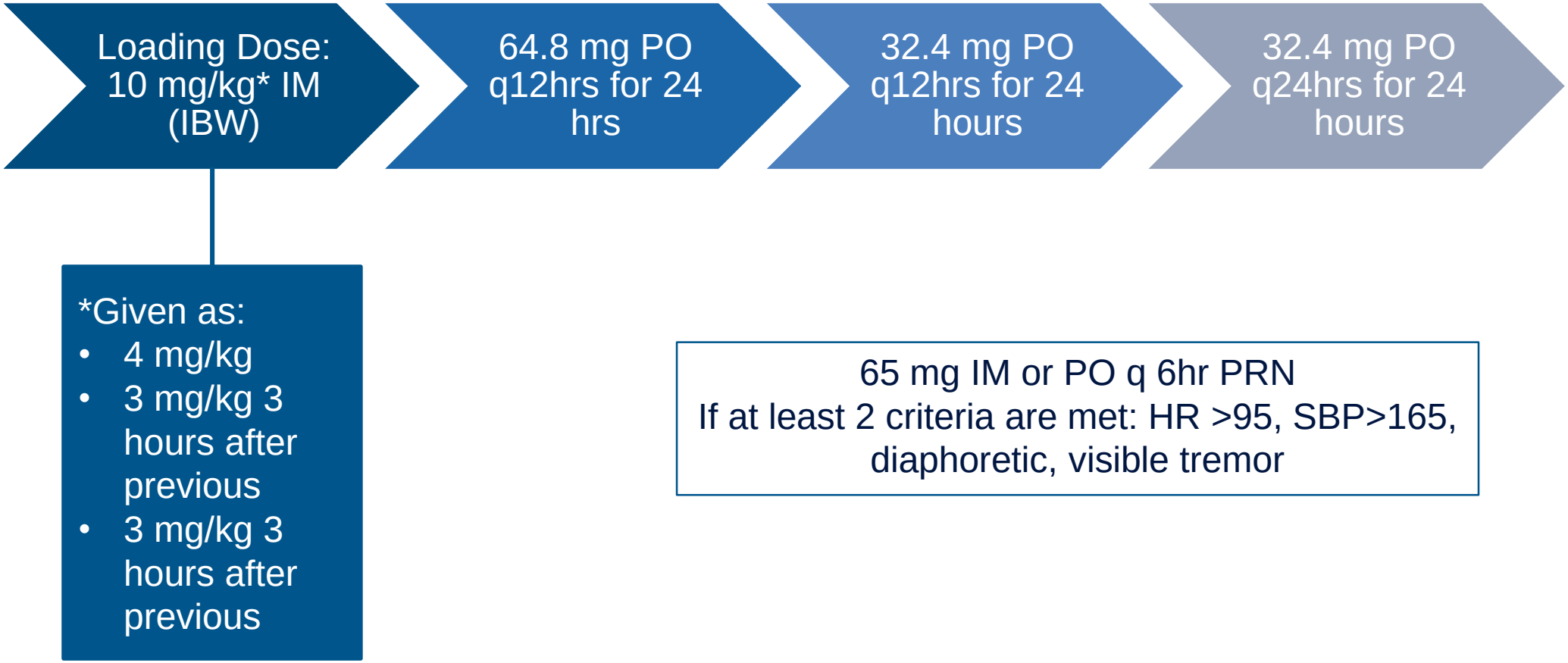
Kessel KM, Olson LM, Kruse DA, et al. Phenobarbital Versus Benzodiazepines for the Treatment of Severe Alcohol Withdrawal. Annals of Pharmacotherapy; 2024: 1-9. doi: 10.1177/10600280231221241.

Population	• Patients admitted to the progressive unit or ICUs with severe AWS
Interventions	• Phenobarbital (n=126 encounters) • Benzodiazepines (n=98 encounters)

Endpoints	• Primary: hospital length of stay
	• Secondary:
	  • Progressive or ICU length of stay
	  • Incidence of adjunctive pharmacotherapy
	  • Incidence/duration of mechanical ventilation

Results	• Shorter median hospital length of stay (2.8 vs 4.7 days; p <0.0001) • Shorter median progressive/ICU length of stay (0.7 vs 1.3 days; p<0.0001) • Lower incidence of dexmedetomidine (6 vs 53 patients; p<0.0001) and antipsychotic initiation (7 vs 36 patients; p<0.0001) • Fewer patients received new mechanical ventilation (1 vs 6, p=0.045) • Similar median duration of mechanical ventilation (1.2 vs 1.6 days; p=1.00) • Median total phenobarbital dose (952.7 mg (13.2 mg/kg) vs 978.8 mg (13.7 mg/kg); p=0.43
Conclusion	A fixed-dosed strategy of phenobarbital for severe AWS was associated with a decreased hospital length of stay when compared to benzodiazepines.

Phenobarbital Versus Benzodiazepines for the Treatment of Severe Alcohol Withdrawal



IBW: ideal body weight; mg: milligram; kg: kilogram; IM: intramuscularly; PO: by mouth
q:every; hrs: hours; HR: heart rate; SBP: systolic blood pressure

Source: Kessel KM, et al. Annals of Pharmacotherapy; 2024: 1-9.

Literature Conclusions

- Phenobarbital appears to be associated with:
  - Decreased ICU and hospital length of stay
  - Decreased need for continuous IV sedation
  - Decreased need for mechanical ventilation
  - Minimal adverse events
- Phenobarbital is safe and effective for alcohol withdrawal treatment as monotherapy or adjunctive therapy
  - History of seizures or delirium tremens with AWS
  - Severe alcohol withdrawal
  - Benzodiazepine-resistant alcohol withdrawal

Assessment Question #3

True or False – The current available literature supports the use of phenobarbital for the treatment of acute alcohol withdrawal?

A. True

B. False

Assessment Question #3 – Correct Response

True or False – The current available literature supports the use of phenobarbital for the treatment of acute alcohol withdrawal?

A. True

B. False

Remaining Gaps

- Ideal dosing strategy remains questionable
  - Multiple dosing strategies/protocols that exist throughout the literature
  - Weight to use in obesity remains unknown (if weight-based dosing)
- Majority of literature in ICU setting
  - Caution for general ward patients with decreased monitoring

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Contact:

Ali Goforth

P: 629-212-5190

E: Ali.Goforth@hcahealthcare.com

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HEALTHTRUST Performance Group®

1100 Dr. Martin L. King Jr. Boulevard, Suite 1100
Nashville, TN 37203

healthtrustpg.com