Alcohol Withdrawal in the ICU

Michael Kenes, PharmD
Jakob McSparron, MD
Objectives

• Explain the mechanism of alcohol withdrawal

• Describe strategies to manage severe alcohol withdrawal

• Define key differences between benzodiazepine and phenobarbital

• List adjunctive treatment options for patients with alcohol withdrawal
Research Needs for Inpatient Management of Severe Alcohol Withdrawal Syndrome
An Official American Thoracic Society Research Statement

Tessa L. Steel, Majid Afshar, Scott Edwards, Sarah E. Jolley, Christine Timko, Brendan J. Clark, Ivor S. Douglas, Amy L. Dzierba, Hayley B. Gershengorn, Nicholas W. Gilpin, Dwayne W. Godwin, Catherine L. Hough, José R. Maldonado, Anuj B. Mehta, Lewis S. Nelson, Mayur B. Patel, Darius A. Rastegar, Joanna L. Stollings, Boris Tabakoff, Judith A. Tate, Adrian Wong, and Ellen L. Burnham; on behalf of the American Thoracic Society Assembly on Critical Care, Assembly on Behavioral Science and Health Services Research, and Assembly on Nursing

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- Syndrome lacking clear definitions and assessments of severity
  - difficult to differentiate from other etiologies
- Evidence not directly translatable across severity of syndrome
- Objective baseline/risk factor assessment does not predict severity of withdrawal
- Multiple challenges in conducting robust clinical trials

Group poses three questions:
1. Optimal 1st line therapy?
2. Ideal dosing strategy?
3. Protocolized/bundled-care vs. “usual care”? 
A familiar case...

• 47 year old man with history of alcohol use disorder, prior admissions for withdrawal, presents with severe nausea, emesis, headache, tremors

• His last drink was approximately 14 hours prior to presentation
History

• Medical / Surgical history:
  • Alcohol use disorder (prior seizures, prior ICU admission)
  • Hypertension
  • Previous GI bleed due to gastric ulcer

• Medications:
  • Not taking prescribed antihypertensive medication
Exam

- Afebrile
- HR 110 bpm
- BP 170/88 mmHg
- RR 24
- SpO2 97%

Labs unrevealing
AST/ALT slightly elevated
EtOH/UDS negative

- Cachectic, ill appearing
- Tremulous and diaphoretic
- OP clear with dry mucous membranes
- Tachycardic, regular
- Lung clear bilaterally
- Abdomen nondistended, +BS, nontender
- Hyperreflexic
Clinical Course

• Patient increasingly agitated and restless, refusing care, notes seeing things on the wall that are not there.

• Next step?
Clinical Course

• Patient receives 6mg IV lorazepam for EtOH withdrawal with minimal improvement in symptoms. He has witnessed seizure activity and receives additional 4mg IV lorazepam with cessation of seizure activity.

• He continues to demonstrate adrenergic symptoms, intermittently combative.

• Next step?
Clinical Course

- Patient receives increasing doses of lorazepam over next 30 minutes with subsequent prolonged generalized seizure. He is intubated and sedated with propofol. His course is notable for VAP, delirium. He is extubated on hospital day 7 and discharged home on day 12.
Homeostasis – even balance

- GABA
  - CNS depression
- Glutamate
  - CNS excitation
Occasional Alcohol ➔ Intoxication / CNS Depression
Homeostasis: Chronic Alcohol Use

GABA + Alcohol

Glutamate
Alcohol Withdrawal $\rightarrow$ CNS Hyperexcitation
Mechanism of Withdrawal – complex and heterogenous

• **Acute alcohol consumption**
  • Activates *inhibitory* gamma-aminobutyric acid (GABA) receptors at high concentrations
  • Inhibits *excitatory* N-methyl-D-aspartate (NMDA) receptors

• **Chronic alcohol consumption**
  • Downregulation of inhibitory "GABA-ergic" system
  • Upregulation of excitatory NMDA receptors
  • --> Upregulation of excitatory glutamine receptors
Mechanism of Withdrawal — complex and heterogenous

• Withdrawal sx mainly caused by unoccupied, up-regulated NMDA receptors

• Multiple, repeated intoxication/withdrawal episodes contribute a “kindling effect”

• Other mechanisms often present
  • Increased dopamine (→ hallucinations)
  • Increased adrenergic (→ sympathetic hyperactivity)
  • Increased HPA activation (→ increased cortisol)
Severity and Spectrum of Alcohol Withdrawal Syndrome (AWS)

- Alcohol consumption is common (55% of adults)
- Lifetime prevalence of AUD 29%
- Complex and dynamic
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<th>Awareness</th>
<th>Psychiatric</th>
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<td>Tachycardia</td>
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Benzodiazepines

- Binds to inhibitory GABA receptor -> Increase influx of chloride ions in channel
  - Increases **frequency** of channel opening
  - But remember... Alcohol use disorder down-regulates GABA receptors

- Historically regarded as 1st line therapy
  - Control psychomotor agitation
  - Effective at reducing risk of withdrawal seizures and DTs
  - 2011 Cochrane review of 7,333 patients
    - BZDs reduced seizures compared to placebo (RR 0.16) and antipsychotics (RR 0.24)
    - No statistical difference between BZD agents (trend toward benefit with chlordiazepoxide?)

- Selection generally guided by pharmacokinetics
  - IV administration preferred (oral when able); variable absorption with IM

Hammond D. Hospital Pharmacy. 2017.
# Pharmacokinetics of Select Benzodiazepines

<table>
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<tr>
<th>Medication</th>
<th>Time to Peak Plasma Level (Hours)</th>
<th>Elimination Half-Life, Parent (Hours)</th>
<th>Metabolic Pathway</th>
<th>Clinically Significant Metabolites</th>
<th>Protein Binding (%)</th>
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<tbody>
<tr>
<td>Chlordiazepoxide</td>
<td>1-4</td>
<td>5-30</td>
<td>N-Dealkylation</td>
<td>Desmethyldiazepoxide</td>
<td>96</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Oxidation</td>
<td>Demoxepam</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>DMDZ</td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.5-2</td>
<td>20-80</td>
<td>Oxidation</td>
<td>DMDZ</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Oxazepam</td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>2-4</td>
<td>10-20</td>
<td>Conjugation</td>
<td>—</td>
<td>85</td>
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DMDZ = desmethyldiazepam; half-life 50-100 hours
Strategies for Use of Benzodiazepine

- **Symptom-triggered**
  - Patients need to be symptomatic, coupled with regular (re-) assessment
  - Most common scale = Addiction Research Foundation Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)
    - Not validated in ICU (intubated)
  - ICU → Richmond Agitation-Sedation Scale (RASS)?

- Medication only given when exhibiting symptoms
  - Generally, prefer short-acting (i.e., lorazepam, diazepam)
  - Longer acting not contraindicated (i.e., chlordiazepoxide)

- Historically demonstrated to lead to shorter treatment duration, reduced risk of oversedation compared to fixed-dosing

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Strategies for Use of Benzodiazepine

- **Loading dose** or "Front-loading"
  - Generally thought to be appropriate for initial severe presentations
    - i.e., CIWA-AR >19
  - Caution in those who might experience AE (elderly, severe liver disease, DDIs)

- **Fixed-dose** – effective, but high risk for "over-dosing"
  - Close monitoring for sedation/respiratory depression needed
  - No superiority vs. symptom-triggered, may be beneficial w/history of DTs/seizures
  - May be beneficial if symptoms do not align with scoring tools
Barbiturates - Phenobarbital

- Binds to inhibitory GABA receptor -> increase time chloride channels are open (synergistic effect w/BZDs)
  - Secondary mechanism – inhibits the excitatory (up-regulated) NMDA receptor
  - No paradoxical agitation (?or delirium)

- Rapid onset (<5 minutes) with IV administration
- Long half-life/duration of action (2-5 days)
  - Some accumulation of doses within 24-48 hours

- Single-compartment model or "linear dose/concentration"

- Therapeutic drug monitoring available
  - Epilepsy = 15-40 mcg/mL
  - Ataxia/nystagmus = ~50 mcg/mL
  - Coma/stupor = >65 mcg/mL

Phenobarbital Clinical Pearls

• Organ Dysfunction

• Metabolized in liver (~60-80%), but also eliminated unchanged in kidneys

• Half-life increases in cirrhosis
  • Kidney compensates to increase excretion

• Does not result in higher peaks; half-life/duration increases (i.e., longer "self-taper")

"Changes [to PB metabolism in liver disease] are modest .. because excretion of unchanged PB via the kidneys tends to moderate the importance of impaired hepatic function."

THE EFFECT OF LIVER DISEASE IN MAN ON THE DISPOSITION OF PHENOBARBITAL 

JOHN ALVIN, TOM MC HORSE, ANASTACIO HOYUMPA, MILTON T. BUSH AND STEVEN SCHENKER

Departments of Pharmacology and Medicine, Vanderbilt University School of Medicine and Veterans Administration Hospital, Nashville, Tennessee

Accepted for publication July 8, 1974

ABSTRACT


The disposition of phenobarbital (PB) was studied in normal individuals and in patients with cirrhosis or acute viral hepatitis to determine 1) if there is significant impairment of PB metabolism in hepatic disease and 2) to what extent such abnormal disposition of the drug affects its disappearance from blood. The diagnosis of liver disease was based on characteristic clinical findings, biochemical liver "function" tests and liver biopsy when necessary. All individuals had normal renal function and were free of other drug and alcohol intake for at least 3 weeks. With radionuclide methodology, PB and its principal metabolites, p-hydroxyphenobarbital (PBOH) and conjugated PBOH (PBOC), were monitored in blood and urine for 5 days after a single dose of 14C-PB administered intraduodenally. PB blood half-life (T1/2) in the control group was 36 ± 3 hours (S.E.). In cirrhosis the T1/2 was prolonged to 130 ± 15 hours (P < .001) and this was accompanied by a 50% reduction in urinary PBOC excretion (P < .05). Urinary excretion of PB and PBOH was unaltered by cirrhosis. In patients with acute viral hepatitis, PB T1/2 was not significantly prolonged and urinary excretion of PB and its metabolites was in the normal range (P > .05). No PBOH and only traces of PBOC were detected in the blood of either control individuals or patients with liver disease. Urinary excretion of unchanged PB was an important elimination pathway of the drug in all groups. As a result of this, PB T1/2 in cirrhosis was only moderately prolonged.
Phenobarbital Clinical Pearls

• Drug-Drug Interactions
  • Minor substrate of CYP 2C19/2C9/2E1
  • Induces
    • CYP 3A4 (strong)
    • CYP 1A2/2A6/2B6/2C9 (weak)
    • UGT1A1 (weak)

• Induction generally occurs 1 week after initiation (maximal at 2-3 weeks); de-induction 1 week after discontinuation
  • Unclear and potentially insignificant effect of short period of exposure
  • Assess risk/benefit of individual drug interactions
    • Consult drug information resources and/or clinical pharmacist
Example Phenobarbital Protocol

Initial load + small PRN doses

Vs.

Symptom-trigger PRN doses (65mg vials, usually stocked in unit)

~10mg/kg dose *generally* produces a peak concentration of 10-15 mcg/mL (subtherapeutic for epilepsy indication)

General max dose is 15/20/25 mg/kg

Higher dosing requirements prompts investigation of other causes (or adjuncts)
Comparing the options

Benzodiazepines

- Symptom triggered > fixed dosing
  - Decreased dosage, Decreased time on MV, Decreased ICU LOS

- Multiple agents with varying onset/duration
  - Provider familiarity
  - Comfort in all patient care settings

Hammond D. Hospital Pharmacy. 2017.
Comparing the options

**Benzodiazepines**
- Symptom triggered > fixed dosing
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  - Comfort in all patient care settings

**Phenobarbital**
- Effective for BZD "nonresponsive" AWS
- Severe AWS often requires intubation
  - 2/2 large BZD doses
- Front-loading PHB instead? Does it mitigate agitation/delirium/resp depression?
- Limited data on PHB monotherapy
- ?use outside of ED or ICU

Hammond D. Hospital Pharmacy. 2017.
Current Evidence

• 2023 SR/MA of BZD vs PHB presenting to ED, treated in ICU/ED
  • PHB "used alone or with other pharmacological agents"
  • 12 studies (1934 patients); mostly observational, significant heterogeneity
  • No difference in risk of intubation (RR 0.70, 95% CI 0.36-1.38)
  • Similar rates of seizures (RR 0.70, 95% CI 0.29-1.89)
  • No difference in ICU/hospital LOS

• Similar conclusions from a 2017 SR/MA by Hammond
  • Slightly more favorable outcomes for PHB - included broader scope of patients
Current Evidence

2023 Alwakeel, Pre/Post study

Medical ICU
- BZD: CIWA-AR – PRN Lorazepam/Diazepam
- PHB: 260mg PHB load + 130mg q15-30min PRN (max 15mg/kg)

No medication cross-over in ICU (unknown prior to ICU admission)

Regression analysis – 40% (95% CI 25.8-53.5) decrease in ICU LOS with PHB
Current Evidence

2023 Malone Pre/Post study

ED->ICU; 4-day PHB course

Load: 6-10 mg/kg IBW (3 IM injections 3hrs apart)

Daily maintenance: 60mg PO q12 x2->30mg PO q12 x3

PRN Breakthrough: 65mg IM/IV q6hr

Vs.

BZD = CIWA-Ar PRN dosing

Similar cohorts, but PHB had higher admission BAL

Total dose in study:

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<th>Median</th>
<th>Mean</th>
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<tr>
<td>Phenobarbital</td>
<td>968 mg</td>
<td>803 mg</td>
</tr>
<tr>
<td>Lorazepam equivalents</td>
<td>86 mg</td>
<td>40 mg</td>
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Adjunctive Therapy

• Dexmedetomidine
  • Alpha-2 agonist - decreased sympathetic overdrive
    • More selective for Alpha-2 vs Alpha-1 than clonidine (1620:1 vs. 220:1)
  • "Cooperative sedation" without need for intubation – BZD-sparing effect
  • No GABA activity – does not prevent seizures or DTs!!

• Propofol
  • Enhances inhibitory GABA, decreases excitatory NMDA. Minimal literature support
Adjunctive Therapy (continued)

• Anti-epileptics (carbamazepine, valproate, gabapentin, levetiracetam..)
  • Potential role for prevent seizures or DTs
    • Potentially neuroprotective by decreasing excessive neuronal activity
  • Reports demonstrate widespread used – Cochrane review of 56 studies found no benefit

• Antipsychotics
  • Potentially reduce withdrawal symptoms, especially in protracted courses
  • AEs: Increase QT interval, lower seizure threshold
Adjunctive Therapy (continued)

- Thiamine (first, and then glucose)
  - Prevents and treats Wernicke's encephalopathy
  - Often difficult to differentiate from AWS/DTs
  - Prevents thiamine-related cardiomyopathies
  - Broadly recommended, despite lack of concrete evidence
    - Uncertainty with dosing (100-500mg dose, every 6-24 hours)

- Magnesium
  - Could low serum levels precipitate "hyper-excitability"?
  - No evidence for support per 2013 Cochrane Review

- Multivitamins
Current Unknowns

• Transitioning from one class to another
  • "Failure of BZD" / dose threshold?

• Comfort with liver dysfunction
  • PK demonstrates general safety; clinical data currently lacking

• When to discharge from ICU

• Refractory withdrawal cases
Conclusions

• Alcohol withdrawal is common in the ICU

• Abrupt cessation in alcohol consumption → deficient GABA activity and excessive NMDA activity → CNS hyperexcitation

• Benzodiazepines (GABA) and Phenobarbital (GABA and NMDA) both treat delirium

• Adjunctive agents may be necessary for specific symptoms
Alcohol Withdrawal in the ICU

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