Management of Alcohol Withdrawal in Critically Ill Patients

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Disclosure

- I do not have (nor does any immediate family member have):
  - a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity
  - any affiliation with an organization whose philosophy could potentially bias my presentation

Pharmacist Objectives

- Identify challenges and clinical tools for assessing alcohol withdrawal syndrome
- Discuss symptom-triggered versus fixed-schedule doses of benzodiazepines for alcohol withdrawal syndrome in critically ill patients
- Evaluate non-benzodiazepine pharmacological therapies utilized in alcohol withdrawal protocols and their effects on clinical outcomes

Epidemiology

- Alcohol is the most abused drug in the United States
- ~17 million adults have an alcohol use disorder (AUD)

Hospitalized Patients with AUD

- 37 Million Hospital Admissions per Year in the United States
- 10% will have AWS

Intensive Care Unit (ICU) Admissions per Year in the United States

- ~6 Million ICU Admissions per Year in the United States
- 16-31% will have AWS

How Much Alcohol Is Too Much?

- 60% of the United States population reports alcohol consumption
- Moderate alcohol consumption
  - ≥ 2 drinks daily in men
  - ≥ 1 drink daily in women
- Binge drinking within a period of two hours at least once a week
  - ≥ 5 drinks in men
  - ≥ 4 drinks in women
- Heavy alcohol use is defined by the Substance Abuse and Mental Health Services Administration (SAMHSA) as:
  - Binge drinking on 5 or more days in the past month

Alcohol Withdrawal Timeline

<table>
<thead>
<tr>
<th>Stage</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tremor, autonomic activity, tachycardia, hyperventilation, headache, sweating, anorexia, nausea, vomiting</td>
</tr>
<tr>
<td>2</td>
<td>Distractibility, tonic-clonic seizures, visual, tactile, or auditory hallucinations, autonomic instability, diarrhea</td>
</tr>
<tr>
<td>3</td>
<td>Delirium tremens, severe autonomic instability, confusion, disorientation, extreme agitation</td>
</tr>
</tbody>
</table>

Time Since Last Drink

- Up to weeks

Stage Starts

- Stage 1: 6-24 hrs
- Stage 2: 24-48 hrs
- Stage 3: 49-96 hrs

If left untreated
Complications of AWS

Severe Symptoms
- Cardiovascular and respiratory collapse
- Arrhythmias
- Dehydration
- Electrolyte imbalances
- Multi-organ dysfunction

Increased mortality
- 5 – 15% for untreated
- 1 – 2% for treated

Costs $249 Billion
- Total United States
- Justice
- Productivity
- Health
- Collisions
- Hospital

Severity of alcohol dependence (quantity, frequency, duration of alcoholism)
- Higher blood or breath alcohol level on admission (i.e. > 200 mg/dl)
- Abnormal liver function (elevated AST)

Other medical conditions
- Cardiovascular and respiratory collapse
- Severe respiratory distress
- Psychoses (delirium tremens)
- Cardiac arrhythmias

Screening Tools Used to Detect AUD

<table>
<thead>
<tr>
<th>Tool</th>
<th>Development</th>
<th>Description</th>
</tr>
</thead>
</table>
| CAGE | Ewing JA, et al. [1984] | 4-question tool for the detection of alcohol abuse: 1. Have you ever felt you should Cut down on your drinking? 2. Have people Annoyed you by criticizing your drinking? 3. Have you ever felt bad or Guilty about your drinking? 4. Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover? 
Primary Care Setting |
| Michigan Alcohol Screening Test (MAST) | Seider M et al. [1971] | 25-question screening tool to identify drinking behavior, alcohol dependence, or adverse consequences of alcohol drinking. Shorter 13-question version developed for hospital use in 1975 (Short MAST) 
Primary Care Setting |
| Alcohol Use Disorders Identification Test (AUDIT) | Babor TF, et al. [1989] | 10-question screening tool used to identify 3 aspects of an AUD: excessive drinking pattern, hazardous drinking, and harmful consumption of alcohol. Scores range from 0 – 40 (0 indicates potentially hazardous alcohol intake). Several shortened versions also developed (AUDIT C, AUDIT PC) 
Primary Care Setting |

Prediction Tool of Complicated AWS

- Systematic online literature search for clinical factors associated with the development of alcohol withdrawal syndromes (AWS)
- Total # of articles found: N = 5753
- Duplicate articles were removed: N = 2802
- Articles meeting inclusion criteria: N = 446
- Unique articles describing predictive factors of AWS: N = 233
- 10 items were identified that correlated with complicated AWS

Diagnosis of Alcohol Use Disorder (AUD)

Diagnostic and Statistical Manual of Mental Disorders (DSM-5) Criteria for AUD
- The presence of at least 2 of these symptoms indicates an AUD
- a. Alcohol is often taken in larger amounts or over a longer period than was intended.
- b. There is a persistent desire or unsuccessful efforts to cut down or control alcohol use.
- c. There is a need for markedly increased amounts of alcohol to achieve intoxication or desired effect.
- d. A markedly diminished effect with continued use of the same amount of alcohol.
- 1. Alcohol is often taken in larger amounts or over a longer period than was intended.
- 2. There is a persistent desire or unsuccessful efforts to cut down or control alcohol use.
- 3. There is a need for markedly increased amounts of alcohol to achieve intoxication or desired effect.
- 4. A markedly diminished effect with continued use of the same amount of alcohol.

Primary Care Setting

Costs $28 Billion

Risk Factors for Severe Alcohol Withdrawal

- Prior episodes of AWS including delirium tremens or other delirium
- Older age
- Moderate to severe withdrawal symptoms at baseline (CIAA-Ar)
- Concomitant medical or surgical illness (trauma, infections, sepsis, liver disease, etc.)
- Higher blood or breath alcohol level on admission (i.e. > 200 mg/dl)
- Severity of alcohol dependence (quantity, frequency, duration of alcoholism)
- Abnormal liver function (elevated AST)
- Time since last drink

Primary Care Setting

Diagnosis of Alcohol Withdrawal (AWS)

Diagnostic and Statistical Manual of Mental Disorders (DSM-5) Criteria for AWS
- A. Consumed (or reduction in) alcohol use that has been heavy and prolonged
- B. Two (or more) of the following, developing within several hours to a few days after the cessation of (or reduction in) alcohol use described in Criterion A:
  1. Autonomic hyperactivity (eg, sweating or pulse rate greater than 100)
  2. Increased hand tremor
  3. Insomnia
  4. Increased appetite or weight gain
  5. Transient visual, tactile, or auditory hallucinations or illusions
  6. Psychomotor agitation
  7. Anxiety
  8. General malaise
C. The symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.
Validation Study of the Prediction of Alcohol Withdrawal Severity Scale (PAWSS)

- Prospective study (12 month period)
  - Hospitalized to general medicine and surgical units (N = 403)
  - Compared PAWSS < 4 (low risk); N = 374 to PAWSS ≥ 4 (high risk); N = 29

<table>
<thead>
<tr>
<th>Threshold PAWSS</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥4</td>
<td>93.5%</td>
<td>99.5%</td>
<td>95.5%</td>
<td>99.5%</td>
</tr>
</tbody>
</table>

Not Studied in Critically Ill Patients


Additional Symptoms Assessment Tools

- Modified Minnesota Detoxification Scale (mMINDS)
- CIWA-Ar

Correlation Between mMINDS and CIWA-Ar Scoring Tools

- Modified Minnesota Detoxification Scale (mMINDS)
  - More detailed definitions for assessing tremor, delusions, hallucinations
  - The Richmond Agitation Sedation Scale (RASS) is used to assess the scale of agitation
    - Single-centred prospective correlation study
    - mMINDS ≥ 4 or ≥ 10 (high risk) sensitivity 93.5% Specificity 99.5%
    - mMINDS scores were collected in 30 patients
    - Included adults admitted to a medical intensive care unit or a medical step-down unit
    - Pearson correlation coefficient across all scores was 0.82 (strong correlation)
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- CIWA-Ar
  - Clinical Institute Withdrawal Assessment (CIWA-Ar)
  - CIWA-Ar: Clinical Institute Withdrawal Assessment
  - Ectoholism

- Pearson correlation coefficient across all scores was 0.82 (strong correlation)

- CIWA-Ar: Clinical Institute Withdrawal Assessment

- Ectoholism

- Pearson correlation coefficient across all scores was 0.82 (strong correlation)

- CIWA-Ar: Clinical Institute Withdrawal Assessment

- Ectoholism

Sensitivity 93.5%
Specificity 99.5%
Positive Predictive Value 95.5%
Negative Predictive Value 99.5%

Maldonado JR, et al. Alcohol and Alcoholism. 2015

Symptoms Assessment Tool – Clinical Institute Withdrawal Assessment (CIWA-Ar)

- Severity of symptoms (max = 67):
  - ≤ 8 = mild withdrawal
  - 8 – 15 = moderate withdrawal
  - > 20 severe withdrawal

- Treatment is recommended for scores > 8
- Additional PRN medication is needed for scores > 15
- Requires patient to be able to logically respond to 7 of the 10 criteria

- Not validated in critically ill or in patients requiring mechanical ventilation

Riker Sedation Agitation Scale (SAS)

- Scales: 1-4
- Pain group (n = 41) had an increase in the max individual dose of diazepam (32 mg vs. 65 mg; p = 0.01), total amount of diazepam (248 mg vs. 562 mg; p = 0.01), and phenobarbital use (17% vs. 58%; p = 0.01). This was associated with a reduction in the need for mechanical ventilation (47% vs. 22%; p = 0.03).
Richmond Agitation Sedation Scale (RASS)

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Primary Outcome</th>
<th>Goal RASS</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duby JJ, et al. J Trauma Acute Care Surg. 2014</td>
<td>Retrospective pre (N=60)-post (N=75) study of adults with AWS admitted to an ICU. Symptom-triggered doses of diazepam (max = 120 mg) every 15 – 30 minutes until target sedation level was achieved. Phenobarbital was given as an adjunct every 30 minutes (max = 240mg).</td>
<td>ICU LOS</td>
<td>POST group had decrease in mean ICU LOS from 9.6 ± 10.5 to 5.2 ± 6.4 days (p=0.0004), fewer ventilator days (5.6 ± 13.9 vs 1.3 ± 5.6 days, p&lt;0.0001) and a decrease in BZD usage (319 mg ± 1084 mg vs 93 mg ± 171 mg, p=0.002).</td>
<td></td>
</tr>
</tbody>
</table>

AWS: alcohol withdrawal syndrome; ICU: intensive care unit; LOS: length of stay; BZD: benzodiazepines

Limitations of the Clinical Tools

- Diagnosis of AUD/AWS: DSM-5 criteria
- Structured interview could be difficult, and it is conceptually unnecessary because patients suffering from AWS usually show agitation and confusion
- Screening Tools to detect AUD: CAGE, MAST, AUDIT
- Developed in the primary care setting not in critically ill patients
- Prediction Tool: PAWSS
- Validated in medical inpatients only
- Not studied in critically ill patients

- Symptom Assessment Tools
- CIWA-Ar
- Majority of research was conducted in outpatient detoxification units
- Not validated in critically ill patients
- Requires patient to be able to logically respond to 7 of the 10 criterion
- Cannot be used in up to 45% of patients due to lack of communication
- MINDS
- Based on 1 single center study
- Not validated
- SAS / RASS
- Not validated

Most Common Clinical Tool for Assessing Severity of AWS

- Survey questionnaire sent to hospitals with ≥ 100 beds located in the northeast region of the United States
- 90 hospitals in nine states were included

Which Clinical Tool?

- Guidelines
  - Support titrating medications to scores using clinical tools and judgment
  - Do not describe which tool maybe the best for critically ill or intubated patients

- Based on Evidence
  - Using the CIWA-Ar or MINDS tool in patients capable of communicating in combination with the SAS or RASS when patients could no longer communicate

Preferred First – Line Agent

- Benzodiazepines (BZDs) are the most studied and preferred due to their efficacy and safety profile
- Better at controlling signs and symptoms and are superior to placebo in stopping the progression to delirium tremens (DTs)
- BZDs approved by the Food and Drug Administration for the treatment of AWS are:
  - Chlordiazepoxide
  - Diazepam

Drug | Half-life | Active Metabolites | Metabolism | Excretion | Equiv. Dose, mg |
<table>
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<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>Oral: 1 – 2 h</td>
<td>Desmethyldiazepam (40-120h)</td>
<td>Oxazepam (5 – 15h)</td>
<td>Hepatic – urinary(metabolites)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>IV: 1 – 5 min</td>
<td>Temazepam (5 – 10h)</td>
<td>Desmethyldiazepam Hepatic – urinary(metabolites)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>Oral: 2 h</td>
<td>Dextromethochloridiazepoxide (10h)</td>
<td>Oxazepam (5 – 15h)</td>
<td>Glucuronide</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>IV: 1 – 2 min</td>
<td>Temazepam (5 – 10h)</td>
<td>Oxazepam (5 – 15h)</td>
<td>Glucuronide</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>Oral: 1 – 2 h</td>
<td>None</td>
<td>None</td>
<td>Hepatic</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>IV: 30 – 60 min</td>
<td>None</td>
<td>None</td>
<td>Glucuronide</td>
<td>20</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Oral: 1 – 3 h</td>
<td>Apl-trihydroxydiazepam</td>
<td>CYP3A4</td>
<td>Glucuronide</td>
<td>5</td>
</tr>
</tbody>
</table>
Controversies of Benzodiazepine Treatment for AWS

- Who should receive treatment (low or high risk patients)?
- Which benzodiazepine is better?
- What dose should be used?
- How should benzodiazepines be administered?
- Symptom triggered or fixed doses


MINDS Symptom-Driven Lorazepam Protocol in ICU Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Goal</th>
<th>Primary Outcomes</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeCarolis DD, et al.</td>
<td>Retrospective observational study included 36 adult medical ICU patients with severe AWS at VA medical center</td>
<td>Symptom-driven Lorazepam Protocol</td>
<td>MINDS score &lt; 15</td>
<td>Non-protocol midazolam continuous infusion (standard local practice) vs. Symptom-driven lorazepam protocol (see next slide)</td>
<td></td>
</tr>
</tbody>
</table>

MINDS: Minnesota Detoxification Scale


Study Description Primary Outcome Goal Treatment

- Time till MINDS score < 20
- Total dose of BZD
- Time on continuous BZD infusion
- ICU and hospital LOS
- Complications of treatment
- Use of multiple BZD

MINDS: Minnesota Detoxification Scale


Retrospective observational study included 36 adult medical ICU patients with severe AWS at VA medical center.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Symptom-Driven Lorazepam Protocol</th>
<th>MINDS score &lt; 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time till the MINDS score was &lt; 20 (hrs)</td>
<td>7.7 ± 4.9</td>
<td>19.4 ± 9.7</td>
</tr>
<tr>
<td>Cumulative BZD dose (mg)</td>
<td>1544 ± 534</td>
<td>1877 ± 937</td>
</tr>
<tr>
<td>Time on continuous-infusion BZD (hrs)</td>
<td>52.0 ± 35.1</td>
<td>122.1 ± 64.4</td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>5.6 ± 1.7</td>
<td>7.7 ± 6.3</td>
</tr>
<tr>
<td>Hospital LOS (days)</td>
<td>11.2 ± 5.4</td>
<td>15.3 ± 8.9</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SD unless otherwise noted. AWS: alcohol withdrawal delirium; ICU: intensive care unit; LOS: length of stay; BZD: benzodiazepine; VA: Veterans Affairs; MINDS: Minnesota Detoxification Scale


Study Description Goal

Two hospitals in the USA

- Adult general medicine inpatients with ETOH withdrawal or dependence N = 47

<table>
<thead>
<tr>
<th>Study</th>
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<th>CIWA-Ar</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maldonado JR, et al. Gen Hosp Psychiatry, 2012</td>
<td>Two hospitals in the USA</td>
<td>CIWA-Ar</td>
<td>&lt; 8</td>
<td>Diazepam fixed dose + pm vs. Lorazepam pm only (symptom-driven)</td>
<td>No significant difference found in the average rate of change of CIWA-Ar scores, total BZD use or absence of symptoms within 72 hrs between the groups</td>
</tr>
</tbody>
</table>

CIWA-Ar: Clinical Institute Withdrawal Assessment: Alcohol scale.


Study Description Goal CIWA-Ar

PRE-POST case audit in adult inpatients being detoxified in a general hospital setting in the UK was conducted to standardize AWS practices using evidence-based regimens

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<tbody>
<tr>
<td>Murdoch J, et al. Br J Nurs. 2014</td>
<td>PRE-POST case audit in adult inpatients being detoxified in a general hospital setting in the UK was conducted to standardize AWS practices using evidence-based regimens</td>
<td>CIWA-Ar</td>
<td>&lt; 8</td>
<td>Diazepam fixed dose + pm vs. Lorazepam pm only (symptom-driven)</td>
<td>To evaluate a symptom triggered protocol (STP) with chlordiazepoxide</td>
</tr>
</tbody>
</table>

Chlordiazepoxide fixed dose + pm vs. lorazepam pm only (symptom-driven) | Chlordiazepoxide fixed dose + pm vs. lorazepam pm only (symptom-driven) | POST STP showed a decrease in the mean CIWA-Ar score by 16.5 mg (the equivalent of ~16 mg of lorazepam) p = 0.001 and a decrease in the mean duration of lorazepam use by 3.8 days (p=0.001) |

Sz: seizure; BZD: benzodiazepines; CIWA-Ar: Clinical Institute Withdrawal Assessment: Alcohol scale.
**CIWA-Ar Symptom-Driven Lorazepam Protocol**

<table>
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<tr>
<th>Study</th>
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<th>Goal CIWA-Ar</th>
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<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sachdeva et al. 2014</td>
<td>Single inpatient detox center in India. AD and uncomplicated withdrawal.</td>
<td>Total amount and duration of lorazepam and the incidence of adverse events or complications</td>
<td>≥ 8</td>
<td>Lorazepam fixed dose + prn vs. Lorazepam pm only</td>
<td>STG had lower lorazepam doses than in the FTDG (6.5 mg vs. 15.9 mg vs. 15.6 mg pg vs. 0.001), shorter duration of time (47.8 h vs. 146 h, p = 0.001). No differences in terms of seizures or delirium tremens.</td>
</tr>
</tbody>
</table>

*Definition: Detox: treatment; BZD: benzodiazepines; AD: alcohol disorder; STG: symptom triggered group; FTDG: fixed tapering dose group; CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol revised detoxification; Tx: treatment; BZD: benzodiazepines; AD: alcohol disorder; STG: symptom triggered group; FTDG: fixed tapering dose group; CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol revised detoxification.*

**Clinical Institute Withdrawal Assessment for Alcohol revised**

*ICU: intensive care unit; BZDs: benzodiazepines; Tx: treatment; mMINDS: modified Minnesota Detoxification Scale; CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol Revised.*

**mMINDS Symptom-Driven BZD Protocol**

<table>
<thead>
<tr>
<th>Study</th>
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<th>Primary Outcome</th>
<th>Goal mMINDS</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heavner et al. 2018</td>
<td>Retrospective Pre (N = 138) and Post (N = 94) protocol in medical ICU patients. Included if only one dose of BZD was received</td>
<td>Need for mechanical ventilation</td>
<td>≥ 15</td>
<td></td>
</tr>
</tbody>
</table>

*M dozen calculation: ICU: intensive care unit; BZDs: benzodiazepines; Tx: treatment; mMINDS: modified Minnesota Detoxification Scale; CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol revised.*

**Symptom-Driven Lorazepam Protocol in ICU Patients**

**Pre-intervention Group**
- CIWA ≥ 10
  - 1 - 3 mg PO LZ q6hrs x 8 doses
  - Midazolam 10 mg IVP and notify provider to assess 15 min
- CIWA 11 – 14
  - 2 mg N LZ q10min PRN max dose 10 mg/hr
- CIWA ≥ 15
  - 0.5 mg N LZ q10min PRN max dose 4 doses

**Post-intervention Group**
- CIWA < 8 or SAS 4
  - Hold LZ and re-assess in 10 min
- CIWA ≥ 8 or SAS 5
  - 2 mg N LZ q10min PRN x 4 doses
- CIWA ≥ 15 or SAS > 5
  - 4 mg N LZ q10min PRN, no max

**Outcome Goal Treatment**
- CIWA-AR
- SAS < 4
  - Proceed to Step 2 in 15 min
- SAS 4 – 15
  - Proceed to Step 2 in 30 min
- SAS > 15
  - No BZD
- CIWA ≥ 15 or SAS > 5
  - Hold LZ and re-assess in 30 min

**Study Description Goal Results**
- retrospective pre (N = 138) and post (N = 94) study in patients with AWS admitted to a medical ICU
  - CIWA < 8 or SAS 4
  - Younger Days: 6.5 (4.0 – 10.0) vs. 9.2 (4.8 – 10.5) p = 0.01
  - Ventilator Days: 4 (1.0 – 9.0) vs. 9.0 (9.0 – 15.9) p < 0.01
  - ICU LOS (days): 7 (4 – 11) vs. 11 (9 – 13) p = 0.01
  - ICU Mortality, n (%) 3 (2.2) vs. 1 (3.1) p = 0.58

**Note:** Values expressed as median interquartile range [25 – 75%] unless otherwise noted. AWS: alcohol withdrawal syndrome; ICU: intensive care unit; Tx: treatment; BZD: benzodiazepines; SAS: Sedation Agitation Scale; CIWA-Ar: Clinical Institute Withdrawal Assessment; LOS: length of stay.
mMINDS Symptom-Driven Lorazepam Protocol

- **Step 2: RN Recalculates modified Minnesota Detoxification Scale (mMINDS) Score**
  - If score remains ≥ 20, provider may increase lorazepam infusion by 4 mg/hr and notify provider to reassess score in 30 min.
  - If score drops ≤ 15, consider adjunctive therapies (phenobarbital 65 mg IVP).
  - If score remains > 20, provider may increase lorazepam infusion by 4 mg/hr and notify provider to reassess score in 30 min.
  - If score drops ≤ 15, consider adjunctive therapies (phenobarbital 65 mg IVP).

- **Step 3: Initiate Lorazepam Infusion**
  - Lorazepam 4 mg IVP and initiate lorazepam infusion at 4 mg/hr.
  - RN reassesses score in 30 min.

Heavner JJ, et al. Pharmacotherapy. 2018
Limitations
• Inpatient studies were mostly specialized detoxification centers not medical/surgical hospital floor patients
• Large proportion of low risk patients
• Smaller sample sizes

Results
• Overall symptom triggered therapy had less lorazepam equivalent doses and shorter duration of therapy

Conclusions
• Value of symptom triggered therapy on major outcomes (mortality, delirium, and seizure) couldn’t be determined due to lack of evidence
• Moderate evidence supported symptom triggered therapy improved duration and total benzodiazepine dose in detoxification centers of low-risk patients
• Results can’t be extrapolated to the inpatient hospital setting

Symptom Triggered vs. Fixed Dose Meta-analysis

Inpatient Pharmacological Management Strategies
• Web-based survey was distributed to Society for Acute Medicine (SAM) members
• 104 acute hospital sites participated across the UK
• 40% used the CIWA-Ar scale
• 80% used chloridiazepoxide and 20% used diazepam

Symptom Triggered or Fixed Dosing?
• Guidelines/Reviews: Guidelines for AWS
• Recommend dosing based on measured symptom-triggered therapy (STT) rather than fixed-dose regimens
• STT is as effective as fixed-dose therapy but requires significantly less medication and leads to a more rapid detoxification
• Superior to fixed dosing in special patient populations (low-risk)

Based on Evidence for STT
• Protocols were inconsistent amongst the literature
• Limited data to support one benzodiazepine (BZD) over others or specific dosing regimens
• Efficacy to support continuous BZD infusions are limited
• Still need additional studies to assess outcomes and dosing strategies in critically ill patients at high risk for withdrawal
• Optimal BZD selection should be based on the severity of withdrawal and concomitant diseases of the patient (ex. elderly or end-stage-liver-disease)


Additional Controversies of Benzodiazepine Treatment for AWS
• Are benzodiazepines (BZD) superior to other non-BZD for the treatment of alcohol withdrawal syndrome (AWS)?
• Which agents should be used to treat BZD-resistant patients?
• What other non-BZD pharmacological therapies are available to treat AWS and what are their effects on clinical outcomes?

Non-BZD Pharmacological Therapies Available For AWS
Phenobarbital
Dexmedetomidine
Propofol
Baclofen
Ketamine
Carbamazepine and Valproic Acid
Enteral Ethanol


SAS Symptom-Driven Diazepam/Phenobarbital Protocol in ICU Patients

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<tr>
<th>Study</th>
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<th>Primary Outcome</th>
<th>Goal SAS</th>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>Gold Ja, et al. Crit Care Med 2007</td>
<td>Retrospective cohort that had 54 patients pre-guideline and 41 patients post-guideline with SAS scores ≥ 5 who were admitted to the medical ICU solely for the treatment of alcohol withdrawal syndrome (AWS)</td>
<td>To determine if escalating doses of BZDs in combination with phenobarbital would improve outcomes</td>
<td>3–4</td>
<td>Pre-guideline: Treated in a symptom-triggered fashion with no established guidelines for dose escalation. BZDs were initiated if the patient’s SAS score was ≥5. Post-guideline: Treatment was based on symptoms and the patient’s disability as measured by the Sedation-Agitation Scale (SAS).</td>
</tr>
</tbody>
</table>

BZD: benzodiazepine; AWS: alcohol withdrawal syndrome
SAS Symptom-Driven Diazepam/Phenobarbital Protocol in ICU Patients


**Study Description Goal**

**Results**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre (N = 54)</th>
<th>Post (N = 41)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max individual dose of diazepam</td>
<td>32 mg</td>
<td>96 mg</td>
<td>0.001</td>
</tr>
<tr>
<td>Total amount of diazepam</td>
<td>248 mg</td>
<td>562 mg</td>
<td>0.001</td>
</tr>
<tr>
<td>Phenobarbital use</td>
<td>17%</td>
<td>58%</td>
<td>0.01</td>
</tr>
<tr>
<td>Mechanically intubated</td>
<td>47%</td>
<td>22%</td>
<td>0.01</td>
</tr>
<tr>
<td>Phenobarbital given in 1st 24 hrs (mg)</td>
<td>260 [87.5 – 650]</td>
<td>390 [130 – 1430]</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Values expressed as median interquartile range [25 – 75%] unless otherwise noted. IV: intravenous; EtOH: ethanol infusion; BZDs: benzodiazepines; Tx: treatment; SAS: Sedation Agitation Scale

CIWA Symptom-Driven Lorazepam Compared to Phenobarbital in ED Patients


**Study Description Primary Outcome**

**Goal**

**CIWA-Ar Treatment Results**

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Primary Outcome</th>
<th>Goal CIWA-Ar</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hendey GW, JACM</td>
<td>Prospective randomized study that includes adults with AW in the ED</td>
<td>Compare phenobarbital (300 mg) to lorazepam (2 mg) in the ED at 48 hours</td>
<td>&lt; 8</td>
<td>Lorazepam 2 mg IV vs Phenobarbital 300 mg initial dose of 130 mg for subsequent doses IV</td>
<td>No differences between phenobarbital and lorazepam in baseline CIWA scores (p = 0.3), discharge scores (p = 0.4), ED LOS (267 mins vs 296 mins, p = 0.8), or 48-hour follow-up CIWA scores (5.8 vs 7.2, p = 0.6)</td>
</tr>
</tbody>
</table>

AWS: alcohol withdrawal syndrome; ICU: intensive care unit; LOS: length of stay; BZD: benzodiazepine; RASS: Richmond Agitation Sedation Scale

RASS Symptom-Driven Diazepam/Phenobarbital Protocol in ICU Patients


**Study Description Goal RASS**

**Results**

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<thead>
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<th>Goal RASS</th>
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<td>Duby JJ, JACSC</td>
<td>Retrospective pre (N = 60 episodes) - post (N = 75 episodes) study of 132 adults with AWS admitted to an ICU.</td>
<td>ICU LOS 0 to -2</td>
<td>Pre-intervention (PRE) group were treated with BZD in a non-protocolized fashion (continuous infusions or scheduled doses) vs. Post-intervention (POST) group: see next slide</td>
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AWS: alcohol withdrawal syndrome; ICU: intensive care unit; LOS: length of stay; BZD: benzodiazepine; RASS: Richmond Agitation Sedation Scale

RASS Symptom-Driven Diazepam/Phenobarbital Protocol in ICU Patients


**Study Description Goal RASS**

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RASS Symptom-Driven Diazepam/Phenobarbital Protocol in ICU Patients


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Values expressed as mean ± SD unless otherwise noted. AWS: alcohol withdrawal syndrome; ICU: intensive care unit; LOS: length of stay; BZD: benzodiazepines; RASS: Richmond Agitation Sedation Scale; Cont: continuous
Phenobarbital

- Benefit
  - Low addiction potential given long half-life (~79 hours)
- Concerns
  - Over-sedation and respiratory depression
- Role in therapy
  - Initial dose prior to implementing BZD therapy
  - Second line option for patients who are BZD-resistant
- No advantage over BZDs as an alternative

Dexmedetomidine

- Benefit
  - Light sedation without respiratory depression
  - Anxiolytic/sympatholytic properties that reduce autonomic hyperactivity which support its use in AWS
- Concerns
  - Bradycardia and hypotension (especially with loading dose)
  - Not able to prevent alcohol withdrawal seizures
- Cost
- Role in therapy
  - Adjunctive to BZD and consideration for fixed-dose DEX (Mueller, et al.)
  - Inconclusive data to suggest that DEX would reduce the need for intubation or affect ICU or hospital LOS

Non-BZD Pharmacological Therapies Available For AWS

- Phenobarbital
- Dexmedetomidine
- Propofol
- Baclofen
- Ketamine
- Carbamazepine and Valproic Acid
- Enteral Ethanol

DEX: Dexmedetomidine; AWS: alcohol withdrawal syndrome
Non-BZD Pharmacological Therapies Available For AWS

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| Lorentzen K, et al. Acta Psychiatr Scand 2014 | 70 | RCT | Diagnosed with AWD by ICD-9 criteria and last alcohol/day during the previous 24 h | Baclofen (30 mg) or Chlordiazepoxide (75 mg) or placebo three times per day for 7 days. | Baclofen or placebo which was significantly more effective than chlordiazepoxide in reducing the total CIWA-Ar scores. Both showed reduction in the total CIWA-Ar score (50% vs 20%) in the placebo group and 75% vs 70% in the treatment groups (p<0.05).
| Girish K, et al. Biomed J. 2016 | 70 | Parallel group | Diagnosed with AWD by ICD-9 criteria and last alcohol/day during the previous 24 h | Baclofen (30 mg) in addition to standard protocol or standard protocol alone for 7 days. | Baclofen supplementation, and also showed a better subject satisfaction compared to baclofen and standard protocol.

BZD: benzodiazepines; AWS: alcohol withdrawal syndrome

Propofol

- **Benefit**
  - GABA-receptor agonist activity at an alternative site to BZDs and antagonizes NMDA receptors
  - Quick onset, short duration – allows for rapid titration
- **Concerns**
  - Bradycardia and hypotension
  - Greater degree of sedation could affect ventilator day and LOS
- **Role in therapy**
  - Second line option for patients who are BZD-resistant
  - No advantage over BZDs as an alternative

Non-BZD Pharmacological Therapies Available For AWS

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BZD: benzodiazepines; AWS: alcohol withdrawal syndrome

Baclofen Review for AWS

- **Benefit**
  - GABA-receptor agonist activity at an alternative site to BZDs and antagonizes NMDA receptors
  - Quick onset, short duration – allows for rapid titration
- **Concerns**
  - Only studied orally (not ideal for ICU patients)
  - Role in therapy
  - Adjunctive to BZD in outpatients
  - Further studies need to be conducted in ICU patients

Non-BZD Pharmacological Therapies Available For AWS

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  - Role in therapy
  - Adjunctive to BZD in outpatients
  - Further studies need to be conducted in ICU patients

Propofol

- **Benefit**
  - GABA-agonist activity at an alternative site to BZDs and antagonizes NMDA receptors
  - Quick onset, short duration – allows for rapid titration
- **Concerns**
  - Bradycardia and hypotension
  - Greater degree of sedation could affect ventilator day and LOS
Retrospective Review of Ketamine for AWS

**Study** | **N** | **Design** | **Criteria** | **Treatment** | **Primary Outcome/Results**
--- | --- | --- | --- | --- | ---
Wong A, et al, *Ann Pharmacother* 2015 | 67 | RCS | ICU patients with a CIWA-Ar ≥ 20 requiring LZ infusion | Adjunctive ketamine infusions, in addition to hourly BZD as standard care | A nonsignificant decrease in diazepam equivalents used was seen at 12 hrs (40.0 mg, p=0.110) and 24 hrs (13.3 mg, p=0.330) after ketamine initiation
Shah P, et al, *J Med Toxicol.* 2018 | 30 | RCS | Medical ICU patients with a CIWA-Ar ≥ 20 requiring LZ infusion | Ketamine was initiated after a LZ infusion was inadequate in controlling symptoms and was typically weaned off (starting dose of 0.5 mg/kg/h; max dose of 4.5 mg/kg/h) | Ketamine was initiated ~41 hrs after a LZ infusion was started and the average LZ infusion rate was 14 mg/h at ketamine initiation. 73% of pts were intubated, with an average duration of 5.4 days. Within the first hour of initiation, LZ infusions were decreased at 24 hrs (−4 mg/h; p = 0.01)
Pizon AF, et al, *Crit Care Med.* 2018 | 63 | RCS | ICU pts diagnosed with DT by DSM-IV criteria | PRE: ST BZD and/or phenobarbital POST: ST BZD and/or phenobarbital and ketamine infusion (0.15-0.3 mg/kg/hr) was initiated as adjunct therapy until DT resolved | Median ketamine duration was 47 hrs (mean infusion of 0.19 mg/kg/hr). Ketamine was associated with a significant reduction in ICU LOS (11.2 vs. 5.7 days, p<0.001) and intubation rates (22 vs. 10, p<0.001). Ketamine pts received fewer BZDs and propofol

RCS: retrospective cohort study; LZ: lorazepam; DSM-IV: diagnostic and statistical manual of mental disorders; ST: symptom triggered; CIWA-Ar: Clinical Institute Withdrawal Assessment; AWS: alcohol withdrawal syndrome; BZD: benzodiazepine; LOS: length of stay

Non-BZD Pharmacological Therapies Available For AWS

- Phenobarbital
- Dexmedetomidine
- Propofol
- Baclofen
- Ketamine
- Carbamazepine and Valproic Acid
- Enteral Ethanol

**Carbamazepine and Valproic Acid**

**Benefit**
- VPA has fewer side effects

**Concerns**
- CBZ associated with more adverse events (CNS disturbances)
- Role in therapy
- VPA may be more effective adjunct than CBZ
- More prospective studies need to be conducted that assess VPA or CBZ as adjunct therapy to BZDs for AWS
- Cochrane review on anticonvulsants for alcohol dependence does not recommend anticonvulsants for AWS

**Benefit**
- Mimics the effects of ethanol on the NMDA receptor provides an alternative mechanism

**Concerns**
- Dissociated state at high doses
- Cost

**Role in therapy**
- Does not appear to have any clinically significant impact on the treatment of AWS
- Still no consensus on the appropriate dose, timing of initiation, and the risk of adverse events or affect on ICU or hospital LOS

RCS: retrospective cohort study; CBZ: carbamazepine; VPA: valproic acid; AWS: alcohol withdrawal syndrome

Non-BZD Pharmacological Therapies Available For AWS

- Phenobarbital
- Dexmedetomidine
- Propofol
- Baclofen
- Ketamine
- Carbamazepine and Valproic Acid
- Enteral Ethanol

**Non-BZD Pharmacological Therapies Available For AWS**

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- Propofol
- Baclofen
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- Carbamazepine and Valproic Acid
- Enteral Ethanol

**Carbamazepine and Valproic Acid**

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RCS: retrospective cohort study; CBZ: carbamazepine; VPA: valproic acid; AWS: alcohol withdrawal syndrome
Enteral Ethanol

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</tr>
</thead>
<tbody>
<tr>
<td>Fullwood, J. E., et al. AJCC 2013</td>
<td></td>
<td>Prospective, randomized, controlled trial</td>
<td>Unstable angina or AMI who were admitted to the CCU and were identified as being at high risk for AW using the CAGE questionnaire</td>
<td>LZ or Ethanol and LZ</td>
<td>Safety-associated complication rates (self-extubation, delirium tremens, reinfarction) did not differ between groups (24% LZ vs 18% ethanol; p=0.56). Days spent in the CCU (7% LZ vs 2% ethanol; p=0.32) and overall hospital stay (6% LZ vs 6% ethanol; p=0.72) did not differ between the groups.</td>
</tr>
</tbody>
</table>

This small population, restriction to the CCU, and absence of cumulative dose data make it difficult to extrapolate this information to other ICU populations.

Summary

- Clinical Tool
  - Using the CIWA-Ar or MINDS tool in patients capable of communicating in combination with the SAS or RASS when patients no longer communicate

- Symptom Triggered or Fixed Dosing
  - Recommend dosing based on measured symptom-triggered therapy (STT) rather than fixed-dose regimens
  - Optimal BZD selection should be based on the severity of withdrawal and concomitant diseases of the patient (e.g. elderly or end-stage liver disease)
  - Consider lorazepam for STT as it was the most commonly evaluated

- Non-Benzodiazepine pharmacological therapies for alcohol withdrawal syndrome (AWS)
  - Data regarding non-benzodiazepines is limited (AWS)
  - Phenobarbital has the best available data for BZD-resistant or adjunctive BZD therapy

Management of Alcohol Withdrawal in Critically Ill Patients

Mallory Fiorenza, PharmD, BCPS, BCCCP
Critical Care Specialist
Lee Health, Fort Myers, FL