Treatment of Severe Alcohol Withdrawal

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Disclosures

• These individuals have the following to disclose concerning possible financial or personal relationships with commercial entities (or their competitors) that may be referenced in this presentation.

• The following individuals have nothing to disclose
Objectives

• Discuss the pathophysiology of alcohol withdrawal
• Describe the pharmacologic treatment options for alcohol withdrawal
• Review literature related to pharmacologic therapy for alcohol withdrawal
Definition of Alcohol Withdrawal Syndrome (AWS)

A cluster of symptoms which occurs in alcohol-dependent people after cessation or reduction in heavy prolonged alcohol use.
The Alcohol Abuse Epidemic

An estimated 8.2 million Americans suffer from alcohol dependence

- 1.2 million hospital admissions are related to EtOH abuse
- ~40% of patients in the emergency room (ER) suffer from EtOH dependence
- Incidence of AWS in the intensive care unit (ICU) ranges from 8-40%

NEJM. 2014;371:2109-2113.
Alcohol. 2014;48(4):375-90
Pathophysiology of Non-Alcoholic
Pathophysiology of Occasional and Chronic EtOH User

Intoxication: Occasional User

Chronic and Regular EtOH Use
Pathophysiology of AWS

GABA

Glutamate
Signs and symptoms of alcohol withdrawal

• Autonomic hyperactivity
  – Nausea/vomiting
  – Tremor
  – Diaphoresis
  – Tachycardia
  – Hypertension
  – Insomnia

• Hallucinations
  – Visual
  – Auditory
  – Tactile

Signs and symptoms of alcohol withdrawal

• Seizure
  – Affects ~10% of patients with AWS
  – Common in patients with history of multiple detoxifications or seizure
  – Characterized as diffuse, tonic-clonic seizures

• Delirium tremens
  – Affects ~5% of patients with AWS
  – Most severe form of AWS
  – Characterized by rapid fluctuation of consciousness and change in cognition occurring over a short period of time

• Kindling
Stages of AWS

Stage 1: Minor withdrawal symptoms
- 6-8 hours after last drink
- Tremors, diaphoresis, nausea/vomiting, tachycardia, hypertension

Stage 2: Alcoholic hallucinosis
- 10-30 hours after last drink
- Visual, auditory, and tactile disturbances

Stage 3: Alcohol withdrawal seizures
- 12-48 hours after last drink
- Generalized tonic-clonic seizures

Stage 4: Delirium tremens
- 48-96 hours after last drink
- Delirium, psychosis, hallucinations, hyperthermia, malignant hypertension, seizure, coma

DSM-5* Diagnostic Criteria for EtOH Withdrawal

**Criterion A**
- Cessation of or reduction in heavy and prolonged use of EtOH

**Criterion B**
- At least 2 symptoms
  - Autonomic hyperactivity
  - Increased hand tremor
  - Insomnia
  - Nausea/vomiting
  - Transient hallucinations or illusions
  - Psychomotor agitation
  - Anxiety
  - Generalized tonic-clonic seizures

* DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
Treatment of AWS
Treatment Goals

Keep the patient awake, calm, and cooperative

Reduce symptom severity and prevent major complications

Reduce long-term central nervous system complications
Identification of patients at risk for alcohol withdrawal

- Severe history of alcohol dependence
- History of withdrawal, withdrawal seizures, or delirium tremens (DTs)
- Increased duration and amount of drinking
- Binge pattern drinking
- Multiple past detoxifications
Predictors of Severe AWS

- Older age
- Past history of DTs or EtOH withdrawal seizure
- Severe withdrawal symptoms at initial assessment
- Co-morbid medical or surgical illness
- Presence of dehydration
- Electrolyte disturbances
- Deranged liver enzymes
- Presence of structural brain lesions

Prediction of Alcohol Withdrawal Severity Scale (PAWSS)

<table>
<thead>
<tr>
<th>Part A: Threshold Criteria:</th>
<th>Yes or No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you consumed any amount of EtOH (i.e. been drinking) within the last 30 days? OR did the patient have a “+” BAL* on admission?</td>
<td></td>
</tr>
<tr>
<td><em>If the answer to either is YES, proceed with test.</em></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Part B: Based on patient interview:</th>
<th>1 point each</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Have you been recently intoxicated/drunken within the last 30 days?</td>
<td></td>
</tr>
<tr>
<td>2. Have you ever undergone EtOH use disorder rehabilitation treatment or treatment for alcoholism?</td>
<td></td>
</tr>
<tr>
<td>3. Have you ever experienced any previous episodes of EtOH withdrawal, regardless of severity?</td>
<td></td>
</tr>
<tr>
<td>4. Have you ever experienced blackouts?</td>
<td></td>
</tr>
<tr>
<td>5. Have you ever experienced EtOH withdrawal seizures?</td>
<td></td>
</tr>
</tbody>
</table>

*BAL = blood alcohol level
## Prediction of Alcohol Withdrawal Severity Scale (PAWSS)

### Part B: Based on patient interview (continued):

<table>
<thead>
<tr>
<th>Question</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Have you ever experienced delirium tremens or DT's?</td>
<td>1 point each</td>
</tr>
<tr>
<td>7. Have you combined EtOH with other &quot;downers&quot; like benzodiazepines or barbiturates during the last 9 days?</td>
<td>1 point each</td>
</tr>
<tr>
<td>8. Have you combined EtOH with any other substance of abuse during the last 90 days?</td>
<td>1 point each</td>
</tr>
</tbody>
</table>

### Part C: Based on clinical evidence:

<table>
<thead>
<tr>
<th>Question</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. Was the patient's blood alcohol level (BAL) on presentation ≥200?</td>
<td>1 point each</td>
</tr>
<tr>
<td>10. Is there evidence of increased autonomic activity? (i.e. HR &gt;120 bpm, tremor, sweating, agitation, nausea)</td>
<td>1 point each</td>
</tr>
</tbody>
</table>

**Total Score:**

PAWSS score ≥4 suggests high risk of moderate to severe EtOH withdrawal.
Assessment Scales for AWS

- Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A) Scale
- Clinical Institute Withdrawal Assessment for Alcohol Scale, Revised (CIWA-Ar)
- CIWA-AD
- Alcohol Withdrawal Scale
Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar)

- Most extensively studied tool to quantify alcohol withdrawal
- Well documented reliability, reproducibility, and validity
- 10 categories for assessment
  - 0-7 points for each category except clouding of senses
  - Total of 67 points allowed
<table>
<thead>
<tr>
<th><strong>Pulse or heart rate, taken for one minute:</strong></th>
<th><strong>Blood pressure:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NAUSEA AND VOMITING</strong>—As “Do you feel sick to your stomach? Have you vomited?” Observation.</td>
<td></td>
</tr>
<tr>
<td>0 no nausea and no vomiting</td>
<td>0 none</td>
</tr>
<tr>
<td>1 mild nausea with no vomiting</td>
<td>1 very mild itching, pins and needles sensations, any burning, any numbness or do you feel bugs crawling on or under your skin? Observation.</td>
</tr>
<tr>
<td>2</td>
<td>2 mild itching, pins and needles, burning or numbness</td>
</tr>
<tr>
<td>3</td>
<td>3 moderate itching, pins and needles, burning or numbness</td>
</tr>
<tr>
<td>4 intermittent nausea with dry heaves</td>
<td>4 moderately severe hallucinations</td>
</tr>
<tr>
<td>5</td>
<td>5 severe hallucinations</td>
</tr>
<tr>
<td>6</td>
<td>6 extremely severe hallucinations</td>
</tr>
<tr>
<td>7 constant nausea, frequent dry heaves and vomiting</td>
<td>7 continuous hallucinations</td>
</tr>
<tr>
<td><strong>TREMOR</strong>—Arms extended and fingers spread apart. Observation.</td>
<td></td>
</tr>
<tr>
<td>0 no tremor</td>
<td>0 not present</td>
</tr>
<tr>
<td>1 not visible, but can be felt fingertip to fingertip</td>
<td>1 very mild harshness or ability to frighten</td>
</tr>
<tr>
<td>2</td>
<td>2 mild harshness or ability to frighten</td>
</tr>
<tr>
<td>3</td>
<td>3 moderate harshness or ability to frighten</td>
</tr>
<tr>
<td>4 moderate, with patient’s arms extended</td>
<td>4 moderately severe hallucinations</td>
</tr>
<tr>
<td>5</td>
<td>5 severe hallucinations</td>
</tr>
<tr>
<td>6</td>
<td>6 extremely severe hallucinations</td>
</tr>
<tr>
<td>7 severe, even with arms not extended</td>
<td>7 continuous hallucinations</td>
</tr>
<tr>
<td><strong>PAREOXYSMAL SWEATS</strong>—Observation.</td>
<td></td>
</tr>
<tr>
<td>0 no sweat visible</td>
<td>0 not present</td>
</tr>
<tr>
<td>1 barely perceptible sweating, palms moist</td>
<td>1 very mild sensitivity</td>
</tr>
<tr>
<td>2</td>
<td>2 mild sensitivity</td>
</tr>
<tr>
<td>3</td>
<td>3 moderate sensitivity</td>
</tr>
<tr>
<td>4 beads of sweat obvious on forehead</td>
<td>4 moderately severe hallucinations</td>
</tr>
<tr>
<td>5</td>
<td>5 severe hallucinations</td>
</tr>
<tr>
<td>6</td>
<td>6 extremely severe hallucinations</td>
</tr>
<tr>
<td>7 drenching sweats</td>
<td>7 continuous hallucinations</td>
</tr>
<tr>
<td><strong>ANXIETY</strong>—Ask “Do you feel nervous?” Observation.</td>
<td></td>
</tr>
<tr>
<td>0 no anxiety, at ease</td>
<td>0 not present</td>
</tr>
<tr>
<td>1 mildly anxious</td>
<td>1 very mild sensitivity</td>
</tr>
<tr>
<td>2</td>
<td>2 mild sensitivity</td>
</tr>
<tr>
<td>3</td>
<td>3 moderate sensitivity</td>
</tr>
<tr>
<td>4 moderately anxious, or guarded, so anxiety is inferred</td>
<td>4 moderately severe hallucinations</td>
</tr>
<tr>
<td>5</td>
<td>5 severe hallucinations</td>
</tr>
<tr>
<td>6</td>
<td>6 extremely severe hallucinations</td>
</tr>
<tr>
<td>7 equivalent to acute panic attacks as seen in severe delirium or acute schizophrenic reactions</td>
<td>7 continuous hallucinations</td>
</tr>
<tr>
<td><strong>AGITATION</strong>—Observation.</td>
<td></td>
</tr>
<tr>
<td>0 normal activity</td>
<td>0 not present</td>
</tr>
<tr>
<td>1 somewhat more than normal activity</td>
<td>1 very mild</td>
</tr>
<tr>
<td>2</td>
<td>2 mild</td>
</tr>
<tr>
<td>3</td>
<td>3 moderate</td>
</tr>
<tr>
<td>4 moderately fidgety and restless</td>
<td>4 moderately severe</td>
</tr>
<tr>
<td>5</td>
<td>5 severe</td>
</tr>
<tr>
<td>6</td>
<td>6 very severe</td>
</tr>
<tr>
<td>7 paces back and forth during most of the interview, or constantly thrashes about</td>
<td>7 extremely severe</td>
</tr>
</tbody>
</table>

This scale is not copyrighted and may be used freely.

**ORIENTATION AND CLOUDING OF SENSORIUM**—Ask “What day is this? Where are you? Who am I?”

| 0 oriented and can do serial additions | |
| 1 cannot do serial additions or is uncertain about date | |
| 2 disoriented for date by no more than 2 calendar days | |
| 3 disoriented for date by more than 2 calendar days | |
| 4 disoriented for place and/or person | |

| **Total CIWA-A Score:** | |
| **Rater’s Initials:** | |
| **Maximum Possible Score:** 67 | |
CIWA-Ar Classification of Severity

• Score 0-7 = minimum to mild withdrawal
  – Generally does not require treatment
  – Consider outpatient treatment

• Score 8-20 = moderate withdrawal
  – Closer monitoring required
  – Will require pharmacologic treatment

• Score ≥20 = severe withdrawal
  – Close monitoring required
  – Will require pharmacologic treatment
Supportive Care

- Fluid resuscitation
- Electrolyte replacement
- Vitamin repletion
  - Multivitamin
  - Thiamine
  - Folic acid
- Correction of hypoglycemia

*NEJM.* 2014;371:2109-2113.
*Cleveland Clinic Journal of Medicine.* 2016;83:67-79.
Pharmacologic Treatment

• First Line Therapy
  – Benzodiazepines (BZDs)

• Adjunctive Therapy
  – Severe or Refractory AWS: phenobarbital, propofol, and dexmedetomidine
  – Agitation: haloperidol
  – Cardiac adrenergic symptoms: clonidine, beta-blockers
Benzodiazepines

• Use as first-line therapy established in a 1969 study comparing different medications
  – Lowest incidence of DTs
  – Lowest incidence of EtOH withdrawal seizures
• Replace the inhibitory effect of alcohol which has been discontinued
• Choice of agent depends on dosage forms, pharmacokinetics, patient-specific factors, and cost

NEJM. 2014;371:2109-2113.
# Benzodiazepines Used in AWS

<table>
<thead>
<tr>
<th>Dosage Forms</th>
<th>Chlordiazepoxide</th>
<th>Diazepam</th>
<th>Lorazepam</th>
<th>Oxazepam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equivalent Dosages</td>
<td>Oral</td>
<td>Oral, Gel, IM, IV</td>
<td>Oral, IM, IV</td>
<td>Oral</td>
</tr>
<tr>
<td>25mg</td>
<td>5mg</td>
<td>1mg</td>
<td>15mg</td>
<td></td>
</tr>
<tr>
<td>Half-life</td>
<td>5-15 hours with active metabolites &gt;100 hours</td>
<td>30-60 hours with active metabolites &gt;100 hours</td>
<td>10-20 hours</td>
<td>5-20 hours</td>
</tr>
<tr>
<td>Lipid Solubility</td>
<td>Less lipophilic than diazepam; slower onset of action</td>
<td>Highly lipophilic; quick onset of action</td>
<td>Less lipophilic than diazepam, slower onset of action</td>
<td>Less lipophilic than diazepam; slower onset of action</td>
</tr>
<tr>
<td>Effect of Hepatic Disease</td>
<td>Half-life increases in cirrhosis</td>
<td>Half-life increases in cirrhosis, acute viral hepatitis, chronic active hepatitis</td>
<td>Half-life increases in cirrhosis</td>
<td>Half-life increases in cirrhosis</td>
</tr>
<tr>
<td>Effect of Renal Disease</td>
<td>No effect</td>
<td>Decreases protein binding</td>
<td>Half-life increase; impaired elimination</td>
<td>No effect</td>
</tr>
<tr>
<td>Effect of Older Age</td>
<td>Slower absorption; half-life increases</td>
<td>Half-life increases; decrease in protein binding</td>
<td>No effect on half-life; decreased protein binding</td>
<td>No effect on half-life; decreased protein binding</td>
</tr>
</tbody>
</table>
# Benzodiazepine Treatment Strategies

<table>
<thead>
<tr>
<th><strong>Fixed-Schedule</strong></th>
<th><strong>Symptom-Triggered</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Set amount of BZD administered at regular intervals</td>
<td>• BZD given only if patient is symptomatic as determined by screening tool such as CIWA-Ar</td>
</tr>
<tr>
<td>• Additional doses can be given if needed</td>
<td>• Significantly reduces the amount of BZD given</td>
</tr>
<tr>
<td>• Preferred for patients who cannot be routinely monitored/outpatient setting</td>
<td>• Significantly reduces duration of treatment</td>
</tr>
<tr>
<td></td>
<td>• <strong>NOT</strong> recommended for patients with polysubstance abuse</td>
</tr>
</tbody>
</table>

101 patient admissions to detoxification unit

Symptom-triggered
n = 51

Chlordiazepoxide administered for CIWA-Ar ≥8

Symptom-triggered used 4 x less drug than fixed schedule and had shorter duration of treatment

Fixed-schedule
n = 50

Chlordiazepoxide taper administered q6hrs

Symptom-Triggered Therapy for Alcohol Withdrawal Syndrome in Medical Inpatients

Thomas M. Jaeger, MD; Robert H. Lohr, MD; and V. Shane Pankratz, PhD

216 patients admitted to general medical services

Preimplementation Group
n = 84

Post-implementation Group
n = 132

BZDs administered via usual care

BZDs administered via symptom-triggered protocol

Symptom-triggered was associated with decreased occurrence of DTs, but did not result in shorter duration of treatment

36 patients admitted to medical ICU

Preprotocol Group: Fixed-schedule
n = 16 episodes

Protocol Group: Symptom-triggered
n = 24 episodes

Midazolam administered as continuous infusion

Lorazepam administered based on Minnesota Detoxification Scale

Symptom-triggered was associated with decreased symptom control, amount of sedative required, and time spent receiving benzodiazepine infusion.

Dosing BZDs Using Symptom-Triggered Therapy

• Start BZD therapy with CIWA-Ar score ≥8, with subsequent dosing based on score reassessment
  – Suggested starting dose: chlordiazepoxide 25-50mg, lorazepam 1-2mg, or oxazepam 15mg

• Subsequent doses should be titrated upward, increasing by 1.5 to 2 times the previous dose
  – Reassess CIWA-Ar score at least every 1-2 hours after dose is administered
Dosing BZDs Using Symptom-Triggered Therapy

- When CIWA-Ar score <8 monitoring can be extended to every 4-8 hours
- If CIWA-Ar score ≥20 consider treatment and monitoring in the ICU
## Examples of Symptom-Triggered Dosing and CIWA-Ar Scores

<table>
<thead>
<tr>
<th>CIWA-Ar Score</th>
<th>Chlordiazepoxide Dose (oral)</th>
<th>Lorazepam Dose (oral or IV)</th>
<th>Reassess CIWA-Ar and Vital Signs, and Redose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-7</td>
<td>No medication necessary</td>
<td>No medication necessary</td>
<td>Every 2 hours</td>
</tr>
<tr>
<td>8-10</td>
<td>25-50mg</td>
<td>1-2mg</td>
<td>Every 2 hours</td>
</tr>
<tr>
<td>11-15</td>
<td>50-75mg</td>
<td>2-3mg</td>
<td>Every 1-2 hours</td>
</tr>
<tr>
<td>16-19</td>
<td>75-100mg</td>
<td>3-4mg</td>
<td>Every 1-2 hours</td>
</tr>
<tr>
<td>20 or greater</td>
<td>Evaluation for patient transfer to the ICU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIWA-Ar &lt;8 for 3 consecutive checks</td>
<td>Reassess every 4 hours. If score remains &lt;8 every 4 hours on 3 checks, reassess or redose every 8 hours. If CIWA-Ar score is &lt;8 for 48 hours, discontinue monitoring.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pharmacologic Treatment

- **First Line Therapy**
  - Benzodiazepines (BZDs)

- **Adjunctive Therapy**
  - Severe and/or refractory AWS: phenobarbital, propofol, dexmedetomidine
  - Agitation: haloperidol
  - Cardiac adrenergic symptoms: clonidine, beta-blockers
Phenobarbital

- Barbiturate historically used in treatment of epilepsy
- Enhances the binding of GABA to the receptor and increases the duration of GABA mediated inhibitory currents
- Phenobarbital may achieve synergistic effects when administered with BZDs
- Reserved for patients who are refractory to BZDs

NEJM. 2014;371:2109-2113.
Phenobarbital versus diazepam for delirium tremens – a retrospective study

Ida Hjermø Michaelsen¹, John Erik Anderson², Anders Fink-Jensen³, Peter Allerup⁴ & Jakob Ulrichsen¹

194 patients who received treatment for DTs

Phenobarbital
n = 106

Diazepam
n = 88

Phenobarbital 100-200mg PO/IV q1hr

Diazepam 10-20mg IV q1hr

Length of DT and hospitalization, mortality, and rate of pneumonia were not affected by treatment

Dan Med Bul. 2010;57:A4169
102 patients with acute AWS seen in the ED

Phenobarbital + symptom-triggered therapy  
\[ n = 51 \]

Placebo + symptom-triggered therapy  
\[ n = 51 \]

Phenobarbital 10mg/kg IV once

Placebo 100mL IV once

Single dose of phenobarbital combined with symptom-triggered therapy resulted in decreased ICU admissions

A strategy of escalating doses of benzodiazepines and phenobarbital administration reduces the need for mechanical ventilation in delirium tremens*

Jeffrey A. Gold, MD; Binaya Rimal, MD; Anna Nolan, MD; Lewis S. Nelson, MD
Propofol

- Agonist at the GABA receptor within the central nervous system and inhibits N-methyl-D-aspartate (NMDA) glutamate receptors

- Use in AWS is primarily reserved for severe AWS refractory to BZDs in patients requiring mechanical ventilation

NEJM. 2014;371:2109-2113.
Management of benzodiazepine-resistant alcohol withdrawal across a healthcare system: Benzodiazepine dose-escalation with or without propofol

Adrian Wong, Neal J. Benedict, Brian R. Lohr, Anthony F. Pizon, Sandra L. Kane-Gill

<table>
<thead>
<tr>
<th>AWS Treatment Outcomes</th>
<th>BZD only (n = 33)</th>
<th>BZD plus propofol (n = 33)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of mechanical ventilation, median d (IQR)</td>
<td>2.5 (1.0, 10.3)</td>
<td>7.0 (4.0, 16.0)</td>
<td>0.017</td>
</tr>
<tr>
<td>Nosocomial pneumonia, n (%)</td>
<td>1 (3.0)</td>
<td>12 (36.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Time to resolution of AWS, median d (IQR)</td>
<td>5.0 (2.8, 7.3)</td>
<td>7.0 (6.3, 9.8)</td>
<td>0.025</td>
</tr>
<tr>
<td>Diazepam equivalent of BZD in 7 day period, median mg (IQR)</td>
<td>576.7 (178.4, 1515.3)</td>
<td>743.3 (240.5, 1220.0)</td>
<td>0.378</td>
</tr>
<tr>
<td>Length of stay, median d (IQR)</td>
<td>4.0 (2.5, 8.5) 6.7 (3.0, 11.4)</td>
<td>10.0 (6.0, 17.3) 16.2 (10.0, 23.8)</td>
<td>&lt;0.001 &lt;0.001</td>
</tr>
</tbody>
</table>
Use of Propofol-Containing Versus Benzodiazepine Regimens for Alcohol Withdrawal Requiring Mechanical Ventilation

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Propofol Infusion (n=8)</th>
<th>Propofol Plus BZD infusion (n=39)</th>
<th>BDZ Infusion (n=18)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to resolution of AWS, days</td>
<td>8 (6-11)</td>
<td>9 (5-14)</td>
<td>7 (5-10)</td>
<td>0.63</td>
</tr>
<tr>
<td>Duration of time on continuous infusion, hours</td>
<td>28 (6-36)</td>
<td>49 (18-92)</td>
<td>48 (38-93)</td>
<td>0.08</td>
</tr>
<tr>
<td>BDZ boluses while on continuous sedation, mg</td>
<td>15 (3-76)</td>
<td>10 (5-27)</td>
<td>36 (15-100)</td>
<td>0.16</td>
</tr>
<tr>
<td>Hospital length of stay, days</td>
<td>9 (7-15)</td>
<td>10 (7-16)</td>
<td>10 (7-16)</td>
<td>0.99</td>
</tr>
<tr>
<td>ICU length of stay, days</td>
<td>3 (2-5)</td>
<td>4 (3-9)</td>
<td>4 (3-9)</td>
<td>0.66</td>
</tr>
<tr>
<td>Mechanical ventilation, days</td>
<td>3 (2-3)</td>
<td>4 (3-8)</td>
<td>3 (3-6)</td>
<td>0.09</td>
</tr>
</tbody>
</table>
Dexmedetomidine

- Centrally acting alpha-2 agonist which activates receptors in the medullary vasomotor center
- Lacks GABA receptor activity required to prevent withdrawal related seizures
- Clinical effects include sedation, anxiolysis, and sympatholysis
- Use in severe refractory AWS in combination with BZDs

_Cleveland Clinic Journal of Medicine_. 2016;83:67-79.
### Comparison of Clinical Outcomes in Nonintubated Patients with Severe Alcohol Withdrawal Syndrome Treated with Continuous-Infusion Sedatives: Dexmedetomidine versus Benzodiazepines

Angela L. Crispo, Mitchell J. Daley, Jodie L. Pepin, Paul H. Harford, and Carlos V.R. Brown

<table>
<thead>
<tr>
<th>Efficacy and safety endpoints</th>
<th>BZD group (n = 33)</th>
<th>Dexmedetomidine group (n = 28)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite efficacy endpoint</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>3 (9.1)</td>
<td>2 (7.1)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Seizure</td>
<td>3 (9.1)</td>
<td>2 (7.1)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1 (3.6)</td>
<td>0.46</td>
</tr>
<tr>
<td>RASS score &lt; +1 within 24 hours</td>
<td>33 (100)</td>
<td>28 (100)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Hospital length of stay, days</td>
<td>9.7 +/- 7</td>
<td>10.2 +/-</td>
<td>0.88</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>5 (15.2)</td>
<td>13 (46.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypotension</td>
<td>4 (12.1)</td>
<td>12 (42.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cost/hospitalization, $</td>
<td>11,467.69 +/- 1568.48</td>
<td>17,014.60 +/- 2180.62</td>
<td>0.11</td>
</tr>
</tbody>
</table>

# Retrospective Review of Critically Ill Patients Experiencing Alcohol Withdrawal: Dexmedetomidine Versus Propofol and/or Lorazepam Continuous Infusions

*Kimberly A. Ludtke, PharmD, BCPS\*; Kevin S. Stanley, PharmD, BCPS\*; Natalie L. Yount, PharmD, BCPS\*; and Richard D. Gerkin, MD†*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients treated with dexmedetomidine (n = 15)</th>
<th>Patients treated with propofol and/or lorazepam (n = 33)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean CIWA-Ar score</td>
<td>23.1</td>
<td>15</td>
<td>0.39</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>2</td>
<td>10</td>
<td>0.006</td>
</tr>
<tr>
<td>Mean length of intubation, days</td>
<td>0.95</td>
<td>4.1</td>
<td>0.264</td>
</tr>
<tr>
<td>Mean ICU length of stay, days</td>
<td>2.2</td>
<td>4.8</td>
<td>0.016</td>
</tr>
<tr>
<td>Mean hospital length of stay, days</td>
<td>5.7</td>
<td>10</td>
<td>0.008</td>
</tr>
</tbody>
</table>
Evaluating the effects of dexmedetomidine compared to propofol as adjunctive therapy in patients with alcohol withdrawal
A Randomized, Double-Blind, Placebo-Controlled Dose Range Study of Dexmedetomidine as Adjunctive Therapy for Alcohol Withdrawal*

Scott W. Mueller, PharmD; Candice R. Preslaski, PharmD; Tyree H. Kiser, PharmD, FCCP, FCCM; Douglas N. Fish, PharmD, FCCP, FCCM; James C. Lavelle, MD; Stephen P. Malkoski, MD, PhD; Robert MacLaren, PharmD, MPH, FCCP, FCCM

24 patients admitted to the medical ICU with severe AWS

- Lorazepam with placebo \( n = 8 \)
- Lorazepam with dexmedetomidine 0.4mcg/kg/hr \( n = 8 \)
- Lorazepam with dexmedetomidine 1.2mcg/kg/hr \( n = 8 \)

Adjunctive dexmedetomidine for severe alcohol withdrawal maintains symptom control and reduces lorazepam exposure in the short term

Pharmacologic Treatment

• First Line Therapy
  – Benzodiazepines (BZDs)

• Adjunctive Therapy
  – Severe and/or refractory AWS: phenobarbital, propofol, dexmedetomidine
  – Agitation: haloperidol
  – Cardiac adrenergic symptoms: clonidine, beta-blockers
Therapies to Avoid in Severe AWS

- Ethanol
- Antiepileptics
  - Lack benefit as monotherapy or adjunctive therapy
- Magnesium
  - No clinical benefit in patients with normal serum concentrations

NEJM. 2014;371:2109-2113.
Summary

• Alcohol dependence affects a large number of Americans
• Symptoms of AWS are due to a down-regulation of GABA and up-regulation of glutamate
• Symptoms can range from mild discomfort to severe withdrawal (seizure, DTs)
• BZDs remain the drug of choice for patients who experience significant symptoms of withdrawal
Summary

• Use of a symptom triggered strategy for BZD administration has been associated with decrease in BZD use and duration of treatment

• Adjunctive therapy may be considered in conjunction with BZDs in severe or refractory AWS
Treatment of Severe Alcohol Withdrawal

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