Phenobarbital: Taking a Shot at Alcohol Withdrawal
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November 8th, 2019

Objectives

• Review a patient case, and discuss available treatment options for AWS
• Discuss the mechanism of action of phenobarbital and alcohol within the brain
• Review AWS screening protocols and first line treatment options
• Perform a literature review comparing lorazepam and phenobarbital in the treatment of AWS

Patient Case

AJ is a 45-year-old female who arrives to the emergency department with a CC of “Not feeling right, and thinks she’s seeing things.” Prior to arrival, this patient reports experiencing anxiety, tremors, N/V, and thought she had a seizure which prompted her to seek medical attention. The ED physician learns that the patient has had a long history of alcoholism and has been treated several times for AWS at different OSHs. The patient states that whenever she’s admitted to the hospital for these symptoms, she “never feels better with the meds that they give her and she’s in the hospital for longer than she wants to be.”

PMH: HTN, Afib, Cirrhosis of the liver, history of substance abuse including cocaine, methamphetamines, and alcohol

Home Medication List:
- Lisinopril 10 mg QDay
- Warfarin 5 mg QDay
- Metoprolol succinate 100 mg QDay

Vitals
- Temp: 100.2
- HR: 110 bpm
- BP: 134/92
- RR: 26
- Wt: 90 kg

Conflicts of Interest

- I have no conflicts of interest to disclose.

Abbreviations

- Afib: Atrial Fibrillation
- AWS: Alcohol Withdrawal Syndrome
- CC: Chief Complaint
- CD: Chlordiazepoxide
- CIWA: Clinical Institute Withdrawal Assessment for Alcohol
- CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol (revised version)
- CNS: Central Nervous System
- DT: Delirium Tremens
- HTN: Hypertension
- Hx: History
- ICU: Intensive Care Unit
- IM: Intra-muscular
- IDR: Inter-Quartile Range
- L2: Lorazepam n. number
- N/V: Nausea/Vomiting
- OSH: Outside Hospital
- PR: Phenobarbital
- PMH: Past Medical History
- TCU: Telemetry Care Unit
- TID: Three times a day

Patient Case

After assessing the patient with the CIWA-Ar scale, which resulted as 21, the ED doctor identifies that the patient is again experiencing alcohol withdrawal syndrome and begins medical management. The ED doctor, who is just beginning to practice medicine, queries pharmacy on treatment options for severe alcohol withdrawal syndrome. You suggest:

A. Diazepam 10 mg IV initially, followed by 5-10 mg 3-4 hours later PRN
B. Lorazepam 2-4 mg IV Q1H PRN
C. Chlordiazepoxide 50-100 mg PO, repeat as necessary to a max of 300 mg/day
D. Phenobarbital 260 mg IV loading dose, followed by 130 mg IV PRN
Pathophysiology of Alcohol Withdrawal Syndrome

- Alcohol is a central nervous system depressant which enhances the inhibitory tone and inhibits the excitatory tone within the CNS.
- Alcohol enhances the effect of GABA on GABA\textsubscript{A} receptors and causes the brain to reduce the production of endogenous GABA. With alcohol cessation, decreased inhibitory tone results.
- Alcohol inhibits glutamate excitation and excessive use over time leads to increased levels of glutamate receptors in order to maintain a normal rate of arousal.
- For patients with alcohol dependence, the abrupt discontinuation of alcohol results in overactivity of the central nervous system.

Pathophysiology of AWS

- Gamma-aminobutyric acid (GABA): The major inhibitory neurotransmitter in the brain that binds to GABA\textsubscript{A} receptors.
- Glutamate: A major excitatory amino acid that binds to N-methyl-D-aspartate (NMDA) receptors that leads to neuronal excitation.

Manifestations of AWS from CNS over-activity

- Minor alcohol withdrawal symptoms:
  - Gastrointestinal upset
  - Anxiety
  - Insomnia
  - Sweating
  - Palpitations
  - Headache
  - Tremulousness

- Major alcohol withdrawal symptoms:
  - Seizures which are generalized tonic-clonic convulsions
  - Alcoholic hallucinations are usually visual but can also be auditory
  - Delirium Tremens which is defined by disorientation, tachycardia, hypertension, hyperthermia, agitation, hallucinations, and sweating

Benzodiazepine MOA

- Benzodiazepines act as positive allosteric modulators on GABA\textsubscript{A} receptors.
- Benzodiazepines produce a conformational change on the GABA\textsubscript{A} receptor \( \alpha \) and \( \gamma \) sub-units allowing GABA to bind to the receptor.

Phenobarbital MOA

- Phenobarbital is a long acting derivative of barbituric acid that binds to the GABA\textsubscript{A} receptors.
- This process mimics the body's own natural GABA neurotransmitter and allows the influx of chloride ions. This in turn reduces neuronal excitability.
- Phenobarbital also inhibits glutamate induced depolarization.
**Determining the need for Alcohol Withdrawal Management**

- **Clinical Institute Withdrawal Assessment Scale for Alcohol (CIWA-Ar)**
  - Most studied and most widely used scale to help determine alcohol withdrawal management. 10 scale components include:
    - Nausea and Vomiting
    - Headache
    - Sweating
    - Anxiety
    - Auditory Disturbances
    - Visual Disturbances
    - Agitation
    - Tremor
    - Tactile Disturbances
    - Orientation and Clouding of Sensory Score:
      - <10: Very mild withdrawal
      - 10-15: Mild withdrawal
      - 16-20: Modest withdrawal
      - >20: Severe withdrawal


**Approaches to Management of AWS**

- **Symptom-Triggered Dosing:** Most common approach
  - Medications are dosed based on symptom manifestations from alcohol withdrawal.

- **Fixed-Scheduled Dosing:**
  - Medication doses are given at fixed intervals, and then tapered off gradually with additional doses given as required.

Hoffman RS, Weinhouse GL. UpToDate.com Sept. 2019

**Management of AWS**

- **Symptom-Triggered Approach:**
  - CIWA-Ar score is used to determine the severity of AW, more severe symptoms are treated with benzodiazepines.
  - Acute Withdrawal: Diazepam 5-10 mg IV or Chlordiazepoxide 25-100 mg PO
  - Severe Liver Disease: Lorazepam 2-4 mg IV or Oxazepam 10-30 mg

- **Refractory Delirium Tremens:** Patients who are still experiencing DT despite being treated with high-dose benzodiazepines.
  - Barbiturates may be an option when benzodiazepines have failed.
  - Phenobarbital 130-260 mg IV repeated every 15-20 minutes until symptom control.

Hoffman RS, Weinhouse GL. UpToDate.com Sept. 2019

**Comparison of Phenobarbital Vs. Lorazepam**

<table>
<thead>
<tr>
<th>Pharmacodynamics</th>
<th>Phenobarbital IV</th>
<th>Lorazepam IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>5 mins</td>
<td>2-3 min</td>
</tr>
<tr>
<td>Duration</td>
<td>&gt;6 hrs</td>
<td>~6-8 hrs</td>
</tr>
<tr>
<td>Half-life</td>
<td>&gt;79 hrs</td>
<td>~14 hrs</td>
</tr>
<tr>
<td>Symptom-triggered dosing</td>
<td>Initial: 260 mg IV</td>
<td>Maintenance: 130 mg PRN</td>
</tr>
<tr>
<td>Fixed schedule dosing</td>
<td>Oral: 60 mg QID on 1st day, 60 mg BD 2nd day, 30 mg BD on day 3. IM: 130 mg may be administered PRN for more substantial withdrawal symptoms</td>
<td>2-4 mg IV every hour PRN</td>
</tr>
</tbody>
</table>

Phenobarbital. Lexi-Drugs. Lexicomp. Online.lexi.com
Lorazepam. Lexi-Drugs. Lexicomp. Online.lexi.com

What if phenobarbital was used as the primary treatment of AWS?

**Primary Literature Review**
Tidwell et al., 2018

### Treatment of Alcohol Withdrawal Syndrome: Phenobarbital Vs CIWA-Ar Protocol

#### Design
- Retrospective Cohort Study

#### Objective
- Compared a symptom-triggered benzodiazepine protocol used in conjunction with the CIWA-Ar scale to a phenobarbital protocol
- Patients were grouped into two different arms: CIWA-Ar Protocol and Phenobarbital Protocol

#### Primary Outcomes
- Intensive care unit length of stay between the two protocols

#### Secondary Outcomes
- Hospital length of stay, incidence of invasive mechanical ventilation, and use of adjunctive pharmacotherapy

#### Inclusion Criteria
- Patients identified by the attending or admitting physician with confirmed or suspected AWS

#### Exclusion Criteria
- Patients who received CIWA-Ar based treatment for more than 24 hours before starting the phenobarbital protocol
- Received no doses of either protocol
- Pregnancy/Positive pregnancy test
- Left against medical advice
- Died within 24 hours of presentation
- Outpatient phenobarbital maintenance medication

### Patient Demographics

<table>
<thead>
<tr>
<th>CIWA-Ar Arm (N=60)</th>
<th>Phenobarbital Arm (N=60)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SD), y</strong></td>
<td>52 (15.5)</td>
<td>45 (11.4)</td>
</tr>
<tr>
<td><strong>Race, No. (%) of patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>57 (95)</td>
<td>57 (95)</td>
</tr>
<tr>
<td>Black of African American</td>
<td>2 (3)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2)</td>
<td>2 (3)</td>
</tr>
<tr>
<td><strong>Male sex, No. (%) of patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>43 (72)</td>
<td>44 (73)</td>
<td>.84</td>
</tr>
<tr>
<td><strong>Left against medical advice, No. (%) of patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (2)</td>
<td>3 (5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Comorbid conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorder</td>
<td>29 (48)</td>
<td>10 (17)</td>
</tr>
<tr>
<td>Polysubstance abuse</td>
<td>13 (22)</td>
<td>9 (15)</td>
</tr>
<tr>
<td>Seizure disorder</td>
<td>5 (8)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Reactive airway disorder</td>
<td>8 (13)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>14 (23)</td>
<td>16 (27)</td>
</tr>
<tr>
<td>Previous delirium tremens or withdrawal seizures</td>
<td>27 (45)</td>
<td>32 (53)</td>
</tr>
<tr>
<td>Coadministration on admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal vitals</td>
<td>30 (50)</td>
<td>29 (49)</td>
</tr>
<tr>
<td>Active alcohol withdrawal/initial treatment</td>
<td>25 (42)</td>
<td>26 (43)</td>
</tr>
</tbody>
</table>

### Outcome or Clinical Characteristic

<table>
<thead>
<tr>
<th>CIWA-Ar Arm (N=60)</th>
<th>Phenobarbital Arm (N=60)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ICU Stay (midnights), Mean (SD)</strong></td>
<td>4.4 (3.8)</td>
<td>2.4 (1.5)</td>
</tr>
<tr>
<td><strong>Hospital Stay (midnights), mean (SD)</strong></td>
<td>6.9 (6.6)</td>
<td>4.3 (3.4)</td>
</tr>
<tr>
<td><strong>Total Lorazepam equivalents mean (SD), mg</strong></td>
<td>35.2 (95.5)</td>
<td>11.3 (18)</td>
</tr>
<tr>
<td><strong>Ventilator use, No. or patients</strong></td>
<td>14 (23)</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>Deviseditude barbiturate use, No. of patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>4</td>
<td>.032</td>
</tr>
<tr>
<td><strong>Olanzapine use, No. of patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>.54</td>
</tr>
<tr>
<td><strong>Haloperidol use, No. of patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>4</td>
<td>.06</td>
</tr>
<tr>
<td><strong>Quetiapine use, No. of patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>.26</td>
</tr>
</tbody>
</table>

#### Overall Conclusions of study:
- Phenobarbital may show promise as an alternative for AWS.
- Patients treated with phenobarbital may have decreased ICU/hospital stay, and may incur decreased costs by minimizing ICU and hospital stay.
- Since phenobarbital has a long half life, it requires less frequent administration as compared to CIWA-Ar symptom triggered protocols—this may benefit nursing staff.

#### Limitations of study:
- Small sample size
- Retrospective design
A prospective, randomized trial of phenobarbital versus benzodiazepines for acute alcohol withdrawal

**Hendey et al., 2009**

**Objective:** Aim was to compare phenobarbital versus lorazepam in the treatment of AW during initial ED visit and at 48 hours.

**Intervention:** Patients were assessed using a modified CIWA score and given phenobarbital or lorazepam for AWS. Upon discharge the patients who received lorazepam were given chlordiazepoxide and the phenobarbital patients were given a placebo.

**Primary Outcome:** Reduction of CIWA scores from baseline to discharge.

**Secondary Outcome:** Differences between groups, time spent in the ED, % of patients admitted to the hospital, number of doses and total dose of treatments, % of patients who sought additional medical care after ED discharge, and change in AW scores from baseline to 48-hour reassessment.

**Inclusion Criteria:** Adult patients who arrived in the ED with known or suspected AWS. These patients had symptoms which included tremulousness, N/V, and hyperadrenergic manifestations in the abstinence from alcohol.

**Exclusion Criteria:**
- Under 18 years of age
- Severe symptoms/AMS that rendered the patient unable to provide consent
- Significant comorbid medical illness
- Allergy to study medications
- Pregnancy
- Patients under the influence of alcohol or other drugs

**Study Procedures**

- Modified CIWA Score (4 components):
  - Agitation
  - Nausea/vomiting
  - Anxiety
  - Tremor
- Max score of 28 with a range of each category being 0-7.
- Estimated a difference of 3 points in AW scores would be considered statistically significant.
- CIWA scores were recorded at baseline, at 30-minute intervals, and at ED discharge/time of admission.
- The number and timing of doses was at the discretion of the treating physician.
- Patients were discharged, given either chlordiazepoxide or placebo, and asked to return 48 hours later to assess AWS symptoms.

**Overall Conclusion of Study:**
- PB was found to be just as effective as LZ in the treatment of Acute AW.
- Authors witnessed that even at the 48 hour follow up, patients in the PB group who received no additional medication after discharge still had control of symptoms.
- This study supports the idea of providing no additional medications upon discharge to control AW symptoms with PB after a patient leaves the hospital.

**Limitations of Study:**
- Small sample size
- Not adequately powered to detect differences in small group at the 48-hour follow up period.
- Less than half of the study patients returned for 48-hour follow up; these patients were lost to follow up which is very important, especially the PB group.
- Only patients with Mild-Moderate AW were enrolled, no severe AW patients within study.
Rosenson et al., 2013
Phenobarbital for acute alcohol withdrawal: a prospective randomized double-blind placebo-controlled study

### Design
Randomized, Double-Blind, Placebo-controlled Study

### Objective
To determine if a single dose of IV PB combined with a standardized LZ-based AW protocol decreased ICU admission in ED patients with AWS.

### Intervention
Patients were randomized to receive either a single dose of IV PB (10 mg/kg in 100 mL NS) or placebo (100 mL NS). All patients placed on a symptom-triggered LZ AWS protocol. A modified CIWA protocol was used to assess AWS.

### Primary Outcome
Initial level of hospital admission (ICU vs Telemetry vs Floor Ward)

### Secondary Outcome
Use of continuous lorazepam infusion, hospital length of stay, total amount of lorazepam used per patient, incidence of adverse events.

### Inclusion Criteria
All patients over 18 years old who presented to the ED with suspected AWS. Informed consent was provided, consent was initially waived for patients unable to give consent at the time of presentation due to intoxication or AMS.

### Exclusion Criteria
Patients less than 18 years old, pregnancy, allergies to study medications, severe hepatic impairment, inability to obtain IV access, primary admission for another reason other than AWS.

### Subject Characteristic

<table>
<thead>
<tr>
<th></th>
<th>PB (n=51)</th>
<th>Placebo (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: n (%)</td>
<td>46 (90)</td>
<td>45 (88)</td>
</tr>
<tr>
<td>Age, years: median (IQR)</td>
<td>46 (40-52)</td>
<td>48 (37-54)</td>
</tr>
<tr>
<td>Initial AWCA score: median (IQR)</td>
<td>8 (4-10)</td>
<td>7 (4-10)</td>
</tr>
<tr>
<td>Initial Hear Rate: median (IQR)</td>
<td>106 (100-120)</td>
<td>112 (108-120)</td>
</tr>
<tr>
<td>Initial Tremor: n (%)</td>
<td>48 (95)</td>
<td>48 (95)</td>
</tr>
<tr>
<td>Initial Sweats: n (%)</td>
<td>25 (49)</td>
<td>32 (63)</td>
</tr>
<tr>
<td>Initial Agitation: n (%)</td>
<td>20 (40)</td>
<td>21 (41)</td>
</tr>
<tr>
<td>Initial Anxiety: n (%)</td>
<td>35 (68)</td>
<td>43 (84)</td>
</tr>
<tr>
<td>Altered Consciousness: n (%)</td>
<td>30 (58)</td>
<td>35 (68)</td>
</tr>
<tr>
<td>Auditory/Visual Disturbances: n (%)</td>
<td>20 (40)</td>
<td>27 (51)</td>
</tr>
<tr>
<td>Time to initial LZ Admin, mins: median (IQR)</td>
<td>84 (48-146)</td>
<td>84 (40-312)</td>
</tr>
<tr>
<td>Time to study medication admin, mins: median (IQR)</td>
<td>144 (103-263)</td>
<td>150 (100-264)</td>
</tr>
<tr>
<td>Patients with prior AW admission to study institution: n (%)</td>
<td>21 (41)</td>
<td>26 (49)</td>
</tr>
</tbody>
</table>

### Clinical Outcome

<table>
<thead>
<tr>
<th></th>
<th>PB (n=51)</th>
<th>Placebo (n=51)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU admission: n (%)</td>
<td>4 (8)</td>
<td>13 (25)</td>
<td>17 (4–32)</td>
</tr>
<tr>
<td>TCU admission, number: n (%)</td>
<td>23 (45)</td>
<td>20 (39)</td>
<td>6 (25–13)</td>
</tr>
<tr>
<td>Floor admission: n (%)</td>
<td>18 (35)</td>
<td>19 (37)</td>
<td>2 (0.01–17)</td>
</tr>
<tr>
<td>Maximum AWCA score: median (IQR)</td>
<td>8 (5–15)</td>
<td>10 (5–14)</td>
<td>2 (0.5–3)</td>
</tr>
<tr>
<td>Continuous lorazepam infusion: n (%)</td>
<td>2 (4)</td>
<td>16 (31)</td>
<td>27 (14–41)</td>
</tr>
<tr>
<td>Total length of stay, hours: median (IQR)</td>
<td>76 (54-114)</td>
<td>116 (47-190)</td>
<td>42 (4–82)</td>
</tr>
<tr>
<td>ICU length of stay, hours: median (IQR)</td>
<td>34 (25–275)</td>
<td>94 (43–134)</td>
<td>60 (170–434)</td>
</tr>
<tr>
<td>Intubation: n (%)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0 (0.99–0.99)</td>
</tr>
<tr>
<td>Seizure: n (%)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>2 (0.95–0.95)</td>
</tr>
<tr>
<td>Restraints: n (%)</td>
<td>15 (29)</td>
<td>23 (45)</td>
<td>16 (3–54)</td>
</tr>
<tr>
<td>Bedside sitter: n (%)</td>
<td>14 (28)</td>
<td>11 (22)</td>
<td>6 (11–22)</td>
</tr>
</tbody>
</table>

### Overall Study Conclusions:
- A single dose of IV PB resulted in decreased ICU admission rate, decreased use of continuous LZ infusion, and was not associated with increased adverse events.

### Study Limitations:
- Decision to enroll patients was dependent on the ED provider.
- AWCA scale used within study was a simplified version of the CIWA-Ar developed by the medical director of the ICU which is unvalidated.
- At this institution, LZ infusion requires admission to ICU which may have added bias to ICU admission results.
- Researchers were limited to 10 mg/kg of PB at this institution which may not be the optimal regimen to assess PB.
- Lack of sample size.

### Rosenson et al., 2013

Hammond et al., 2017
Patient Outcomes Associated With Phenobarbital Use With or Without Benzodiazepines for Alcohol Withdrawal Syndrome: A Systematic Review
### Systematic Review

**Continuous infusion of BZDs**

Disadvantages:

- Duration of ICU, hospital, ED stay, and mechanical ventilation

There is a clear dose response relationship in regards to serum levels but specific serum levels have not been associated with clinical outcomes.

### Methods

Medline, Cochrane Library, and Scopus were searched for controlled trials and observational studies from 1950-2017. Controlled and observational studies were considered for inclusion, no case studies were included.

A total of 9 studies were included in the systematic review:

- 4 studies included patients that received concomitant BZD and PB
- 5 studies included patients who received PB as monotherapy

### Outcomes Analyzed

- Frequency of ICU admission
- Initial induction for mechanical ventilation
- Continuous infusion of BZDs
- Breakthrough BZD or PB use
- Duration of ICU, hospital, ED stay, and mechanical ventilation
- Cumulative amounts of BZD and PB doses and serum concentrations
- Changes in AWS symptoms and development of adverse effects with PB

### PB Monotherapy Summary:

- **Advantages**
  - The use of oral and IV PB as monotherapy by either route has shown to be just as effective as other GABA agonists for the management of AWS.
  - There is a clear dose response relationship in regards to serum levels but specific serum levels have not been associated with clinical outcomes.
  - From the studies reviewed, these results only apply to patients with mild/moderate AWS.

- **Disadvantages**
  - PB may have provided similar or improved outcomes.
  - However, its difficult to offer recommendations on PB compared to BZDs for the treatment of AWS.
  - No clear dosing guidelines to relate to positive patient outcomes.

### PB with Concomitant BZD Therapy Summary:

- **Benefits**
  - Appears to offer some potential benefits although its difficult to determine if the benefits are due to protocolized care or PB.
  - When PB is used as a large single dose in the ED as part of a front-loading strategy, PB appears to reduce the need for ICU admission rates and is well tolerated.
  - When PB is added to dose escalations of BZDs there is a decrease in length of mechanical ventilation and ICU length of stay.
  - PB may have a role as monotherapy or used concomitantly with BZDs for the treatment of AWS.

### Study Limitations:

- The authors noted that data was heterogeneous which prevented them from performing a meta-analysis to evaluate PB for the treatment of AWS.

### Overall Study Conclusions:

- PB may have a role as monotherapy or used concomitantly with BZDs for the treatment of AWS. However, its difficult to offer recommendations on PB therapy due to lack of data.
- Not enough evidence to provide general recommendations based on AWS severity currently.
- The most favorable results for PB are when its administered early and aggressively dosed.
- Patients with severe AWS who received PB required less escalation of their care and patients with mild/moderate AWS spent less time in the ED and usually didn’t require follow-up care after discharge.

### Advantages/Disadvantages of Phenobarbital for AWS

#### Advantages

- Able to give upfront loading dose upon identifying AWS
- Long half-life reduces the need for re-dosing
- Advantage over BZDs for treating refractory AWS due to difference in MOA
- Less likely to require additional doses upon patient discharge
- Less administration burden on nursing staff as compared to BZD AWS protocols

#### Disadvantages

- No clear dosing guidelines to relate to positive patient outcomes
- Long half-life reduces the need for re-dosing
- Long half-life-potential for drug-drug interactions
- Advantage over BZDs for treating refractory AWS due to difference in MOA
- Less likely to require additional doses upon patient discharge
- Less administration burden on nursing staff as compared to BZD AWS protocols

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**Primary Literature Review Summary**

<table>
<thead>
<tr>
<th>Author</th>
<th>Type</th>
<th>Objective</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidwell et al., 2018</td>
<td>Retrospective cohort study</td>
<td>To compare a symptom-triggered BZD protocol to a PB protocol for AWS.</td>
<td>PB was an effective alternative to the standard of care protocol of symptom-triggered BZD therapy.</td>
</tr>
<tr>
<td>Hendey et al., 2009</td>
<td>Prospective, randomized trial</td>
<td>To compare PB to LZ to treat AWS in the ED and 48 hours later.</td>
<td>PB and LZ were similarly effective in treating patients with mild/moderate AWS.</td>
</tr>
<tr>
<td>Rosenson et al., 2013</td>
<td>Prospective, randomized, double-blind placebo-controlled study</td>
<td>To determine if a single IV dose of PB combined with LZ based AWS protocol decreased ICU admission in ED patients.</td>
<td>A single dose of IV PB combined with symptom-triggered LZ resulted in decreased ICU admission compared to symptom-triggered LZ dosing only. The single dose IV PB arm did not experience increased adverse outcomes.</td>
</tr>
<tr>
<td>Hammond et al., 2017</td>
<td>Systematic Review</td>
<td>To evaluate outcomes with phenobarbital for AWS.</td>
<td>PB with or without concomitant BZD may have provided similar or improved outcomes.</td>
</tr>
</tbody>
</table>
Patient Case

AJ is a 46-year-old female who arrives to the emergency department with a CC of “Not feeling right, and thinks she’s seeing things.” Prior to arrival, this patient reports experiencing anxiety, tremors, N/V, and thought she had a seizure which prompted her to seek medical attention. The ED physician learns that the patient has had a long history of alcoholism and has been treated several times for AWS at different OSFs. The patient states that whenever she’s admitted to the hospital for these symptoms, she “never feels better with the meds that they give her and she’s in the hospital for longer than she wants to be.”

PMH: HTN, Afib, Cirrhosis of the liver, history of substance abuse including cocaine, methamphetamines, and alcohol

Home Medication List:
- Lisinopril 10 mg QD
- Warfarin 5 mg QD
- Metoprolol succinate 100 mg QD

Vitals
- Temp: 100.2
- HR: 110 bpm
- BP: 134/92
- RR: 26
- Wt: 90 kg

After assessing the patient with the CIWA-Ar scale, which resulted as 21, the ED doctor identifies that the patient is again experiencing alcohol withdrawal syndrome and begins medical management. The ED doctor, who is just beginning to practice medicine, queries pharmacy on treatment options for severe alcohol withdrawal syndrome. You suggest:

A. Diazepam 10 mg IV initially, followed by 5-10 mg 3-4 hours later PRN
B. Lorazepam 2-4 mg IV Q1H PRN
C. Chlordiazepoxide 50-100 mg PO, repeat as necessary to a max of 300 mg/day
D. Phenobarbital 260 mg IV loading dose, followed by 130 mg IV PRN

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Phenobarbital: Taking a Shot at Alcohol Withdrawal

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Questions?