The BZDP-Sparing Protocol in the Management of Complicated AWS in the Medically-Ill

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Disclosure:
Jose R. Maldonado, MD

- With respect to the following presentation, there has been no relevant (direct or indirect) financial relationship between Dr. Maldonado (and/or spouse) and any for-profit company in the past 10 years which could be considered a conflict of interest.

- Every drug use discussed during the talk is considered “off label”
AWS in the Medically Ill

- Alcohol use disorder (AUD) is the most serious substance abuse problem worldwide.
- Although AUD has been reported in 20% - 42% of hospitalized medical patients, only about 7% of them are identified by a physician.
- The prevalence of AUD is higher in certain specialized populations of medically ill pts:
  - 40% of ED patients
  - 42% of hospitalized veterans
  - up to 44% of elderly admitted to acute geriatric units
  - 43 – 81% of head and neck surgical patients
  - 59–67% of trauma patients
  - up to 60 % in alcohol-dependent ICU patients
- Both the occurrence of AWS & its treatment are associated with delirium

Alcohol Withdrawal Syndromes (AWS)

Minor Alcohol Withdrawal – “the Shakes”:
- **Onset**: ~12 hrs; **peak**: 24 – 36 hrs
- **Incidence**: up to 50%
- Characterized by tremors, nervousness, irritability, nausea, and vomiting.
- Usually resolves within 72 hours if not complicated by other disorders.

Major Alcohol Withdrawal – “Rum Fits”:
- **Onset**: post-cessation; **peak**: 12 – 48 hrs
- **Incidence**: 5 – 15%
- Characterized by seizures in the context of alcohol withdrawal, usually in the absence of an underlying seizure disorder.
- The greater the amount of alcohol consumed, the greater the risk for seizures.
- About 1/3 of patients who develop alcohol withdrawal seizures will experience only one seizure; 2/3 will have multiple seizures if untreated.
- Only 3% of cases will develop status epilepticus.

Hallucinosis – “The Horrors”:
- **Onset**: ~8 hrs; **peak**: 24 – 96 hrs
- **Incidence**: up to 30%
- Incidence seems to be related to length and amount of alcohol exposure.
- Usually consists of primarily visual misperceptions and tactile hallucinations.
- By definition, the sensorium is clear and vital signs are stable, differentiating it from alcohol withdrawal delirium (DTs); however, some signs of early withdrawal may be present.

Delirium Tremens – “DT”:
- **Onset**: 1 – 3 days; **peak**: 4 – 5 days.
- **Incidence**: ~5%.
- Symptoms usually resolve within 72 hours; if not complicated by medical conditions, the mortality rate is low (~1 – 15%).
- When complicated by medical conditions, the mortality rate may increase to up to 20%.
- Symptoms commonly include confusion, disorientation, fluctuations in consciousness, perceptual disturbances (e.g., auditory hallucinations, visual hallucinations, or illusions), restlessness, agitation, and tachycardia.
- Tactile hallucinations of insects, small animals, or other perceptual distortions can also occur.

Animal and human studies demonstrate that AWS is detrimental to the CNS:

- Neuronal damage may be seen as early as 24-h after experiencing alcohol withdrawal and death.
- AWS potentiates loss of hippocampal neurons; which is later associated with poorer memory performance.
- Each episode of withdrawal worsens the severity and consequences of the next one.
- An increasing number of alcohol withdrawal episodes negatively affect emotional and cognitive functioning and learning.

Graphic representation of the kindling concept during alcohol withdrawal. The term “kindling” refers to the phenomenon that people undergoing repeated cycles of intoxication followed by abstinence and withdrawal will experience increasingly severe withdrawal symptoms with each successive cycle.

Maldonado et al. Alcohol 2014, 1 – 16
The Problem w GABAergic Agents

Sedative agents (mostly GABAergic) and opioids may contribute to the development of delirium by one of the following mechanisms:

(1) interfering with physiologic sleep patterns (e.g., ↓ slow wave sleep → ↑ REM latency → ↓ REM periods duration → REM deprivation)

(2) **BZD have abuse liability:** Concurrent alcohol/benzodiazepine use: 29 – 76% (Busto et al 1991; Ciraulo et al 1988)

(3) interfering with central cholinergic function muscarinic transmission at the level of the basal forebrain and hippocampus (i.e., causing a centrally mediated acetylcholine deficient state)

(4) Psychomotor retardation, cognitive blunting, ataxia and poor balance, ↓ mobility

(5) increasing compensatory up-regulation of N-methyl D-aspartate and kainite receptors and Ca\(^{2+}\) channels

(6) disrupting thalamic gating function

(7) CNS-Depressant Withdrawal

(8) disrupting the circadian rhythm of melatonin release. *
The Problem w Benzodiazepines

Potential problems with the use of BZDP:

9. Increased risk of developing BDZP-induced delirium.

- Interfering with central cholinergic function muscarinic transmission at the level of the basal forebrain and hippocampus (i.e., causing a centrally mediated acetylcholine deficient state)
  - New evidence suggests that BZDP use may be associated with an increased risk of dementia (de Gage et al BMJ 2012).

10. Interfering with physiologic sleep patterns (e.g., ↓ slow wave sleep → ↑REM latency → ↓ REM periods duration → REM deprivation)
Pathophysiology of Ethanol

Agonistic/Allosteric effect at GABAa receptors contributing to impulse to drink

Inhibits GLU receptors (NMDA, AMPA, kainate & Metabotropic GLU)

Agonistic/Allosteric effect at GABAa receptors of NE & its metabolite (MHPG) in plasma & CSF

Enhances release of GABA from presynaptic neuron

Inhibits voltage-gated Ca+ channels

Dose-dependent in 5HT neurotransmission in NA → activates DA reward system

HPA-axis activation via CRF releasing cortisol & mesolimbic DA signaling further amplifying positive reinforcing effects of ETOH

Adaptive suppression of GABA activity (1) internalization, (2) down-regulation & (3) desensitization of receptors; (4) GABAa rec shift composition to contain more α4 subunits (↑32%) & more α6 subunits (↑76%) → less responsive to GABA signaling (61% ↓ α1 subunits);

GABA A

Dependence

↑ GLU transmission to NA up-regulation & hypersensitization of NMDA receptors complexes

Desensitization of α2 receptors or lack of α2 agonist activity* inhibits the sensitivity of autonomic adrenergic systems, with a resulting up-regulation ↑ extracellular DA in NA Is likely responsible for impulse to drink

Confusion, psychosis (hallucination, illusions, delusions), agitation, delirium

↑[NE] trigger neuronal damage by inducing imbalances btw cerebral O2 demand & supply → sensitivety of pyramidal neurons to excitatory effect of GLU & ↓ perfusion. Also ↑NE →↑GLU

Physical Sx's of W/D = excessive sympathetic drive

↑ GABA levels (mean plasma GABA level: 14.7 ± 7.3 vs. 57.4 ± 12.0 ng/ml in controls [Coffman 1985; Kumar 2002; Mhatre & Ticky 1992).
Cytokines, “Sickness Behavior” & Behavioral Changes

IFN-γ
Picolinic Acid
Aminocarboxymuconate semialdehyde decarboxylase (ACMSD)
(kinase metabolite)

kynurenic acid (NMDA antagonist, anticonvulsant & neuroprotective)

LPS
Cytokines, “Sickness Behavior” & Behavioral Changes

Alcohol Withdrawal Delirium as a Pathoetiologic Model for Acute Brain Failure

Inhibitors

- ↓ GABA
- ↓ Mg
- ↓ 5HT
- ↓ Mel

Stimulants

- ↑ DA
- ↑ NMDA-r/GLU
- ↑ NA
- ↑ CRF

Associated Clinical Sx

- Hallucinosis
- DT
- AWSz
- Kindling
- Adrenergic Storm
- Depressed Mood
- Sleep Disturbance
# AWS Management Alternatives – Glutamate & Ca+ ch modulators

<table>
<thead>
<tr>
<th>Drug</th>
<th>T ½</th>
<th>Product Availability</th>
<th>Bioavailability</th>
<th>Metabolism</th>
<th>Protein Binding</th>
<th>Mechanism Action</th>
</tr>
</thead>
</table>
| carbamazepine| 25 h   | PO                   | −100%           | Hepatic            | 55 %           | • Stabilizes neuronal membranes  
• inhibits voltage-sensitive Na+ channels and/or Ca+ channels → ↓ cortical GLU release  
• Calcium Channel Blockers  
• Excitatory Amino Acid Antagonists |
| VPA          | 9-16 h | PO / IV              | 90%             | Hepatic conjugation| 90 %           | • GABA transaminase inhibitor → ↑ GABA  
• inhibits voltage-sensitive Na+ channels → ↓ cortical GLU release  
• ↓ release of the epileptogenic amino acid gamma-hydroxybutyric acid (GHB) |
| gabapentin   | 5 – 7 h| PO                   | 60%             | None               | <3%            | • voltage-gated Ca+ channel blockade → ↓ cortical GLU release  
• NMDA antagonism  
• activation of spinal alpha2-adrenergic receptors  
• Attenuation of Na+ dependent action potential |
| vigabatrin   | 5 – 8 h| PO                   | 50%             | None sig           | −0%            | • block the reuptake of GABA & inhibits the catabolism of GABA → ↑ GABA concentrations; no receptor agonist.  
• inhibition of voltage-sensitive Na+ channels |
| tiagabine    | 7 – 9 h| PO                   | 90%             | Hepatic; P450 CYP1A, CYP1A2, CYP2D6 or CYP2C19 | 96%            | • block the reuptake of GABA → ↑ GABA concentrations; no receptor agonist.  
• inhibition of voltage-sensitive Na+ channels |

Maldonado JR. Crit Care Clin, 2017
## Alcohol Withdrawal Treatment – Non-Benzodiazepine Alternatives

### ACA – 1/2

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>AWS Definition</th>
<th>Outcome</th>
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</table>
| **Stuppaeck et al 1992 DBRCT** | University Med Center Substance Abuse I/P Unit, N = 60 | **OXA** 120 mg (÷) vs. **CBZ** 800 mg (÷) tapering over 7 days. | CIWA-Ar | ➢ *No clinical differences between the two groups*

➢ Greater progression to DTs & Sz in oxazepam group (OXA 7% & 3%; CLO 0% & 0%, respectively) |

| **Malcolm et al 2002 DBRCT** | University Med Center Substance Abuse O/P clinic, N = 136 | **LOR** 6 – 8 mg (÷) on day 1, tapering to 2 mg vs. **CBZ** 600 – 800 mg on day 1, tapering to 200 mg. | CIWA-Ar | ➢ Both drugs were equally efficacious at treating AWS.

• But CBZ had greater efficacy than LOR in preventing post-treatment relapses to drinking over the 12 days of follow-up.

• There was a greater reduction in anxiety symptoms, as measured by the Zung Anxiety Scale, in CBZ group. |

| **Minozzi et al 2010** | Various, Cochrane Review, 56 studies, N = 4076 subjects | anticonvulsant vs placebo vs BZDPs | CIWA-Ar, AWSz, DTs | ➢ carbamazepine was associated with a significant reduction in alcohol withdrawal symptoms (CIWA-Ar mean difference = -1.04, 95 % CI -1.89 to -0.20) when compared with the benzodiazepines lorazepam and oxazepam. |
## Alcohol Withdrawal Treatment – Non-Benzodiazepine Alternatives

### ACA – 2/2

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</thead>
</table>
| **Myrick et al 2000**  
Prospective, randomized, single-blind trial | I/P Detox Unit N=11 | **LOR** 2 mg for CIWA-Ar scores > 6  
Vs. **VPA** 500 mg TID for 4 days plus LOR 2 mg for CIWA-Ar > 6. | CIWA-Ar | The Group-by-CIWA-Ar score interaction was determined to favor VPA significantly ($p \leq 0.01$).  
Patients in the VPA group appeared to use less LOR than those in the control group over the study period. |
| **Longo et al 2002**  
Randomized, open-label study | I/P Detox Unit N=16 | **BZD vs. VPA** (5d detox) vs. VPA (+6 wk maintenance). Loading dose of 20 mg/kg/day in 2 divided doses 6-8 hours apart on day 1, then twice daily thereafter | CIWA-Ar | AWS reduction occurred more rapidly and consistently in the VPA-treatment group than the BZD-control group at 12 and 24 hour intervals (based on CIWA-Ar scores) - not statistically significant.  
Although the protocol allowed for the availability of a “BZD rescue” in the event of VPA non-response, none of the VPA-treated patients required prn BZD. |
| **Eyer et al 2011**  
Restrospective Chart Review | I/P Detox Unit N=827 | **CBZ** (200mg TID) vs. **VPA** 300mg TID | CIWA-Ar | VPA may offer some benefits compared with CBZ in the adjunct treatment of moderate-to-severe AWS:  
- shorter need for pharmacological treatment  
- fewer ICU transfers  
- a more favorable side-effect profile  
Trend that VPA may be more effective than CBZ in reducing complications during AWS, especially WSz. |
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| Mariani et al 2006 ROLCT | University Med Center Substance Abuse I/P Unit, N = 27 | PHE vs GAB  
Day 1. GAB 1200 mg PO loading dose, followed in 6hrs with 600 mg PO, followed in 6hrs with 600 mg PO (total of 2400 mg in the first 24 hrs)  
Day 2. 600 mg PO TID  
Day 3. 600 mg PO TID  
Day 4. 600 mg PO QD | CIWA-Ar | ➢ There were no significant differences in the proportion of patients in each group requiring rescue medication for breakthrough signs and symptoms of AW.  
➢ No group differences on alcohol withdrawal, craving, mood, irritability, anxiety, or sleep were observed.  
➢ There were NO serious adverse events on GAB group. |
| Myrick et al 2009 DBRCT | I/P Detox Unit n = 100 | Randomized to GAB-Low dose (300 mg TID X3d, then 400mg BID on d#4); GAB-High Dose (400mg TID X3d, then 400 mg BID on d#4); vs. LOR (2 mg TID X3d, then 2 mg BID on d#4); f/u up to 12 days. | CIWA-Ar | ➢ High-dose GAB was statistically superior but clinically similar to LOR (p = 0.009).  
➢ During treatment, LOR-treated participants had higher probabilities of drinking compared to GAB-treated (p = 0.0002).  
➢ Post-treatment, GAB-treated participants had less probability of drinking during the follow-up post-treatment period (p = 0.2 for 900 mg) compared to LOR-treated (p = 0.55).  
➢ The GAB groups also had less craving, anxiety, and sedation compared to LOR. |
| Stock et al. 2013 DBRPCT | O/P VA Clinic N=26 | Gabapentin (1200 mg/day starting dose) vs. chlordiazepoxide (100 mg/day starting dose) were administered according to a fixed-dose taper schedule over 6 days | CIWA-Ar scores. | ➢ There were no significant differences in AWS symptoms by medication;  
➢ However, those in the gabapentin group reported decreased daytime sleepiness compared with those who received chlordiazepoxide. |
Alcohol Withdrawal Treatment
Anticonvulsant Agents

- CBZP has been used >25 yrs to treat alcohol withdrawal in Europe (Malcom et al, J Gen Int Med 2002;17:349-355).
- Cochrane Database Analysis of all randomized controlled trials from 1966 – 2004 comparing efficacy of carbamazepine vs. various benzodiazepine agents.
- Main results
  - 48 studies, involving 3610 subjects were included.
  - For the anticonvulsant versus placebo comparison, therapeutic success tended to be more common among the anticonvulsant-treated patients (relative risk (RR) 1.32; 95% confidence interval (CI) 0.92 to 1.91), and anticonvulsant tended to show a protective benefit against seizures (RR 0.57; 95% CI 0.27 to 1.19).
  - For the anticonvulsant versus other drug comparison, CIWA-Ar score showed non-significant differences for the anticonvulsants compared to the other drugs at the end of treatment (weighted mean difference (WMD) -0.73; 95% CI -1.76 to 0.31).
  - For the subgroup analysis of carbamazepine versus benzodiazepine, a statistically significant protective effect was found for the anticonvulsant (WMD -1.04; 95% CI -1.89 to -0.20), p = 0.02), and side-effects tended to be less common in the anticonvulsant-group (RR 0.56; 95% CI 0.31 to 1.02).

Polycarpou et al 2005
**α₂ Agonists**

**Centrally acting α₂-adrenergic receptors agonists:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>α₂/α₁ Selectivity</th>
<th>DT ½ (h)</th>
<th>ET ½ (h)</th>
<th>Product Availability</th>
<th>Bioavailability</th>
<th>Protein Binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guanfacine</td>
<td>2,640</td>
<td>2.5</td>
<td>17</td>
<td>PO</td>
<td>~100%</td>
<td>70%</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>1,600</td>
<td>6</td>
<td>2</td>
<td>IV</td>
<td>70-80%</td>
<td>94%</td>
</tr>
<tr>
<td>Medetomidine</td>
<td>1,200</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>220</td>
<td>11</td>
<td>13</td>
<td>PO TDS</td>
<td>100%PO 60%TDS</td>
<td>40%</td>
</tr>
<tr>
<td>methyldopa</td>
<td>12 m</td>
<td>105 m</td>
<td></td>
<td>PO/IV</td>
<td>50%</td>
<td>&lt;20%</td>
</tr>
<tr>
<td>Guanabenz</td>
<td>60 m</td>
<td>6</td>
<td>6</td>
<td>PO</td>
<td>75%</td>
<td>90%</td>
</tr>
</tbody>
</table>

**Figure:**

- **Guanfacine:** T1/2 = 17 h hepatic→renal
- **Dexmedetomidine:** T1/2=12 h hepatic→renal 95%
- **Methyldopa:** T1/2 = 105 m hepatic→renal 70%
- **Clonidine:** T1/2=142-33 h hepatic→renal 50%
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</thead>
<tbody>
<tr>
<td>Baumgartner &amp; Rowen 1991 DBRPCT</td>
<td>I/P Detox Unit N=50</td>
<td>Fixed titration of chlor Diazepam (over 4d) vs. transdermal CLO (0.2 mg oral loading dose + 0.2 mg/24-hour transdermal patches X2 on day 1).</td>
<td>AWAS</td>
<td>➢ There was no significant difference in patient-reported subjective symptoms of alcohol withdrawal. ➢ Mean systolic and diastolic blood pressure and pulse were significantly lower for patients in the CLO group (p &lt; 0.001 for all). ➢ CLO group had a better response to therapy as assessed by the AWAS, less anxiety as assessed by the Ham-A Rating Scale (p &lt; 0.02), better control of heart rate and blood pressure; better cognitive recovery. ➢ No Sz or DTs in either group.</td>
</tr>
<tr>
<td>Dobrydnjov et al 2004 DBRCT</td>
<td>Surgical patients, n=45</td>
<td>Diazepam vs Clonidine given pre-op to subjects undergoing transurethral resection of the prostate under spinal anesthesia</td>
<td>CIWA-Ar Autonomic reactivity</td>
<td>➢ Median CIWA-Ar score: 12 vs 1 (p&lt;0.001) ➢ Development of AWS: 80% vs 10% (p&lt;0.002) • Anxiety: 67% vs 0% (p&lt;0.001) • Agitation: 40% vs 0% (p&lt;0.05) • Progression to DTs: 27% vs 7% ➢ VS: hyperdynamic circulatory reaction observed in D group; slightly decreased mean arterial BP in Clo.</td>
</tr>
<tr>
<td>Lizotte et al 2014 Retrospective chart review</td>
<td>ICU-AWS N = 41</td>
<td>AW who received adjunctive dexmedetomidine or propofol.</td>
<td>BZDP &amp; haloperidol use; 2ry measures included AWSS and sedation scoring, analgesic use, IUC-LOS, rates of intubation, and adverse events</td>
<td>➢ Among the dexmedetomidine and propofol groups, significant reductions in benzodiazepine (P≤0.0001 and P=0.043, respectively) and haloperidol (P≤0.0001 and P=0.026, respectively) requirements were observed. ➢ Shorter LOS in the dexmedetomidine group (123.6 hours vs 156.5 hours; P=0.125). ➢ Rates of intubation (14.7% vs 100%) and time of intubation (19.9 hours vs 97.6 hours; P=0.002) were less in the dexmedetomidine group. ➢ Incidence of hypotension was 17.6% in the dexmedetomidine group vs 28.5% in the propofol group.</td>
</tr>
</tbody>
</table>
The QROC on N=403 confirms that PAWSS ≥ 4 is the best cut-off point; with an area under the curve (AUC) = 0.9765.
I. Assessment:

- **Patient with H/O ETOH use in the last 30 days or “+” BAL**
  - **PAWSS < 4**
  - **PAWSS > 4**

- **PAWSS**

- **CIWA or AWSS**
  - **CIWA ≥ 15 AWSS ≥ 6**
  - **CIWA < 15 AWSS < 6**

- **Pt already experiencing AWS, proceed to Tx Protocol**

- **Pt is at LOW risk for Moderate or Severe AWS; no prophylaxis is deemed necessary may treat MILD AWS symptomatically**

- **Proceed with BZDP-Sparing Prophylaxis Protocol**
II. Monitoring:
   A. Monitor patient’s progress with an AWS severity scale:

<table>
<thead>
<tr>
<th>AWS Severity</th>
<th>CIWA-Ar</th>
<th>AWSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>≤ 15</td>
<td>≤ 5</td>
</tr>
<tr>
<td>Moderate</td>
<td>16-20</td>
<td>6 – 9</td>
</tr>
<tr>
<td>Severe</td>
<td>≥ 20</td>
<td>≥ 10</td>
</tr>
</tbody>
</table>

III. Non-Pharmacological Management:

A. Implement early mobilization techniques:
   1. Aggressive PT & OT as soon as it is medically safe to do so
      a. In bedridden patients – daily passive range of motion.
      b. Get the patient up and moving as early as possible.
   2. Patients out of bed as much as possible.
   3. Provide patients with any required sensory aids (i.e., eyeglasses, hearing aids).
   4. Promote as normal a circadian light rhythm as possible.
      a. Environmental manipulations
         i. Light control (i.e., lights on & curtains drawn during the day; off at night)
         ii. Noise control (i.e., provide ear plugs, turn off TVs, minimize night staff chatter).
      b. Provide as much natural light as possible during the daytime.
   5. If possible, provide the patient with at least a 6-hrs period of protected nighttime sleep (i.e., no blood draws, tests and medication administrations unless absolutely necessary).

B. Provide adequate intellectual and environmental stimulation:
   1. Encourage visitation by family and friends
   2. Minimize television use.

C. Monitor for seizures.

D. Fall precautions.

E. Basic laboratory tests: CrCl; LFTs; ECG, volatile screen order, toxicology screening test (if not already done).
IV. Fluid & Nutritional Replacement

A. Correct and monitor fluid balances & electrolytes.
   1. Mg+ [1.7 - 2.2 mg/dl]
   2. Na+ [135 - 145 mEq/L]
   3. K+ [3.7 - 5.2 mEq/L]

B. Vitamin supplementation:
   1. Thiamine 500 mg IV/IM/PO – TID x 5 days
      ➢ Followed by Thiamine 100 mg IV/IM/PO x rest of hospital stay (or up to 14 d)
   2. Folate 1 mg by mouth daily
   3. Multivitamin, 1 tab by mouth daily
   4. B complex vitamin 2 tabs by mouth daily
   5. Vitamin K 5 – 10 mg subcutaneously x 1 (if international normalized ratio [INR] is >1.3)

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Stanford’s BDZP-Sparing AWS Management Protocol

V. Pharmacological Prophylaxis:

A. Alpha-2 Agents:
   1. Clonidine transdermal 0.1mg (2 patches)
   2. PLUS administer clonidine 0.1 mg PO/IV q 8hrs (x3 doses)
   3. Alternatively, may use guanfacine 0.5 - 1 mg PO BID; (better anxiolytic effect and is less hypotensive than clonidine)

B. If patient’s VS unable to tolerate α2 effect, or excess anxiety, may instead use gabapentin:
   - Day 0: 1200mg loading dose + 800 mg TID
   - Day 1 – 3: 800 mg PO TID
   - Day 4 – 5: 600 mg PO TID
   - Day 5 – 7: 300 mg PO TID
   - Day 8: D/C
   - DO NOT use gabapentin in patients with severe renal dysfunction who are unable to clear gabapentin (i.e., CrCl is <60).

C. In patient at extremely high risk for severe AWS (i.e., PAWSS≥7 or BAL≥300 on admission) use BOTH clonidine & gabapentin, as above.

D. For adjunct management of insomnia, may use (choose of the following):
   - Melatonin 6 mg PO q HS, plus one PRN:
   - Doxylamine 25 – 50 mg q HS, PRN
   - Hydroxyzine 50 mg PO q HS, PRN
   - Doxepin 10 mg PO q HS, PRN
   - Zolpidem 10 mg PO q HS, PRN

E. For adjunct management of anxiety, may use:
   - Doxylamine 25 – 50 mg q HS, PRN

F. For breakthrough AWS (move to AWS-Tx Protocol):
   - C. If CIWA-Ar >15, lorazepam 1 mg q 4hrs
   - D. If CIWA-Ar >20, lorazepam 2 mg q 4hrs

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VI. Pharmacological Treatment:

A. Alpha-2 Agents:
   1. Transdermal clonidine 0.2mg X2 (total 0.4 mg)
   2. PLUS administer clonidine 0.1 mg PO/IV q 8hrs (x3 doses)
   3. Alternatively, may use guanfacine 0.5 - 1 mg PO BID; (better anxiolytic effect and is less hypotensive than clonidine)
   4. Closely monitor CIWA/AWSS q 4-hrs, if AWS continues (e.g., CIWA ≥ 15; AWSS ≥ 6) add VPA.

B. PLUS, CaCh Modulator (GLU) - either
   1. Gabapentin schedule:
      - Day 0: 1200mg loading dose + 800 mg TID
      - Day 1 – 3: 800 mg PO TID
      - Day 4 – 5: 600 mg PO TID
      - Day 5 – 7: 300 mg PO TID
      - Day 8: D/C
   2. Valproic acid (PO or IV)
      i. Start VPA 250mg PO/IV BID + 500mgq HS
      ii. Cases of late severe AWS may require up to 1.5 gm in first 24-h
      iii. If Sx’s escalate after 12-hrs, increase total dose to 2 gm in divided doses.
      iv. If Sx’s of AWS continue or worsen, add gabapentin.

D. For adjunct management of insomnia:
   o Melatonin 6 mg PO q 1800, plus PRN:
   o Doxylamine 25 – 50 mg q HS, PRN
   o Hydroxyzine 50 mg PO q HS, PRN
   o Doxepin 10 mg PO q HS, PRN
   o Zolpidem 10 mg PO q HS, PRN

C. For breakthrough AWS:
   C. If CIWA-Ar >15, lorazepam 1 mg q 4hrs
   D. If CIWA-Ar >20, lorazepam 2 mg q 4hrs

E. Non-responsive AWS — consider transfer to ICU → add dexmedetomidine drip, 0.4 mcg/kg/hr; titrate every 20 min to effect.
Conclusions

Cochrane review [2nd latest published as of January 2016]: 57 studies, 4051 subjects.

Results:

- Benzodiazepines offered a large benefit against AWSz compared to placebo (relative risk [RR] 0.16; 95% CI 0.04 to 0.69; \( p = 0.01 \)).

- Benzodiazepines had similar success rates as other drugs (RR 1.00; 95% CI 0.83 to 1.21) or anticonvulsants in particular (RR 0.88; 95% CI 0.60 to 1.30) and offered a significant benefit for seizure control against non-anticonvulsants (RR 0.23; 95% CI 0.07 to 0.75; \( p = 0.02 \)), but not against anticonvulsants (RR 1.99; 95% CI 0.46 to 8.65).

- No difference between BZDP and other drugs was seen for CIWA-Ar score reduction at the end of treatment (WMD -0.05; 95% CI -1.18 to 1.08; \( p = 0.93 \); \( p = 0.72 \) for between-study heterogeneity), while BZDP tended to be less effective when compared to anticonvulsants (WMD -1.04; 95% CI -3.45 to 1.38; \( p = 0.40 \); \( p = 0.87 \) for between-study heterogeneity).

- **Authors' Conclusions:** BZDP are effective against alcohol withdrawal symptoms, in particular seizures, when compared to placebo. It is not possible to draw very precise conclusions about the relative effectiveness and safety of benzodiazepines against other drugs in alcohol withdrawal, because of the large heterogeneity of the trials both in interventions and assessment of outcomes. Nevertheless, the available data do not show differences between benzodiazepines and other drugs in broadly defined success rates. Moreover not all patients may need pharmacological treatment and it is unknown whether different BZDP and different regimens of administration (e.g. fixed versus symptom-triggered schedule) may have the same merits.

Ntais et al 2008
Are BZDPs Effective for AWS?

The evidence for the benefit of BZDP use in the Management of AWS comes from:

- BZDP vs PBO: 3 trials
- BZDP vs Other Rx (eg, GHB, TCAs, paraldehyde, APA, hydroxyzine, bromocriptine): 6 trials
- BZDP for AWSz: 11 trials
- BZDP for AWS-D: 7 trials
- BZDP vs BDZP: 13 trials
- BZDP-fixwd vs Sx triggered: 3 trials

### Table 1: Summary of randomized controlled trials of efficacy of benzodiazepines in the treatment of acute alcohol withdrawal

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>No. of patients with successful outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BZDP vs PBO</td>
<td>BZDP vs Other Rx (eg, GHB, TCAs, paraldehyde, APA, hydroxyzine, bromocriptine)</td>
</tr>
<tr>
<td>Sellers et al.1993</td>
<td>Diazepam vs placebo</td>
<td>18/25</td>
</tr>
<tr>
<td>Barros et al.1983</td>
<td>Chlordiazepoxide vs placebo</td>
<td>9/10</td>
</tr>
<tr>
<td>Narang et al.1983</td>
<td>Lorazepam vs placebo</td>
<td>20/21</td>
</tr>
<tr>
<td>Total</td>
<td>47/56</td>
<td>35/56</td>
</tr>
</tbody>
</table>

\* Holbrook et al.1999

\* Ntais 2008
Are BZDPS Effective for AWS?

- **Cochrane Review**: AU searched Cochrane Drugs and Alcohol Group Register of Trials, PubMed, EMBASE, CINAHL
- 64 studies; N = 4,309 participants were included in this review.
- Results:
  - The reviewed studies evaluated benzodiazepines against placebos, benzodiazepines against other medications (including other anticonvulsants), and one benzodiazepine against a different benzodiazepine.
  - Studies were small, had large heterogeneity, and had variable assessment outcomes, and most did not reach statistical significance.
  - Even with multiple studies, the only statistically significant finding in this review was that benzodiazepines were shown to be more effective than placebo for preventing withdrawal seizures; however, they were not shown to be superior to anticonvulsants or other medications.

*Schaefer & Hafner 2013*
American Delirium Society
8th Annual Meeting
Westin St. Francis Hotel
San Francisco, California  June 10-12, 2018