MEDICAL UNIVERSITY OF SOUTH CAROLINA
VALUE INSTITUTE
Evidence-Based Practice Brief
Alcohol Withdrawal Prophylaxis

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ASK THE QUESTION

Question: In hospitalized medical/surgical patients, what is the optimal prophylaxis for alcohol withdrawal syndrome?

SEARCH FOR EVIDENCE

Databases: PubMed, Scopus, CINAHL

PubMed search strategy: alcohol withdrawal AND (prophylaxis OR prevention)

Filters: Humans, English, Published in last 10 years

CRITICALLY ANALYZE THE EVIDENCE

There were six primary studies found addressing the use of a variety of medications for prophylaxis of alcohol withdrawal syndrome (AWS) in hospitalized medical/surgical patients. Three were systematic reviews (Awissi et al., 2013; Ungur et al., 2013; Sarai et al., 2013), all of which supported the equivalence various medications for this purpose. Awissi et al. (2013) supported the equivalence of IV EtOH, benzodiazepines, clonidine, antipsychotics, while Ungur et al. (2013) supported the equivalence of IV EtOH and benzodiazepines. Sarai et al. (2013) evaluated the use of magnesium and found insufficient evidence to draw conclusions. Similarly, Fullwood et al. (2013) performed an RCT of lorazepam vs ethanol/orazepam for preventing AWS. They found that overall hospital stay, time in ICU, and the ability to safely withdraw from the assigned drug regimen within 3 days were shorter with ethanol/orazepam combination treatment, but not statistically significant, while safety-related factors were no different. There were also two studies (Eberly et al., 2016; Muzyk et al. 2017) that reported the results of implementing a standard AWS prophylaxis and treatment protocol. Both protocols were benzodiazepine-based (diazepam, lorazepam). Eberly et al. (2016) reported significant reductions in mean and cumulative diazepam doses, as well as a significant reduction in the mean duration of treatment for AWS. There were no significant changes in LOS. Muzyk et al. (2017) reported a 1 day (95% CI, 1-2) reduction in median hospital LOS after the implementation of a lorazepam-based AWS protocol for prophylaxis and treatment.

Maldano, J. (2017) reported on the development of a novel, alternative, benzodiazepine-sparing protocol for the prophylaxis and treatment of AWS. It was based on assessment of AWS based on the Prediction of Alcohol Withdrawal Severity Scale (PAWSS) tool to identify patients at high risk for AWS and either the Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar) or Alcohol- Withdrawal Syndrome Scale (AWSS) to examine severity of symptoms. AWS
pharmacological prophylaxis includes the use of the alpha-2 agent, clonidine with the use of guanfacine (GUA) and gabapentin (GAB), as needed based on individualized patient needs. The algorithm and protocol are shown below:

**PICO Question:** In hospitalized medical/surgical patients, what is the optimal prophylaxis for alcohol withdrawal symptoms?

**Author/Date/Journal:** Awissi et al., 2013, Intensive Care Medicine

**Purpose of Study:** To review published manuscripts for prevalence, risk factors, screening

**Study Design:** Systematic review

**Sample & Setting:** 34 articles -AWS prevention (n=4) -only publications with high or moderate GRADE and Oxford

**Outcomes:** The benefit of alcohol withdrawal prophylaxis is unproven, and proposed regimens appear equivalent (IV EtOH, benzodiazepines).

**Design Limitations:** Study Limitations =  
- None
- **Systematic Review**
- Review did not address focused clinical question
<table>
<thead>
<tr>
<th><strong>tools, prophylactic and treatment strategies, and outcomes for alcohol withdrawal syndrome (AWS) and delirium tremens (DT) in the critically ill</strong></th>
<th>levels of evidence included</th>
<th>clonidine, antipsychotics) -criteria for beginning AWS prophylaxis varied (ranged from hx of consumption to alcohol dependence based on different criteria)</th>
<th>□ Search was not detailed or exhaustive □ Quality of the studies was not appraised or studies were of low quality □ Methods and/or results were inconsistent across studies</th>
</tr>
</thead>
</table>

**| **Ungur et al., 2013, Alcoholism: Clinical and Experimental Research** | **To perform a synopsis of controlled trials of alcohol withdrawal syndrome (AWS) prevention in therapy in the ICU** | **Systematic review** | **14 controlled trials -AWS prevention (n=6) -only LoE 1b, 1b- or 2b included (based on Oxford Centre for EBM criteria) Prevention: benzodiazepines (BZO), ethanol (EtOH), and clonidine were evaluated as single agents, and BZO, clonidine, clomethiazol and haloperidol were studied in drug combinations** | **There is sufficient evidence proving that BZO are effective for AWS prevention in single administration (n=2) and in combination with haloperidol or clonidine (n=2) Clonidine as single agent might be inferior compared to EtOH or midazolam (n=1) Combinations containing clomethiazol should not be preferred in critically ill patients because of bronchial hypersecretion (n=1) Moderately dosed IV EtOH (2-4 g/h) seems to be safe and as effective other agents in preventing AWS (n=3) Author note: IV EtOH or BZO can be advised for AWS prevention on ICU patients with alcohol dependence, but EtOH is not allowed for therapy of AWS** | **Study Limitations = □ None**  
**Systematic Review**  
**Review did not address focused clinical question**  
**Search was not detailed or exhaustive**  
**Quality of the studies was not appraised or studies were of low quality**  
**Methods and/or results were inconsistent across studies** |

**| **Sarai et al., 2013, Cochrane Database of Systematic Reviews** | **To assess the effects of magnesium for the prevention or treatment of AWS in hospitalized adults** | **Systematic review** | **4 studies (317 patients) -oral magnesium (12.5mmol/day to 20 mmol/day; n=3) -parenteral magnesium (16.24 mEq every 6 hours for 24 hours)** | **No study measured all of the identified primary outcomes and met the objectives of this review (seizure, DTs, Clinical Institute Withdrawal Assessment for Alcohol score of < 10) -there is insufficient evidence to determine whether magnesium** | **Study Limitations = □ None**  
**Systematic Review**  
**Review did not address focused clinical question**  
**Search was not detailed or exhaustive**  
**Quality of the studies was not appraised or studies were of low quality** |

**| **Publication Bias** | **(e.g. pharmaceutical company sponsors study on effectiveness of drug)** | **Increase Quality Rating if:**  
□ Large effect (When the relative risk of association between two factors is large or very large)  
□ Dose response (When the dose-response relationship increases the confidence than an effect is real and substantial)** | **DATE: 4/16/18**

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<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Journal/Purpose</th>
<th>Study Design</th>
<th>Participants</th>
<th>Methods and Results</th>
<th>Quality</th>
<th>Study Limitations</th>
</tr>
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<tbody>
<tr>
<td>Fullwood et al., 2013, American Journal of Critical Care</td>
<td>To evaluate the safety and efficacy of lorazepam vs ethanol/lorazepam for preventing alcohol withdrawal syndrome in patients with acute coronary syndromes</td>
<td>RCT</td>
<td>57 patients (93% male) with MI screened for alcohol dependence using the CAGE (cut down, annoyed, guilty, eye-opener) questionnaire -lorazepam (2mg IV every 6 hr; n= 29) -ethanol/lorazepam (50-100% of reported alcohol intake every 24 hr + lorazepam 2mg IV every 12 hr; n= 28) -all patients reported consuming 3 or more drinks per day and scored 2 or more on the CAGE screening survey -PO or NG ethanol based on patients drinking history (beer, vodka) -started at 50% and advanced to 100% of reported ethanol intake on the basis of the progression of symptoms Minimum of 3 days, Maximum of 1 week</td>
<td>Safety-related factors were not significantly different between the groups: -self-extubation (3% lorazepam vs 4% EtOH+lorazepam, p=0.98), -delirium tremens (21% lorazepam vs 18% EtOH+lorazepam, p=0.79) -reinfarction (0% lorazepam vs 4% EtOH+lorazepam, p=0.31) No significant difference in ability to safely withdraw from the randomized, assigned drug regimen within 3 days, once the MI had stabilized, was detected however the two were quite different (24% for lorazepam vs 86% for EtOH+lorazepam, p = .15) Fewer days were spent in the cardiac ICU (median: 2 vs 1, p= .32) but it was not statistically significant Overall hospital stay (median: 6 vs 5, p = .72) was shorter but not statistically different</td>
<td>Methods and/or results were inconsistent across studies</td>
<td>None</td>
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<tr>
<td>Eberly et al., 2016, Hospital Pharmacy</td>
<td>To evaluate the safety and efficacy of an alcohol withdrawal protocol based on results of the Clinical Institute Withdrawal Assessment of Alcohol, Revised (CIVA-Ar) scale</td>
<td>Quasi-experimental (pre, post) -retrospective</td>
<td>174 patients treated before and after the creation of a standardized protocol for prevention and treatment of AWS based on the patient's CIVA-Ar score at a single institution (Lexington VA Medical Center) -majority white men</td>
<td>Mean (pre 12.05 mg vs post 5.36 mg, p &lt;0.001) and cumulative (pre 77.57 mg vs post 35.0 mg, p&lt;0.001) diazepam doses were significantly lower post-protocol -mean duration of diazepam treatment was also lower post-protocol (pre 4.70 d vs post 2.21 d, p&lt;0.001)</td>
<td>None</td>
<td>None</td>
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Level of evidence for studies as a whole:
- High
- Moderate
- Low
- Very Low
<table>
<thead>
<tr>
<th>Study</th>
<th>Objective</th>
<th>Method</th>
<th>Results</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Muzyk et al. 2017, Journal of Psychiatric Practice</td>
<td>To determine if the implementation of a hospital-specific alcohol withdrawal treatment pathway used in a medical-surgical patient population decreased hospital length of stay (LOS) compared with the standard of care</td>
<td>Retrospective observational</td>
<td>582 patients treated before and after the creation of a standardized alcohol withdrawal treatment pathway for med-surg patients at a single academic medical center (Duke)</td>
<td>Study Limitations = □ None</td>
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<td>-majority male, white (55-60%) or black (32-34%)</td>
<td>Non-Experimental/Observational Studies (case-control, cohort, cross sectional, longitudinal, descriptive, epidemiologic, case study/series, survey)</td>
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<td>-all admitted for or with AWS</td>
<td>□ Insufficient sample size</td>
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<td>-pre: n=275 (2010)</td>
<td>□ Sample not representative of patients in the population as a whole</td>
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<td>-post: n=307 (2012)</td>
<td>□ Variables (confounders, exposures, predictors) were not described and accounted for</td>
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<td>Lorazepam-based protocol for prophylaxis and treatment of AWS (see below for details)</td>
<td>□ Outcome criteria not objective or were not applied in blind fashion</td>
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<td>□ Insufficient follow-up, if applicable</td>
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<td></td>
<td>89% pathway usage after implementation</td>
<td>□ For prognostic study, sample not defined at common point in course of disease/condition</td>
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<td>After adjusting for covariates, there was a 1 day (95% CI, 1-2) reduction in median hospital LOS between the two cohorts, 5 versus 4 days</td>
<td>□ For diagnostic study, gold standard not applied to all patients</td>
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<td>There was an increase in the proportion of subjects admitted to the ICU after the implementation of the alcohol withdrawal treatment pathway (24% in 2010 vs. 29.3% in 2012), but a decrease in the proportion of patients discharged with a diagnosis of DTs (17.8% in 2010 vs. 15.3% in 2012)</td>
<td>□ For diagnostic study, no independent, blind comparison between index test and gold standard</td>
</tr>
</tbody>
</table>
Eberly et al. (2016): AWS Protocol

**Step 1:** Does patient have history of alcohol use?

Yes

**Step 2:** Does patient have any of the following (MID to evaluate)?
- Current intoxication?
- If intubated, re-assess every 8 hours, and proceed with protocol when clinically appropriate
- Suspected overdose of CNS depressants prior to admission? Do not use this protocol
- Mechanical ventilation? Should have separate sedation orders with RASS score parameters

No

**Step 3:** Does patient have a documented history of alcohol related seizures and/or delirium tremens?

No

Yes

MD to order diazepam 10mg by mouth every 4 hours x 3 doses while proceeding with symptom-based alcohol protocol (Step 4)

**Step 4:** Initiate symptom-based alcohol protocol. Note doses depend on CIWA - Ar score

<table>
<thead>
<tr>
<th>CIWA - Ar Score</th>
<th>Orders</th>
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</table>
| **0 – 7**  
(absent/minimal withdrawal) | GIVE NO medicine. Repeat CIWA q1h x 24h, then q2h x 72h, then discontinue checking CIWA. |
| **8 – 15**  
(mild to moderate withdrawal) | Diazepam 1mg po q1h as needed. Repeat CIWA in 1 hour to assess effectiveness of prn medication. Or Lorazepam 1mg po q1h as needed. Repeat CIWA in 1 hour to assess effectiveness of prn medication. |
| **>15**  
(severe withdrawal) | Diazepam 10mg po q1h as needed. Repeat CIWA in 1 hour to assess effectiveness of prn medication. Or Lorazepam 2mg po q1h as needed. Repeat CIWA in 1 hour to assess effectiveness of prn medication. |

Note: If patient requires 2 or more ‘every hour’ doses of medication, contact MD after assessing prn effectiveness (prior to administering 3rd dose).

CIWA-Ar = CINIC INSTITUTE METHADONE Assessment for Alcohol – Revised scale

Nursing orders:
1. Complete baseline CIWA then follow the protocol for vital sign frequency and to assess patient's need for symptom-based treatment.
2. If patient is sleeping, do not wake the patient up to give diazepam/lorazepam or assess the patient's CIWA score when patient awakens.
3. If patient requires 2 or more ‘every hour’ doses of medication, contact MD after assessing prn effectiveness (prior to administering 3rd dose).
4. If after diazepam/lorazepam dose, CIWA score remains unchanged or increases, contact MD.
5. Notify MD for: Temp > 101°F, SBP > 160 mmHg, SBP < 90 mmHg, HR > 120, HR < 60, RR > 24, RR < 10, CIWA > 20, Increase in CIWA score of > 10, altered mental status, seizures

**Step 5:** MD to order ancillary meds as appropriate. * Nutrition: Thiamine, folic acid, multivitamins. * Nausea/vomiting: Ondansetron

**Figure 1:** Symptom-based alcohol withdrawal protocol. CNS = central nervous system; h = hour; HR = heart rate; MD = physician; PO = oral; prn = as needed; RASS = Richmond Agitation-Sedation Scale; RR = respiratory rate; q1h = every hour; q4h = every 4 hours; q12h = every 12 hours.
### TABLE 1. Alcohol Withdrawal Pathway Symptom Assessment and Treatment

<table>
<thead>
<tr>
<th>Treatment Path</th>
<th>History*</th>
<th>Vital Signs</th>
<th>Signs and Symptoms</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| Path 1: Prophylaxis | Positive | Normal | None | Scheduled: lorazepam 0.5 mg PO/IV q 6 h  
“As needed” lorazepam 0.5 mg PO/IV q 4 h  
Assess patient q 4 h |
| Path 2: Mild-to-moderate withdrawal | Positive | Temperature normal  
1 or 2 vital sign abnormalities  
SBP 140-160 mm Hg  
DBP 80-110 mm Hg  
HR 80-120 bpm | ≥2 Sxs of mild intensity  
Anxiety, agitation, tremor, insomnia, or diaphoresis | Scheduled lorazepam 1 mg PO/IV q 4 h  
“As needed” lorazepam 1 mg PO/IV q 2 h  
Assess patient q 2 h |
| Path 3: Moderate-to-severe withdrawal | Positive | 1 or 2 vital sign abnormalities  
SBP>160 mm Hg  
DBP>110 mm Hg  
HR>120 bpm  
T>38.3°C | ≥2 Sxs of moderate intensity  
Anxiety, agitation, tremor, insomnia, or diaphoresis | Scheduled lorazepam 2 mg PO/IV q 4 h  
“As needed” lorazepam 2 mg PO/IV q 2 h  
Assess patient q 2 h |
| Path 4: Severe withdrawal or alcohol withdrawal delirium/DTs | Positive | 2 or more vital sign abnormalities  
SBP>160 mm Hg  
DBP>110 mm Hg  
HR>120 bpm  
T>38.3°C | ≥2 Sxs of severe intensity  
Anxiety, agitation, tremor, insomnia, or diaphoresis  
AND ≥1 Sx of disorientation, hallucinations, or sensorium clouding | “As needed” lorazepam 4 mg PO/IV q 1 h  
Assess patient q 1 h or before each lorazepam dose |

The acronym CAGE is taken from key words in the 4 questions that make up this tool:
(1) Have you ever felt you needed to Cut down on your drinking?
(2) Have people Annoyed you by criticizing your drinking?
(3) Have you ever felt Guilty about drinking?
(4) Have you ever felt a need for a drink first thing in the morning (Eye-opener) to steady your nerves or to get rid of a hangover?

*History of alcohol withdrawal, withdrawal seizures, DTs, or positive CAGE.

DBP indicates diastolic blood pressure; DTs, delirium tremens; HR, heart rate; SBP, systolic blood pressure; sx, symptom; T, temperature.
REFERENCES


### Appendix A: GRADE criteria for rating a body of evidence on an intervention

Developed by the GRADE Working Group

#### Grades and interpretations:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Further research is very unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</td>
</tr>
<tr>
<td>Low</td>
<td>Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</td>
</tr>
<tr>
<td>Very low</td>
<td>Any estimate of effect is very uncertain.</td>
</tr>
</tbody>
</table>

#### Type of evidence and starting level

<table>
<thead>
<tr>
<th>Evidence Type</th>
<th>Starting Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized trial</td>
<td>High</td>
</tr>
<tr>
<td>Observational study</td>
<td>Low</td>
</tr>
<tr>
<td>Any other evidence</td>
<td>Very low</td>
</tr>
</tbody>
</table>

#### Criteria for increasing or decreasing level

**Reductions**
- Study quality has serious (−1) or very serious (−2) problems
- Important inconsistency in evidence (−1)
- Directness is somewhat (−1) or seriously (−2) uncertain
- Sparse or imprecise data (−1)
- Reporting bias highly probable (−1)

**Increases**
- Evidence of association† strong (+1) or very strong (+2)
- Dose-response gradient evident (+1)
- All plausible confounders would reduce the effect (+1)

†Strong association defined as significant relative risk (RR 2-5 or 0.5-0.2) based on consistent evidence from two or more studies with no plausible confounders;
Very strong association defined as significant relative risk (RR >5 or <0.2) based on direct evidence with no threats to validity.