# UC Health
# Alcohol Withdrawal
# Medication Guideline

## I. Benzodiazepines

Benzodiazepine therapy is the backbone of alcohol treatment. Benzodiazepines act on the same GABA receptors as alcohol, thereby mimicking the effect. They are the only class of medication demonstrated to prevent development of complicated forms of alcohol withdrawal syndrome (AWS) and reduce incidence of seizures, alcohol withdrawal delirium (AWD) and mortality. Medication therapy consists of benzodiazepine therapy given in either PRN or scheduled regimen plus or minus adjunctive therapies. Adjunctive therapies help decrease the amount of benzodiazepine provided in patients requiring increasing doses.

Symptom triggered (or PRN) approach is preferred to scheduled benzodiazepine dosing as it results in less benzodiazepine exposure and decreased ICU length of stay and pneumonia. If the patient is failing PRN approach scheduling benzodiazepine or benzodiazepine infusion may be considered, though close monitoring for drug accumulation should be performed. Oral benzodiazepines are comparable to intravenous administration in less severe alcohol withdrawal; however, IV administration is reasonable if treatment teams desire faster onset or are concerned with decreased enteral absorption.

**Table 1: Pharmacologic Properties of Common Benzodiazepine Agents**

| | Dosage Form | Half-life | Metabolite | Clearance | Time to Peak | Administration Location |
|---|---|---|---|---|---|---|
| Diazepam | Oral<br>IV | 20-50 hours | Yes (active); hepatic | Renal* | Oral: 1-2 hr<br>IV: 1-5 mi | Refer to IVP and continuous infusion grids at http://intranet.uchealth.com/Departments/Pharmacy/Pages/Medication-Policies.aspx |
| Lorazepam | Oral<br>IV<br>IM | 9-16 hours | No | Renal | Oral: 30-60 min<br>IM: 20-30 min<br>IV: 5-20 min | |
| Midazolam | IM<br>IV | 5-10 hours | Yes (active); hepatic | Renal* | IM: 10-15 min<br>IV: 1-2 min | |

**IV**: *intravenous*; **IM**: *intramuscular*; **min**: *minutes*; **hr**: *hour*; **IVP**: *intravenous push*

* Diazepam and midazolam effect will accumulate with repeat dosing and in the setting of renal and hepatic impairment

## II. Adjunctive Agents

Primary adjunctive agents focus on decreasing side effects of alcohol withdrawal syndrome (AWS) related to increased norepinephrine and dopamine release seen in AWS. These agents do not help prevent against seizure, and should be used in conjunction with benzodiazepine therapy.

**Table 2: Pharmacologic Properties of Primary and Secondary Adjunctive Agents**

| | Mechanism of Action | Effect | Dosage Forms | Half-life | Dose | Administration Location |
|---|---|---|---|---|---|---|
| Clonidine | Central alpha2 agonist | Vasodilation Sedation | Oral; Transdermal patch | Oral: 12-16 hours Patch: 20 hours | Oral: 0.2-0.6 mg/day in 3 divided doses OR 0.2mg followed by 0.2mg patch | Refer to IVP and continuous infusion grids at http://intranet.uchealth.com/Departments/Pharmacy/Pages/Medication-Policies.aspx |
| Dexmedetomidine | Central alpha2 agonist | Vasodilation Bradycardia Sedation | IV; Continuous infusion | 2.7 hours | IV: 0.2-1.5 mcg/kg/hr | |
| Phenobarbital | GABA agonist | Vasodilation Sedation *Can decrease respiratory drive, use with caution | IV Oral | 53-140 hours | IV: 260mg x 1 followed by 130mg as needed | |
| Haloperidol | Dopamine antagonist, 1st generation antipsychotic | Sedation in face of delirium | IV (off label route); IM; Oral | IV: 14-26 hours Oral: 14-36 hours | IV: 5-10 mg every 15-30 minutes | |
| Ketamine | NMDA antagonist | Sedation Pain Relief | IV | 15 minutes | 2.5-5 mcg/kg/min continuous infusion | |

GABA: gamma-aminobutyric acid (GABA) receptors; NMDA: N-methyl-D-aspartate (NMDA) receptor
*Continuation of oral phenobarbital can be considered if good response to IV given in the emergency department

## III. Alcohol Withdrawal Risk Categorization

a. High Risk = Patients with a history of more than 12 alcoholic beverages/day, a history of severe alcohol withdrawal, or history of seizure related to alcohol withdrawal
   - Consider benzodiazepine load followed by scheduled regimen
     - Initial CIWA ≥ 16: Diazepam 20mg IV or PO load followed by diazepam 10mg every 8 hours IV or PO
     - Initial CIWA < 16: Diazepam 10mg IV or PO followed by diazepam 5mg every 8 hours IV or PO

b. Low Risk = Patients that do not meet criteria for high risk (<12 drinks/day, no history of withdrawal seizure, no history of severe withdrawal).
   - Consider benzodiazepine load if initial CIWA >16.

## IV. When to transfer to a higher level of care

a. Hold medication if vital signs are decreasing (HR <60, SpO2 <90%, SBP <100, RR <12) or unable to rouse patient (RASS -1) and notify the provider.
b. CIWA-AR score > 35 or if CIWA-AR > 10 every hour x 4 despite treatment

# UC Health Treatment of Alcohol Withdrawal
## Non-ICU Level of Care

Patients will be categorized by the provider as low vs. high risk (see Section III of Alcohol Withdrawal Medication Guideline).
High risk patients may have a benzodiazepine loading dose and/or scheduled benzodiazepine ordered; check MAR.
Low risk patients may have a prn benzodiazepine loading dose available for initial CIWA-Ar >16; check MAR.
If initial loading dose given, wait 10 minutes before proceeding to next box.

CIWA-Ar Assessment
*Rally Pack (thiamine, MVI, folic acid) PO/IV;* check MAR

**CIWA-Ar Score ≤10**
*No PRN lorazepam indicated*

**CIWA-Ar Score >10**
*Administer PRN lorazepam as ordered on MAR*
CIWA 11-16: Lorazepam 1-2 mg IV/PO
CIWA >16: Lorazepam 2-4 mg IV/PO

Monitor CIWA-Ar based on level of care:
Floor: every 4 hours
Step Down: every 2 hours
***If CIWA-Ar <10 x48 hours, assess for discontinuation***

Repeat CIWA-Ar ***1 hour*** after lorazepam given

**CIWA-Ar Score ≤10**
*No PRN lorazepam indicated*

**If CIWA-Ar remains >10** and RR >12, *give additional dose of PRN lorazepam as ordered on MAR per CIWA-Ar*

Monitor CIWA-Ar based on level of care:
Floor: every 4 hours
Step Down: every 2 hours

Repeat CIWA-Ar ***1 hour*** after lorazepam given

**CIWA-Ar Score ≤10**
*No PRN lorazepam indicated*

**If CIWA-Ar remains >10** and RR >12, *give additional dose of PRN lorazepam as ordered on MAR per CIWA-Ar*

Monitor CIWA-Ar based on level of care:
Floor: every 4 hours
Step Down: every 2 hours

Repeat CIWA-Ar ***1 hour*** after lorazepam given.
If 3 doses given in 3 hours and CIWA-Ar remains >10, notify physician before re-dosing and consider adjunctive therapy.

**Adjunctive Therapies**
Consult provider for ordering and appropriate monitoring. All adjunctive therapies should be used in addition to PRN benzodiazepine.

***Haldol 5 mg IV every 6 hours***
PRN agitation
(monitor for QTc prolongation)

***Clonidine 0.1 mg every 8 hours scheduled*** for hypertension or tachycardia associated with alcohol withdrawal

*If patients need further adjunctive therapies such as continuous infusion sedatives then Stepdown or ICU transfer should occur

**Abbreviations**

- CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol revised
- HR: heart rate
- IV: intravenous
- MAR: medication administration record
- PO: oral
- PRN: as needed
- RR: respiratory rate
- SBP: systolic blood pressure
- SpO2: oxygen saturation

Notify provider at any time if concerned for inadequate control of symptoms (e.g. CIWA-Ar >35 despite treatment)
or HR <60, SpO2 <90%, SBP <100, RR <12, or seizure activity

# UC Health Treatment of Alcohol Withdrawal
## ICU Level of Care - Protocol for Non-Mechanically Ventilated Patients*

CIWA-Ar Assessment
*Rally Pack (thiamine, MVI, folic acid) IV*

*Patients with traumatic brain injury are excluded

Total CIWA-Ar Score
- ≥ 10
- < 10 → See "*Maintenance Control*" Box

### *Initial Control*

Delirium Subtotal ≥ 3 AND CAM-ICU(+)? — Yes → Haloperidol 5-10* mg IVP every 30 minutes PRN until Delirium Subtotal is < 3.
Call MD if Delirium Subtotal remains ≥3 after total of 30 mg of haloperidol.
→ CIWA-Ar < 10? — Yes → (to Maintenance CIWA Assessment)
CIWA-Ar < 10? — No → (to next step)

No

CNS Subtotal ≥ 4 AND RASS ≥ +2? — Yes → Lorazepam 2 mg IVP every 15 minutes PRN until CNS Subtotal is < 4 AND RASS ±1.
Call MD if CNS Subtotal remains ≥ 4 OR RASS ≥ +2 after 30 minutes.
→ CIWA-Ar < 10? — Yes → (to Maintenance CIWA Assessment)
CIWA-Ar < 10? — No → (to next step)

No

***Only for patients with no evidence of ongoing blood loss***

Adrenergic Subtotal ≥ 3? — Yes → Clonidine 0.1 mg po/per-tube every 1 hour until Adrenergic Subtotal < 3 OR SBP <140; DBP < 90 mmHg.
If Adrenergic Subtotal remains ≥ 3 AND SBP > 140; DBP > 90 after 3 doses of above, then administer clonidine 0.2 mg po/per-tube every 1 hour until until Adrenergic Subtotal < 3 OR SBP <140; DBP < 90 mmHg.
* Hold parameters for all clonidine orders SBP < 100 of DBP < 60 mmHg.
→ CIWA-Ar < 10? — Yes → (to Maintenance CIWA Assessment)
CIWA-Ar < 10? — No → **Return to top of "*INITIAL CONTROL*" and call MD**
**Consider Secondary Adjunctive Therapies (Page 6)**

*Haloperidol range orders: administer lower dose first and if no improvement in CAM score, use higher dose
Lorazepam range orders: administer lower dose first and if no improvement in RASS score, use higher dose

### *Maintenance Control*

**Maintenance CIWA Assessment**
CIWA-Ar every 1 hour for initial 24 hours then every 4 hours thereafter.
If Total CIWA-Ar ≥10 at any time, then do CIWA-Ar every 1 hour.
If Total CIWA-Ar is <10 for 2 consecutive hours, then do every 4 hour assessment.

CIWA Assessment

- < 10 → Continue Maintenance CIWA Assessment
- 10 to 20
- > 20 → Return to "*Initial Control*" Box

10 to 20:

- Delirium Symptoms: Haloperidol 5-10* mg IVP every 30 minutes PRN for Delirium Subtotal ≥3 per CIWA and CAM-ICU (+).
  Check bedside QTc interval every 12 hours.
- CNS Excitation Symptoms: Lorazepam 2 mg IVP every 15 minutes PRN for CNS Subtotal ≥ 4 per CIWA and RASS ≥ +2.
- Adrenergic Hyperactivity Symptoms: Clonidine 0.1 mg po/per-tube every 1 hour if Adrenergic Subtotal is ≥ 3 per CIWA.
  * If ≥ 0.6 mg clonidine required in previous 24 hours, schedule clonidine 0.1 mg po/per-tube every 8 hours.
  * Hold parameters for all clonidine orders SBP < 100 of DBP < 60 mmHg.

→ Continue Maintenance CIWA Assessment

## V. Secondary Adjunctive Therapies in the ICU

Secondary adjunctive agents used in the ICU may be considered if treatment is unable to obtain goal CIWA-Ar with ICU algorithm and treatment team has considered benzodiazepine plus primary adjunctive agents (haloperidol and/or clonidine) has failed. Therapies should be initiated in an ICU level of care (see unit specific grid) to provide hemodynamic and respiratory monitoring.

**a.** ***Dexmedetomidine continuous intravenous Infusion 0.2 – 1.5 mcg/kg/hr***

- Titrate every 15-30 minutes by 0.2 mcg/kg/hr to CIWA score goal defined by primary team
- Has been shown to decrease benzodiazepine requirements in patients with AWS but does not possess GABA receptor pharmacology, therefore it is not effective as monotherapy for prevention of AWS or AWD-related seizures.
- Dexmedetomidine monitoring includes blood pressure and heart rate as it causes vasodilation and bradycardia.

**b.** ***Ketamine continuous intravenous infusion 2.5 – 10 mcg/kg/min***

- Use for treatment of alcohol withdrawal in a non-intubated patient requires provider guided titration
- Retrospective data showing reduced benzodiazepine requirements in AWS. Limited data should reserve ketamine for patients who have failed standard benzodiazepine and primary adjunctive agents or those who are not candidates for adjunctive dexmedetomidine due to hypotension or heart rate as observed by the primary team.
- Monitor for side effects including emergence reactions (i.e., psychosis) including agitation and delirium, increased heart rate and/or blood pressure. If side effects occur, recommend decreasing the dose or discontinuing therapy.
- Dose titration in patients without a protected airway should be guided by the provider and not titrated by the bedside nurse.

**c.** ***Benzodiazepine continuous intravenous infusion***

- Midazolam continuous infusion 0.5-10 mg/hr titrate every 15 minutes by 1mg/hr to goal CIWA-Ar defined by providing team. Consider bolus dose of midazolam 2-4mg with every dose increase. Infusion rate may exceed maximum listed here in severe AWS.
- Lorazepam 1-8 mg/hr continuous infusion titrate every 30 minutes by 1 mg/hr to goal CIWA-Ar defined by providing team. Consider bolus dose of lorazepam 2-4 mg with every dose increase. Infusion rate may exceed maximum listed here in severe AWS.
- Benzodiazepine continuous infusion must be titrated carefully as drugs have long half-lives and can accumulate in the body. Do not initiate benzodiazepine infusion as first line AWS treatment, but preserve therapy for patients whose failed standard benzodiazepine and primary adjunctive agents or those who have failed other secondary adjunctive therapies.
- Monitoring includes mental status, sedation, blood pressure, and respiratory status.

**d.** ***Phenobarbital oral and intravenous therapy***

- Maintenance doses of 60mg phenobarbital ORAL therapy every 6 hours followed by a taper can be considered in patients who are responsive early in therapy.
- Phenobarbital intravenous therapy has some data when used in the emergency department in conjunction with benzodiazepine to reduce ICU admission. However, phenobarbital has significant side effects including hypotension, sedation, and respiratory depression that requires close hemodynamic and respiratory monitoring. Therapy should not be initiated in the ICU or floor, but could be considered for continuation of therapy if the patient had a good response in the emergency department.

- UC Health Emergency Department specific protocol: https://static1.squarespace.com/static/53c1a2cce4b0e88e61f99b70/t/5991f10946c3c45209e93c98/1502736650069/Alcohol+Withdrawal+Syndrome+Draft+5.pdf

e. **Other Adjunctive Medications**
   - Other medications that have effect on GABA receptors and may be used as adjunctive therapy in severe ETOH therapy not responsive to standard primary adjunctive therapies include:
     - Propofol infusion (patient must have protected airway as this is a respiratory depressant) 5-80 mcg/kg/min titrated every 15 minutes to goal RASS score
     - Gabapentin 100mg three times daily, increased by increments of 300mg/day up to max of 1800mg daily (side effect is sedation, caution in renal dysfunction)
   - Anti-epileptics including carbamazepine and valproic acid have shown some benefit to reduce standard of care treatment for alcohol withdrawal, however there is minimal randomized, controlled literature to support routine use. Clinicians could consider adjunct therapies in refractory alcohol withdrawal not responsive to primary and secondary adjunctive agents, however anti-epileptic medications often require monitoring for sedation and toxicity. Risk verses benefit should be considered prior to initiating therapy.
   - Ethanol administered wither orally or intravenously is limited by adverse effects including altered mental status, respiratory failure, and tissue damage (IV only). Ethical and safety concerns involve providing a drug (e.g ethanol) that does not promote cessation of alcohol and creating an environment after discharge where the patient could withdrawal without supervision. The use of ethanol is not recommended due to these concerns in addition to lack of controlled trials evaluating its safety or relative efficacy compared to placebo or standard of care.

## VI. Alcohol withdrawal assessment in patients mechanically ventilated on sedation and analgesia

a. CIWA-Ar and CIWA-ICU is not validated in patients on mechanical ventilation who are oftentimes concurrently on continuous sedation and analgesia. Therefore, CIWA-Ar monitoring should NOT be performed on mechanically ventilated patients. Validated assessment scores for agitation such as the Richmond Agitation Sedation Scale (RASS) and pain assessments like the objective pain assessment (OPAS) should be performed per the ICU or stepdown protocol to assess the patient's level of sedation and pain respectively. (http://intranet.uchealth.com/Departments/Pharmacy/pdf/UCMC%20ICU%20Sedation%20Scales%202016.pdf )

a. Medications should be given to obtain a goal RASS score (usually goal of -1 to 1 unless defined otherwise by the primary team)

UC Health Treatment of Alcohol Withdrawal

**ICU Level of Care - Protocol for Mechanically Ventilated Patients**

**Suspected high risk of alcohol withdrawal** (e.g. ≥ 12 alcoholic drinks/day, history of AWD/history of seizures from alcohol withdrawal) or initial RASS > 2

Rally Pack (thiamine, MVI, folic acid) PO or IV

+

RASS and OPAS monitoring per unit policy

**Suspected medium/low risk alcohol, withdrawa**l (e.g. <12 alcoholic drinks/day with history of alcohol use disorder or initial RASS ≤ 2)

***Diazepam 10 mg every 8 hours PO scheduled if enteral access or Lorazepam 2mg IV every 6 hours scheduled if NPO***

*+*

***Lorazepam 0.5-2* mg IV PRN every 15 minutes for RASS > 2***

*+*

***Propofol continuous infusion 5-80 mcg/kg/min*** titrated every 10 minutes to obtain goal RASS as defined by providing team

*+*

*Haloperidol range orders: administer lower dose first and if no improvement in CAM score, use higher dose
Lorazepam range orders: administer lower dose first and if no improvement in RASS score, use higher dose

***Adjunctive Therapies***

Can be considered if patient is persistently RASS **≥** 3 despite 3+ doses of PRN benzodiazepine and maximum infusion rates of analgesia and sedation medications. Consult provider for ordering and appropriate monitoring.

***Haldol 2-5*mg IV every 4 hours*** PRN for CAM+ (monitor for QTc prolongation)

***Clonidine 0.1 mg every 8 hours scheduled*** for hypertension or tachycardia associated agitation

***Ketamine 2.5-10 mcg/kg/min continuous IV infusion*** titrated every 30 minutes to goal RASS defined by providing team

***Dexmedetomidine 0.2-1.5 mcg/kg/min*** can be considered as a bridge off propofol therapy to aide in extubation.

***Lorazepam 0.5-2* mg IV PRN every 15 minutes for RASS ≥ 2***

*+*

***Propofol continuous infusion 5-80 mcg/kg/min*** titrated every 10 minutes to obtain goal RASS as defined by providing team

*+*

***Fentanyl continuous infusion 25-200 mcg/min*** titrated every 10 minutes to obtain goal analgesia (e.g. OPAS< 5) as defined by providing team

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