Hospital Level Inpatient Treatment of Alcohol Withdrawal Syndrome

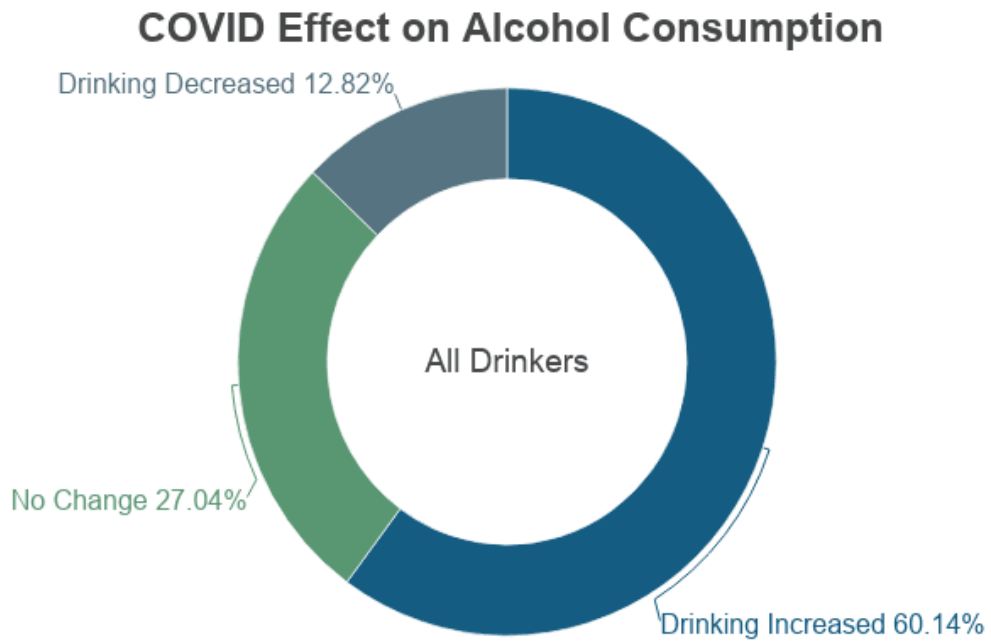
Nicolette Centanni PharmD

Objectives

- Describe the pathophysiology and complications of alcohol withdrawal
- Identify tools for predicting and assessing alcohol withdrawal
- Discuss guidelines, pharmacotherapy and literature for inpatient AWS with a focus on benzodiazepines and phenobarbital
- Outline the role of adjunct medications in alcohol withdrawal

Trends in AUD/AWS

- ~20% Maine adults over 18 binge drink at least once per month
- Up to 42% admitted to general medicine floor have AUD
  - 8% of these will experience alcohol withdrawal
    - Up to 20% of above experience severe alcohol withdrawal symptoms (SAWS) including AWD → mortality up to 20%

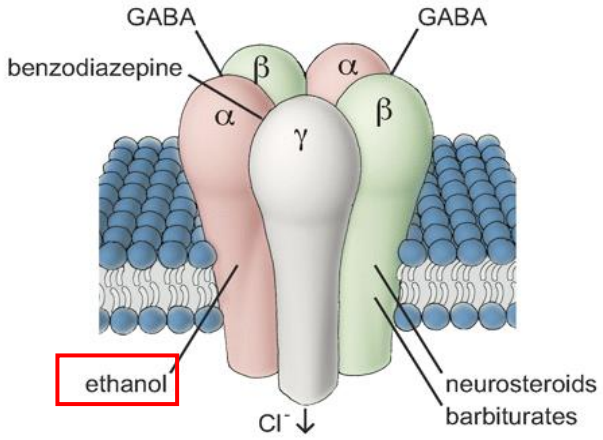


National Center for Drug Abuse Statistics Alcohol Abuse Statistics [2022]: National + State Data - NCDAS (drugabusestatistics.org) accessed 11/5/2022
Goodson et al. Alcohol Clin Exp Res 2014; 38: 2664-2677 DOI:10.1111/acer.12529
Jesse et al. Acta Neurol Scand 2017; 135: 4-16 DOI: 10.1111/ane.12671

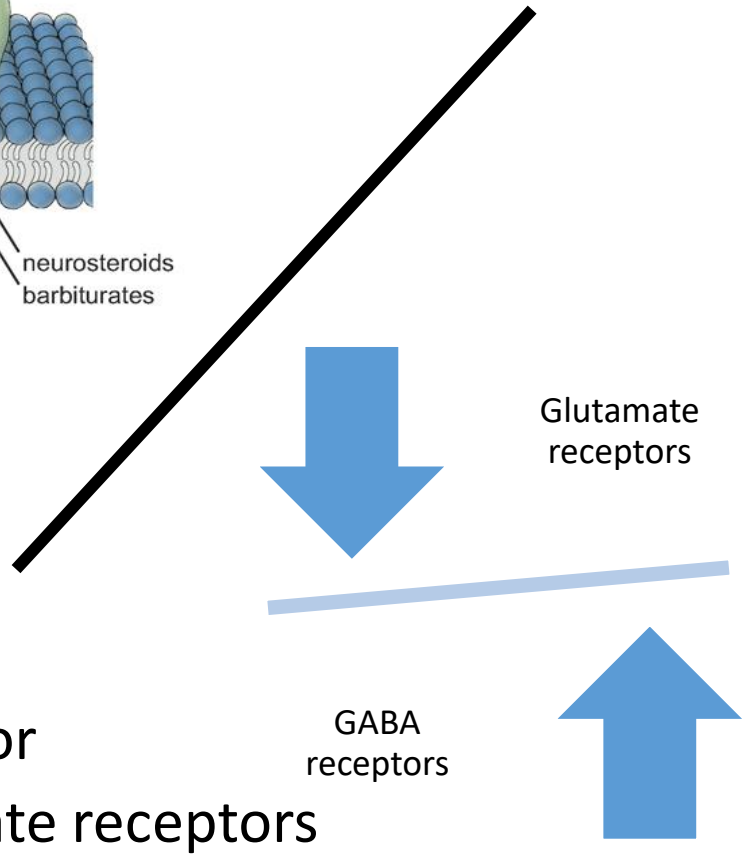
Objectives

- Describe the pathophysiology and complications of alcohol withdrawal
- Identify tools for predicting and assessing alcohol withdrawal
- Discuss guidelines, pharmacology and literature for inpatient AWS with a focus on benzodiazepines and phenobarbital
- Outline the role of adjunct medications in alcohol withdrawal

Pathophysiology

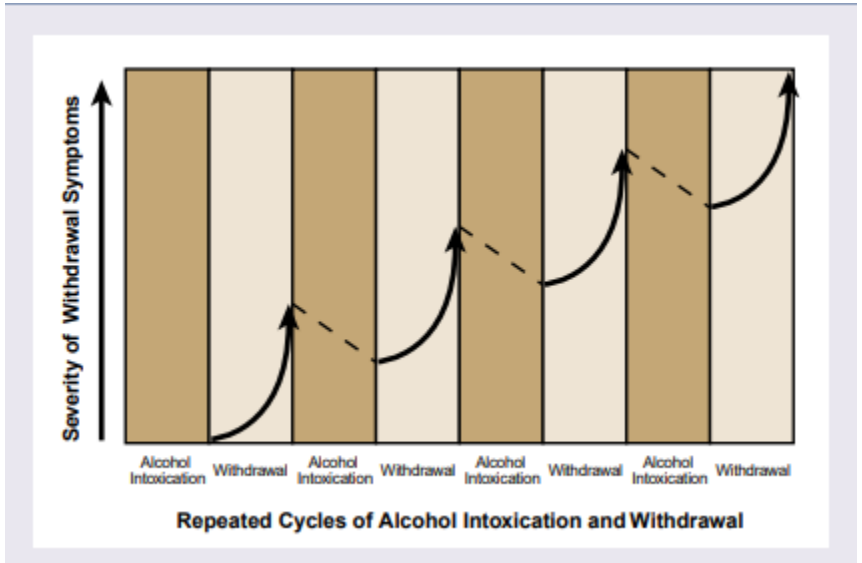


- Gamma-aminobutyric acid (GABA)
  - Major inhibitory neurotransmitter in brain
  - Has binding sites for ethanol, bzd, barbituates
  - Chronic ethanol consumption→downregulate GABA
- Glutamate
  - Major excitatory amino acid via NMDA & AMPA receptor
  - Chronic ethanol inhibits glutamate→increased glutamate receptors
- Withdrawal results in decreased inhibition and unregulated excitation



Kindling effect

- Sensitization of brain to repeated stimulus
- Exacerbation of withdrawal symptoms following repeated withdrawal episodes
- May lead to long-term changes in neuronal circuitry and function
- Supported by several clinical & experimental studies

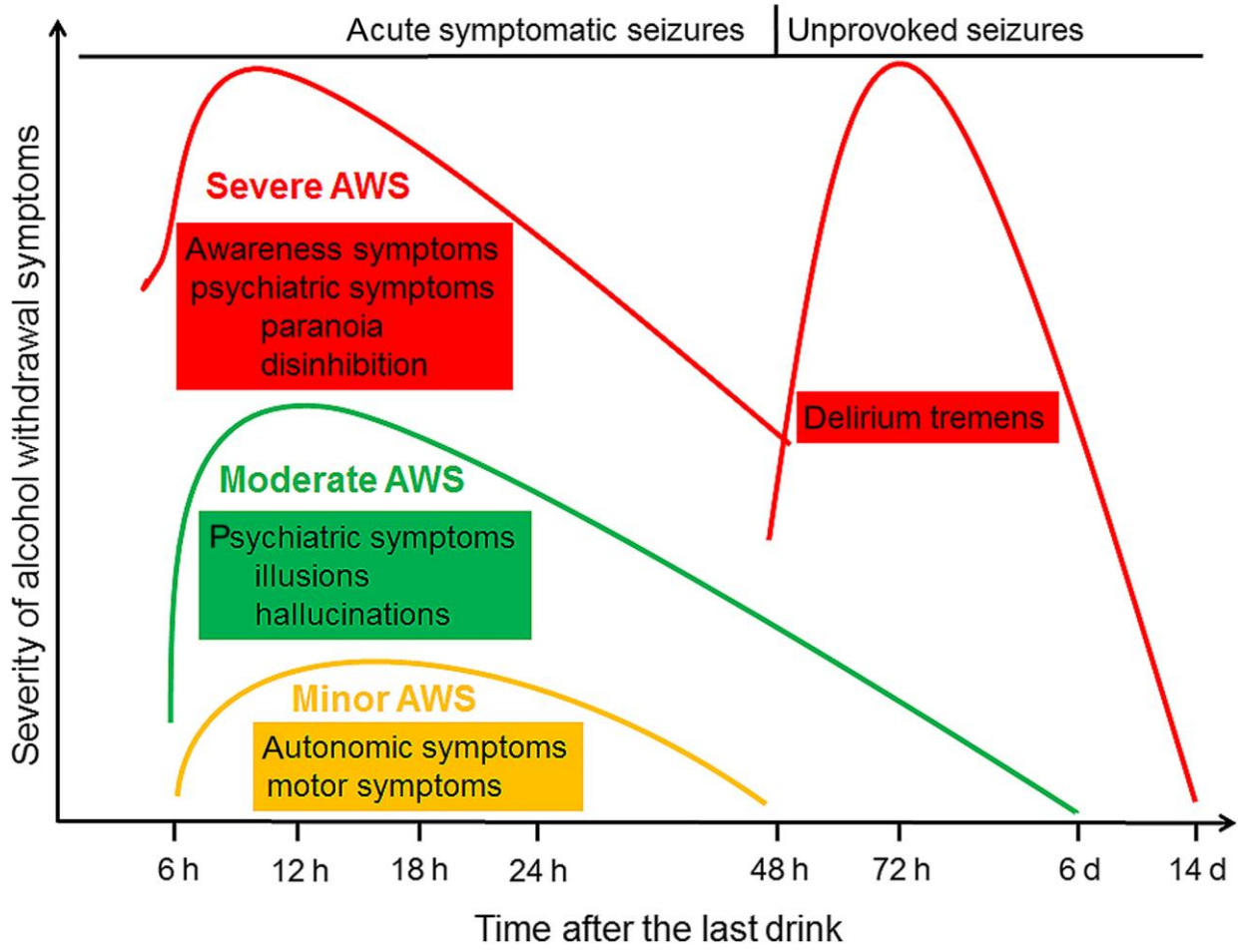


Becker Kindling in Alcohol Withdrawal 1998

Symptoms and timeline of AWS

Box 2: DSM-5 Criteria for Alcohol Withdrawal

A. Cessation of (or reduction in) alcohol use that has been heavy and prolonged.
B. Two (or more) of the following, developing within several hours to a few days after the cessation of (or reduction in) alcohol use described in Criterion A:
   1. Autonomic hyperactivity (e.g., sweating or pulse rate greater than 100 bpm)
   2. Increased hand tremor
   3. Insomnia
   4. Nausea or vomiting
   5. Transient visual, tactile, or auditory hallucinations or illusions
   6. Psychomotor agitation
   7. Anxiety
   8. Generalized tonic-clonic seizures
C. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupation, or other important areas of functioning.
D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.



Jesse S, et al. Acta Neurol Scand 2017 doi: 10.111/ane.12671

Complicated AWS

Seizures

- Occurs in 5-17% of patients experiencing active AWS

Alcohol withdrawal delirium (formerly DTs)

- Occurs in 10% of patients with AWS
- Death in up to 20% of patient

Outcomes

- Increased M&M
- Increased LOS
- Inflated costs
- Increased burden and frustration of medical staff
- Worsened cognitive function

Maldonado J, et al. Alcohol and Alcoholism 2015 doi: 10.1093/alcalc/agv043
Latt N, et al. Internal medicine journal 2014 doi: 10.1111/imj.12522

Objectives

- Describe the pathophysiology and complications of alcohol withdrawal
- Identify tools for predicting and assessing alcohol withdrawal
- Discuss guidelines, pharmacology and literature for inpatient AWS with a focus on benzodiazepines and phenobarbital
- Outline the role of adjunct medications in alcohol withdrawal

Predicting alcohol withdrawal-AUDIT-PC

- Validated in hospitalized non-ICU medical patients
- Sensitivity=91%
- Specificity=90%
- Score ≥4 identified patients who developed AWS

Questions	Scoring System					Your Score
	0	1	2	3	4	
How often do you have a drink containing alcohol?	Never	Monthly Or less	2-4 times per month	2-3 times per week	4+ times per week	
How many units of alcohol do you drink on a typical day?	1-2	3-4	5-6	7-9	10+	
How often in last week were you not able to stop drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during last year have you failed to do what was expected b/c of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
Has anyone been concerned about your drinking and suggest you cut down?	No		Yes, but not in the last year		Yes, during the last year	

Pecoraro A, et al. J Gen Intern Med 2013; 29(1): 34-40

Risk Factors for Severe or Complicated Withdrawal

- **History of AWD or seizure**
- **Numerous prior episodes**
- **Low platelet count**
- **High ALT**
- **Hypokalemia**
- Comorbid medical/surgical illness (TBI)
- Age >65
- Long duration regular, heavy alcohol consumption
- Withdrawal symptoms with positive BAL
- Marked autonomic hyperactivity
- Dependence on GABAergic agents such as BZD or barbiturates

American Society of Addiction Medicine 2020 ASAM CPG on Alcohol Withdrawal Management
Goodson C, et al. Alcoholism: clinical and experimental research 2014

Risk of Withdrawal Severity-PAWSS

- PAWSS score
  - Score ≥4 high risk
- Validated in hospital/ICU
- PPV 93.1/NPV 99.5%

Part A: Threshold Criteria	**1 point each**
1. Have you consumed any amount of alcohol within the last 30 days ***OR*** + BAL on admission?	
Part B: Patient Interview	**1 point each**
2. Have you ever experienced previous episodes of alcohol withdrawal? 3. Have you ever experienced alcohol withdrawal seizures? 4. Have you ever experienced delirium tremens or DT's? 5. Have you ever undergone alcohol rehabilitation treatment? 6. Have you ever experienced blackouts? 7. Have you combined alcohol with other "downers" like benzodiazepines or barbituates during the last 90 days? 8. Have you ever combined alcohol with any other substance of abuse during the last 90 days?	
Part C: Based on clinical evidence	**1 point each**
9. Was the patient's blood alcohol level (BAL) on presentation >200? 10. Is there evidence of increased autonomic activity?	

Maldonado J, et al. Alcohol 2014

Symptom assessment scales

- 18+ scales
  - CIWA-Ar most widely used and validated
  - Insufficient evidence to prefer one over another
- Limitations of CIWA-Ar
  - Scores can be elevated due to comorbid conditions (eg sepsis, withdrawal from other substances)
  - Scores can be falsely suppressed by certain medications (eg beta blockers)
  - Patient must be able to communicate
  - Time consuming

Williams D, et al. Alcohol & Alcoholism 2001
Eloma A, et al. The American Journal of Drug and Alcohol Abuse 2018 https://doi.org/10.1080/00952990.2017.1362418

Clinical Institute Withdrawal Assessment for Alcohol(CIWA-Ar)

Symptoms	
Nausea and vomiting 0 1 2 3 4 5 6 7	Tactile disturbances 0 1 2 3 4 5 6 7
Tremor 0 1 2 3 4 5 6 7	Auditory disturbances 0 1 2 3 4 5 6 7
Paroxysmal sweats 0 1 2 3 4 5 6 7	Visual disturbances 0 1 2 3 4 5 6 7
Anxiety 0 1 2 3 4 5 6 7	Headache and fullness in head 0 1 2 3 4 5 6 7
Agitation 0 1 2 3 4 5 6 7	Orientation and clouding of sensorium 0 1 2 3 4

Score 17-19 assess q1 hour
Score 10-16 assess q2 hour
Score <10 x2 consecutive assessments→q4 hours while awake

Sullivan JT, et al. British Journal of Addiction 1989

ASAM severity guideline

TABLE 1. Alcohol Withdrawal Severity.

Severity Category	Associated CIWA-Ar Range*	Symptom Description
Mild	CIWA-Ar < 10	Mild or moderate anxiety, sweating and insomnia, but no tremor
Moderate	CIWA-Ar 10-18	Moderate anxiety, sweating, insomnia, and mild tremor
Severe	CIWA-Ar ≥19	Severe anxiety and moderate to severe tremor, but not confusion, hallucinations, or seizure
Complicated	CIWA-Ar ≥19	Seizure or signs and symptoms indicative of delirium – such as an inability to fully comprehend instructions, clouding of the sensorium or confusion – or new onset of hallucinations

American Society of Addiction Medicine 2020 ASAM CPG on Alcohol Withdrawal Management

Type Indicator

A-benzos

B-clonidine

C-antipsychotics

AWS Type Indicator

Type A Symptoms (CNS Excitation) Does patient appear:	Cannot Evaluate	No	Yes
1. Anxious or nervous?			
2. Restless?			
3. Bothered by bright light?			
4. Bothered by loud sounds?			
Subtotal number of "Yes" responses for Type A only	Subtotal:		
Type B Symptoms (Adrenergic Hyperactivity)	Cannot Evaluate	No	Yes
5. Is nausea or vomiting present?			
6. Is a tremor visible with or without arms extended?			
7. Is sweat visible on palms or forehead?			
8. Is the systolic blood pressure greater than 140 mm Hg?			
9. Is the diastolic blood pressure greater than 90 mm Hg?			
10. Is the heart rate greater than 100 beats per minute?			
11. Are there extra or skipped beats on apical pulse?			
Subtotal number of "yes" responses for Type B only	Subtotal:		
Type C Symptoms (Delirium) Does the patient:	Cannot Evaluate	No	Yes
12. Respond inappropriately to questions?			
13. Report hearing noises that are not there?			
14. Report seeing something that is not there?			
15. Not know their name?			
16. Not know where they are?			
17. Not know how long they have been hospitalized?			
18. Not know the year?			
19. Not know the month?			
20. Not know the day of the week?			
Subtotal number of "Yes" responses for Type C only	Subtotal:		
Total number of "Yes" responses for Type A + B + C	Grand Total:		

Stanley et al. Pharmacotherapy 2003; 23(7):843-854

Objectives

- Describe the pathophysiology and complications of alcohol withdrawal
- Identify tools for predicting and assessing alcohol withdrawal
- Discuss pharmacology, literature and guidelines for inpatient AWS with a focus on benzodiazepines and phenobarbital
- Outline the role of adjunct medications in alcohol withdrawal

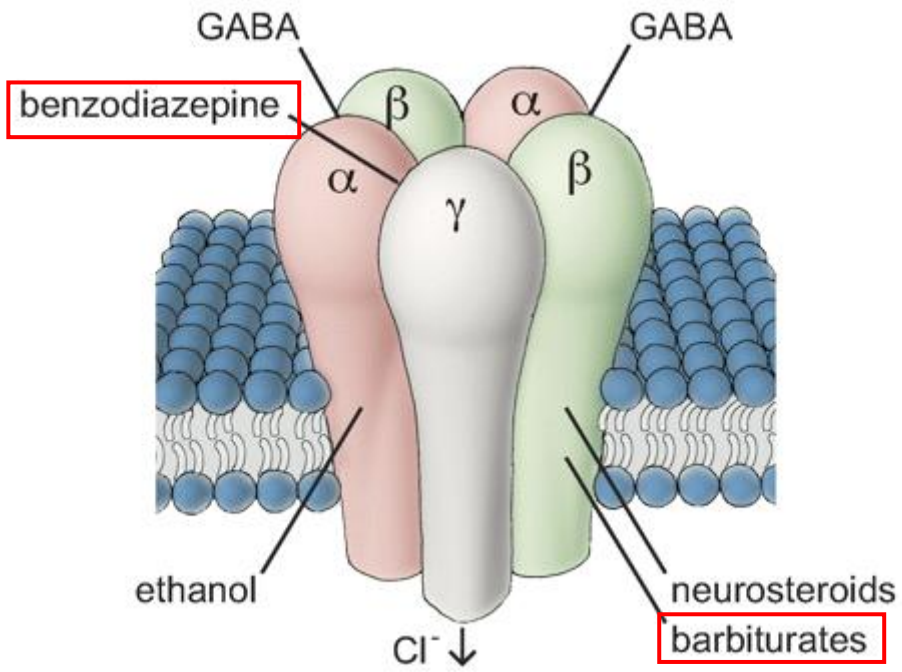
ASAM treatment guidelines

Type (CIWA score)	1st line	2nd line
Mild (<10)	Supportive care ±BZD	PHB, CBZ, gabapentin
Mod (10-18)	BZD	PHB, CBZ, gabapentin
Severe (≥19)	BZD	PHB±BZD
Seizure	BZD (IV)	PHB
Delirium	BZD (IV)	PHB+antipsychotics
RAW	PHB, propofol, dexmedetomidine	

Adjunct medications	Use
Gabapentin & Carbamezapine	Adjunct or monotherapy (only mild)
Valproic acid	Adjunct only
Beta-blockers	Adjunct only
Clonidine (alpha-2 agonists)	Adjunct only
Antipsychotics	Adjunct only

BZD=benzodiazepine, PHB=phenobarbital, CBZ=carbamezapine

GABA-ergic Agents



- Benzodiazepines
  - Increase frequency of Cl- channel opening
  - Require endogenous GABA
- Phenobarbital
  - Increases duration of Cl- channel opening
  - NMDA receptor antagonism

Uusi-Oukari 2010 Pharmacological Reviews 62: 97-135

Benzodiazepines

Drug	Adult oral total daily dose (mg)*	Comparative potency (mg)¶	Onset after oral dose (hours)	Metabolism	Elimination half-life (hours)Δ
Alprazolam	0.5 to 6	0.5	1	CYP3A4 to minimally active metabolites.	11 to 15 16 (older adults) 20 (hepatic impairment) 22 (obesity)
Alprazolam extended release	0.5 to 6 once daily	0.5	1		
Bromazepam◇§	6 to 30	7.5	1	CYP1A2. No active metabolite.	8 to 20
Chlordiazepoxide§	5 to 100	10	1	CYP3A4 to active metabolites.	30 to 100 Prolonged in older adults and hepatic impairment
Clonazepam	0.5 to 4	0.25 to 0.5	0.5 to 1	CYP3A4. No active metabolite.	18 to 50
Clorazepate	15 to 60	7.5	0.5 to 1	CYP3A4 to active metabolite.	36 to 200
Diazepam	4 to 40	5	0.25 to 0.5	CYP2C19 and 3A4 to active metabolites.	50 to 100 Prolonged in older adults and renal or hepatic impairment
Lorazepam immediate release	0.5 to 6 0.5 to 4 (hypnotic)	1	0.5 to 1	Non-CYP glucuronidation in liver. No active metabolite.	10 to 14
Lorazepam extended release	1 to 6 mg¥	1	0.5 to 1	Non-CYP glucuronidation in liver. No active metabolite.	13 to 27
Oxazepam	30 to 120 15 to 30 (hypnotic)	15 to 30	1 to 2	Non-CYP glucuronidation in liver. No active metabolite.	5 to 15
Prazepam◇§	15 to 60	15	2 to 3	CYP3A4 to active metabolites.	30 to 200 Prolonged in older adults

Pharmacology of benzodiazepines used to treat anxiety symtpoms/disorders. UpToDate. Retrieved March 24, 2023.

BZD symptom triggered vs fixed dose

- Symptom triggered lorazepam based on CIWA-Ar score vs fixed dose
  - ↓ duration of treatment
  - ↓ inpatient length of stay
  - ↓ total BZD dose
  - No difference in seizure or DT
- Systematic review/meta-analysis of symptom triggered
  - 6 studies=664 patients
  - No deaths and 1 seizure in each group
  - Same rate of delirium (~2%)
  - DOT 60.4 hours less than FD
  - Total bzd dose 10.5 mg (lorazepam equivalents) less than FD

Sachdeva A, et al. Alcohol and Alcoholism 2014 doi: 10.1093/alcalc/agt181
Holleck JL, et al. J Gen Intern Med 2019 doi: 10.1007/s11606-019-04899-7

Front-loading

- Guideline preferred for patients at high risk for SAW (CIWA-Ar ≥19)
- Mod-high dose long-acting benzodiazepine (diazepam or chlordiazepoxide)
- Outcomes include
  - ↓ duration of treatment
  - ↓ withdrawal seizures
  - ↓ duration of delirium
  - ↓ total BZD dose

- Examples diazepam 10 mg PO Q1 hour CIWA-Ar ≥10 or 20 mg PO q2 hours X 3 doses

American Society of Addiction Medicine 2020 ASAM CPG on Alcohol Withdrawal Management
Muzyk A, et al. The American Journal on Addictions 2013

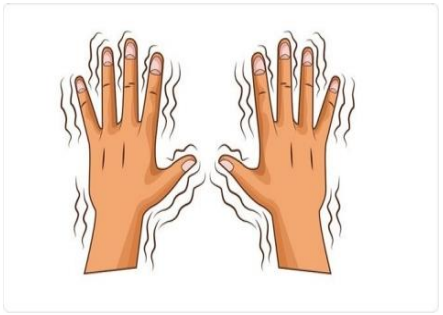
CIWA-Ar symptom triggered

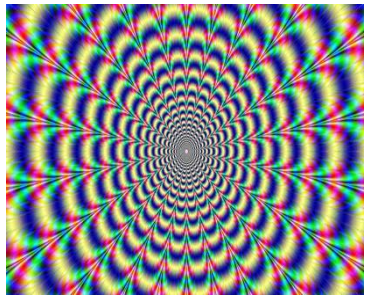
Chlordiazepoxide

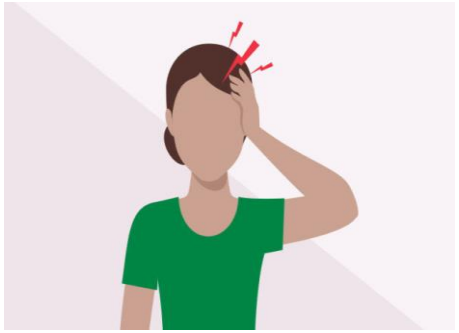
CIWA score	Dose
10-13	25 mg q1 hour prn
14-16	50 mg q1 hour prn
17-20	75 mg q1 hour prn

Lorazepam (PO or IV)

CIWA score	Dose
10-13	1 mg q1 hour prn
14-16	2 mg q1 hour prn
17-20	3 mg q1 hour prn







Benzodiazepines

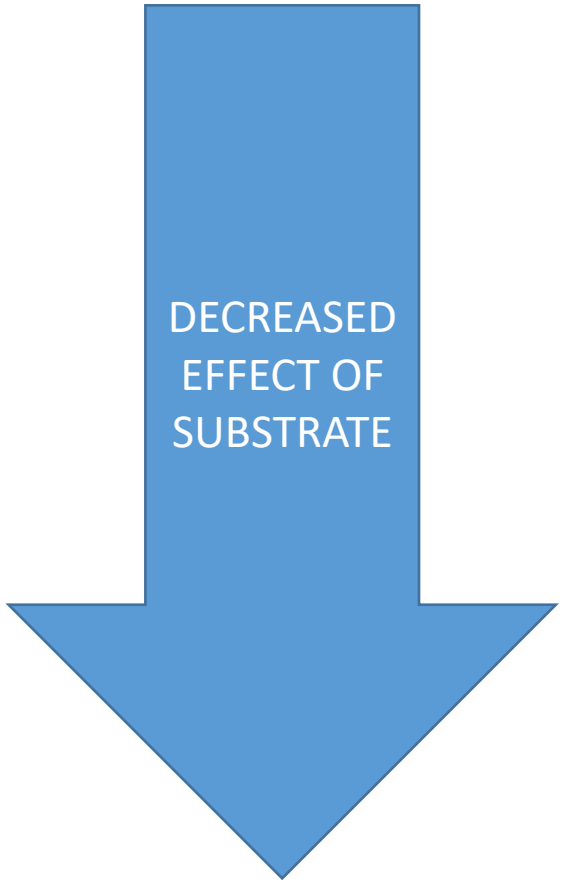
- ASAM guideline recommended 1st line
- Lorazepam, diazepam, chlordiazepoxide most frequently used
- None more effective than other but longer acting preferred
- Symptom triggered > fixed dose
- Front load in patient high risk severe withdrawal

Phenobarbital (off label)

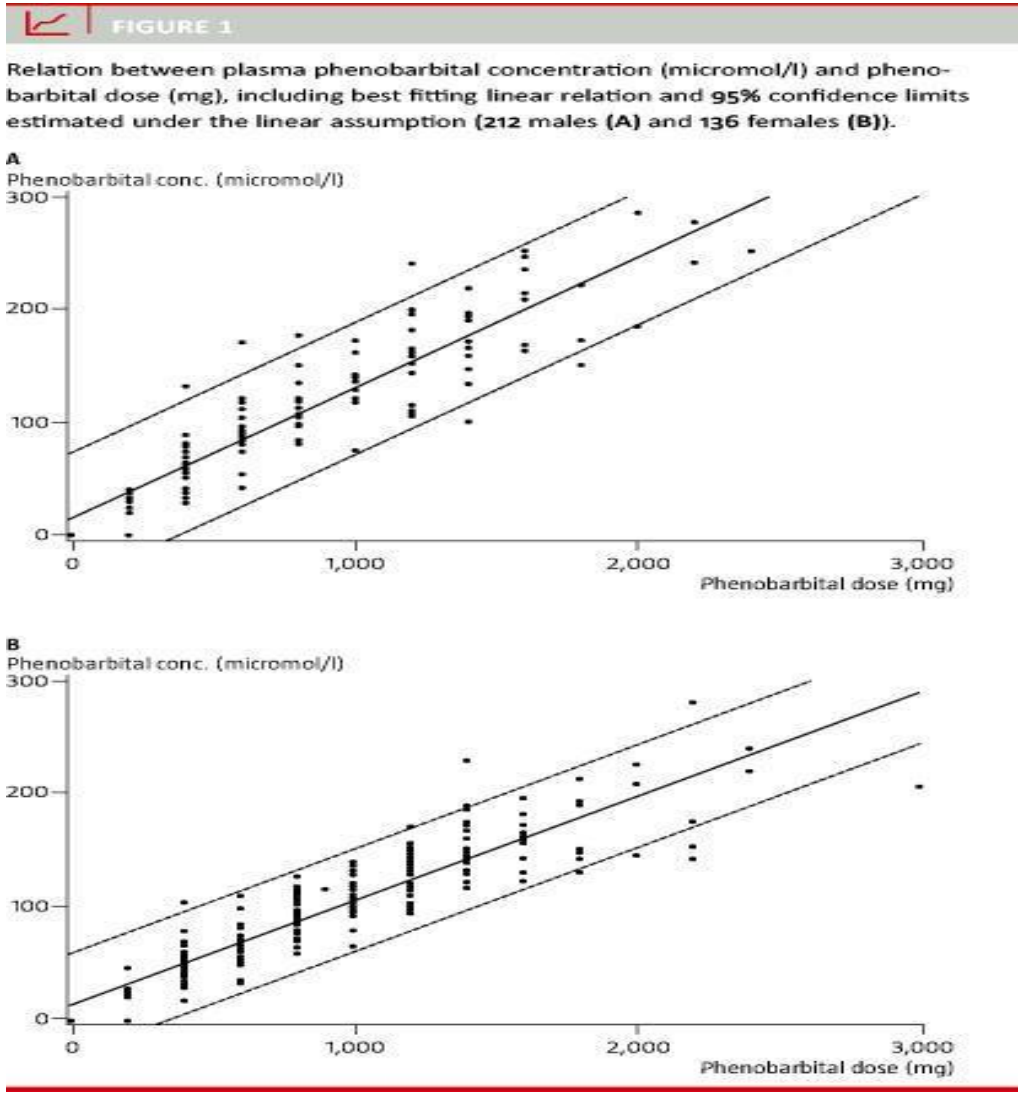
Onset	**IV/IM: 5-30 mins; PO: 60 mins**
Half-life	75-126 hours
Metabolism	**Hepatic via CYP2C9 (others minor)**
Excretion	Renal (25-50% unchanged in urine)
CYP450 Induction-drug drug interactions	**3A4 (strong); 2C9, 1A2, 2A6, 2B6 (weak)** ***De-induction can take up to 2 weeks!***
Adverse effects	Bradycardia, hypotension, somnolence, syncope, hypoventilation
Therapeutic level (seizure disorders)	**10-40 mcg/mL**
Toxic levels (seizure disorders)	>50 mild, >65 severe

Drug interactions with phenobarbital

- Substrates of CYP 3A4 enzyme
  - Apixaban/rivaroxaban
  - Dexamethasone
  - Carbamazepine
  - Cariprazine/brexpiprazole/aripiprazole
  - Methadone
  - Atorvastatin
  - Cyclosporine
  - Tacrolimus



Serum concentrations



- ED study with mean stay 4 hours
- 57/62 (92%) discharged and none returned to ED within next week
- Serum PHB level rose ~1.65 mcg/ml for each mg/kg of IV PHB given

Patient Subgroups (no. of patients)*	IV-PB† Dosage (mean loading dose in mg and mg/kg)		Final Serum PB Level (μg/mL)‡
Tremulous (48)	624	8.5	14.0
Seizures (38)	576	8.3	13.8
ALD§ (21)	561	8.2	13.7
Total AW (62)	598	8.4	13.9

Tangmose KJ, et al. Dan Med Bull 2010; 57(8): A4141
Young et al. Ann Emerg Med. 1987; 16(8):847-50

ASAM guidelines for PHB

- 2nd line after BZD for prevention and treatment of seizures
- Use if RAW (resistant alcohol withdrawal)
  - >150-200 mg diazepam or 30-40 mg lorazepam in first 3-4 hours treatment
- With close monitoring PHB may be used as adjunct to BZD for severe or risk of complicated
- Rationale for 2nd line
  - Inducer of many CYP-450 enzymes
  - Narrow therapeutic window
  - Bradycardia
  - Hypotension
  - SJS

Phenobarbital in ED/ICU

Dosing regimens

- 10 mg/kg IV x1
- Escalating doses (some after max BZD)
- 260 mg X1 then 130 mg IV until resolution
- Day 1: 60 mg QID, Day 2: 60 mg TID, Day 3, 60 mg BID, Day 4 30 mg X1

Outcomes

- ↓ ICU admission*
- ↓ BZD requirements
- ↓ ICU LOS*
- ↓mechanical ventilation*

*Some studies showed no difference in ICU admission, LOS or mechanical ventilation

Hammond et al. Hospital Pharmacy 2017 52(9) 607-616 https://doi.org/10.1177/0018578717720310

Phenobarbital Front Loading

Methods

- Retrospective before and after in ICU, 87 patients

Intervention

- Low intermittent (LI): 260mg x1 f/b 130 mg q15 mins prn
- Front load (FL): 10 mg/kg infusion over 30 mins

Results

- Mechanical ventilation 13 (28%) FL vs 26 (63%) LI-**(OR 4.4; 95% CI 1.8-10.9)**
- Similar total PHB doses, sig less bzd dose in FL vs LI **(86 mg vs 228 mg p<0.01)**

Shah P, et al. Journal of Medical Toxicology 2022. https://doi.org/10.1007/s13181-022-00900-8

Phenobarbital in ICU AWS: A Systemic Review and Meta-Analysis

Outcomes

- Hospital LOS
  - -2.6 (95% CI, -4.48, -0.72, P=0.007)
- ICU LOS
  - No significant difference
- Risk of intubation
  - RR 0.52 (95% CI, 0.25, 1.08, P=0.08)

Limitations

- Included retrospective reviews
- Small sample size
- Heterogeneity among studies
- None focused safety profile of PHB
- No standard dosing protocol

Umar Z, et al. Cureus 2023 DOI: 10.7759/cureus.33695

Phenobarbital in general medicine

Study	Population	Intervention	Effectiveness	Safety
Gashlin 2015 Retrospective cohort study	Mild-mod AWS N=28 (PB=7, BZD=21)	• PHB IV-adjunct with BZDs (65 mgX1, then 130 mg X1, then 260 mg until AWS resolution • DZ PO 20 mg q2H x3 or LZ equivalent	• No difference in CIWA-Ar score @24 hours • ↓PHB group had reduced BZD dose	No difference in intubation or ICU admission
Nisavic 2019 Retrospective chart review	N=562 (PB=143, BZD=419) *16 pt BZD→PB	• PHB 6-15 mg/kg IV load→oral taper up to 7 days • BZD fixed dose	No difference in seizure, hallucinations, ICU admit/LOS, hos LOS	No difference in over sedation or other adverse events
Hawa 2021 Retrospective cohort study	N=606 (BZD=653, PB=63) *3 hospitals	PB vs lorazepam Doses not provided	• **PB:↓hosp LOS, 30-day all cause readmission, ED visits** • No diff in ICU admit or alcohol related readmits	Not reported

MMC Guideline for the use of phenobarbital in non-ICU patients

Purpose

Identify and treat patients at high risk of or already in SAW

Protocol

-Discontinue all benzodiazepines

-Inclusion criteria

Patient is an active drinker (within the last 30 days) with a history of **previous alcohol withdrawal** or has a positive BAL on admission

AND

Has a history of alcohol withdrawal seizures or delirium tremens

OR

CIWA score >16 AND a history of alcohol use AND symptom onset within 48 hours of last drink

- Additional high risk inclusion criteria may be considered per provider discretion

Phenobarbital dosing

Loading (Day 1)

- Low risk of sedation and respiratory compromise
  - **7.5 mg /kg (ABW) IV over 1 hr**
- High risk sedation and respiratory compromise
  - **2.5 mg/kg IV q2H x 3 doses**

Risk factors for sedation/respiratory compromise

- ≥65 years of age
- OSA or other related risk factors
- Hepatic dysfunction or cirrhosis
- Use of opioids, bzd or other sedatives within 12 hours
- Head injury
- Pneumonia/COPD/asthma
- ILD or pulmonary fibrosis
- Head/neck cancer
- Rib fractures
- C-collar/brace

Maintenance dose

Weight <80 kg

Day 1-2 (3 hr after load)	PO: 97.2 mg q8h x3-6 doses IV: 90 mg q8h x 3-6 doses
Day 3	PO: 97.2 mg q12h x 2 doses IV: 90 mg IV q12h x 2 doses
Day 4	PO: 97.2 mg q24h X 1 dose IV: 90 mg q24h x 1 dose
Breakthrough	90 mg IV q2 hours prn agitation, anxiety, restlessness

Weight ≥80 kg

Day 1-2 (3 hr after load)	PO: 129.6 mg q8h x 3-6 doses IV: 130 mg q8h x 3-6 doses
Day 3	PO: 129.6 mg q12 h x 2 doses IV: 130 mg q12h x 2 doses
Day 4	PO: 129.6 mg q24h x 1 dose IV: 130 mg q24 h x 1 dose
Breakthrough	130 g IV q2h pr agitation, anxiety, restlessness

Additional considerations

Oral bioavailability of phenobarbital is ≥95%

Onset of IV is 5 mins with peak ≥15 mins, oral onset >60 mins

Phenobarbital is relatively well tolerated with low incidence of side effects

- Intubation <5% at doses utilized for alcohol withdrawal
- CNS depression may occur with other centrally acting medications
- Other rare side effects include SJS, DRESS and elevated liver enzymes

Phenobarbital is an inducer of CYP3A and CYP2C enzymes, therefore drug-drug interactions must be considered. Onset may be delayed up to a week and take up to 2 weeks to return to baseline

- DOACs, methadone, prednisone/dexamethasone, tacrolimus

Monitoring

- Obtain baseline liver function tests before initiating PHENobarbital
- Monitor vitals every 4 hours
- Continue to document CIWA scores for clinical assessment, but do not use it to determine the need for prn medication
- Obtain daily EKG if antipsychotic is required
- If agitation continues despite 2 prn doses of PHENobarbital, 15 mg of olanzapine or 10 mg of haloperidol, consider calling psychiatry for further recommendations and possible transfer to ICU. If the patient is over-sedated, hold PHENobarbital dose and contact provider

Serum phenobarbital levels

Consider serum level

- TDD ≥10 mg/kg
- Severe liver disease or cirrhosis
- Acute renal failure or ESRD
- Symptoms of barbiturate toxicity (hypotension, bradycardia, severe CNS or respiratory depression)
- If serum concentration ≥40 mcg/mL, dose should be reduced

MH-MMC-Portland Campus research

- Centanni N, Mezoian T, Gilboy J, Evans J, Hudak N, Craig W, Gordon L. Effect of Phenobarbital-Based Alcohol Withdrawal Protocol on Provider Practice and Patient Outcomes-A Quality Improvement Studay. *Hospital Pharmacy* 2024. doi: 10.1177/00185787241247716
- Wang M, Falank C, Simboli V, Ontengco J, Spurling B, Rappold J, Chung B, Smith, K. “ShouldWe Phenobarb-it-All?” A Phenobarbital-Based Protocol for Non-Intensive Care Unit Trauma Patients at High Risk or Experiencing Alcohol Withdrawal. *The American Surgeon* 2024. doi: 10.1177/00031348241244639

Centanni, et al.

Design	Methods	Population
• Before (2017) PHB protocol and after (2019)	• Single-center, QI study of general medicine patients with AWS	• 345 total adult patients • 159 in 2017 • 186 in 2019

Outcomes

Table 2. Process, Effectiveness, and Safety Outcomes.

Variable	Year[a] 2017	2019	*P*-value
N	159	186	
Process outcomes			
Received PHB loading dose (≥2.5 mg/kg)	15 (9.4)	92 (49.5)	<.001[b]
Received concomitant BZD/PHB	46 (28.9)	8 (4.3)	<.001[b]
Total Benzodiazepine dose (LEq)	15.5 (8-32.4)	7.8 (4-13.8)	<.001[c]
N	159	176	
Patient received phenobarbital for AWS	51(32.1)	99(53.2)	<.001[b]
Total phenobarbital dose (mg/kg)	5.7(2.6-10.4)	20.0 (13.6-27.1)	<.001[c]
Safety outcomes			
ICU transfer	3 (1.9)	14 (7.5)	.22[d]
ICU LOS (days)	11 (5-19)	3 (2-5.5)	.04[c]
N	3	14	
Mechanical ventilation	3/3 (100.0)	4/14 (28.6)	.051[d]
Effectiveness outcomes			
Hospital length of stay (days)	4 (3-7)	5 (3-7.2)	.27[c]
Seizure during admission	5 (3.1)	6 (3.2)	1.00[b]
Delirium tremens during admission	9 (5.7)	11 (5.9)	1.00[b]
Use of adjunct medications	72 (45.3)	78 (41.9)	.61[b]

Note. BZD = benzodiazepine; PHB = phenobarbital; LEq = lorazepam equivalents; ICU = intensive care unit.
[a]Data shown as n (%), or, median (interquartile range).
[b]Chi square test.
[c]Mann-Whitney U test.
[d]Fisher's exact test.

Wang, et al.

Design	Methods	Population
• Pre (6/2017-5/2018)/Post (11/2018-10/2019)	• Single center, retrospective • Non-ICU trauma patients at risk of or experiencing AWS	• 110 total adult patients • 51 PRE • 59 POST

Outcomes

Table 2. Clinical Outcomes.

Effectiveness Outcomes	Pre (n = 51)	Post (n = 59)	*P* Value
Patients with AWS complications[a], N(%)	17 (33%)	10 (17%)	.05
Withdrawal seizures	1 (2%)	0 (0%)	.28
Delirium tremens	5 (10%)	2 (3%)	.13
None of the above	45 (88%)	56 (95%)	.19
Transfer to higher level of care, N(%)	10 (20%)	8 (14%)	.40
Patients who received, N(%)			
Benzodiazepines	45 (88%)	25 (42%)[b]	<.0001
Phenobarbital	19 (37%)	48 (81%)	<.0001
Total benzodiazepine received (converted to mg of lorazepam equivalents), median, IQR	11 (4,26)	4 (2,7)	.0004
Duration of treatment (days), median, IQR			
Benzodiazepine	4 (2,5)	1 (1,2)	<.0001
Phenobarbital	3 (1,5)	4 (3,6)	.03
Adjunct medication use[c], N(%)	25 (49%)	32 (54%)	.60
Clonidine use, N(%)	14 (27%)	22 (37%)	.27
Dexmedetomidine use, N(%)	5 (10%)	4 (7%)	.57
Antipsychotic use, N(%)	6 (12%)	6 (10%)	.74
Hospital length of stay, median, IQR	8 (4,12)	8 (5,11)	.09
Safety outcomes			
Medication-related adverse events[d], N(%)	29 (57%)	23 (39%)	.06
CNS depression, N(%)	17 (33%)	13 (22%)	.20
Respiratory depression, N(%)	12 (24%)	10 (17%)	.36
Need for intubation, N(%)	4 (8%)	1 (2%)	.14

[a]complications include seizures, DTs, and transfer to higher level of care.
[b]Only 2 patients received benzodiazepines after administration of phenobarbital in the POST group.
[c]Adjunct medication use includes: clonidine, dexmedetomidine, and all antipsychotics.
[d]Medication-related adverse events include CNS depression and respiratory depression.

Objectives

- Describe the pathophysiology and complications of alcohol withdrawal
- Identify tools for predicting and assessing alcohol withdrawal
- Discuss pharmacology, literature and guidelines for inpatient AWS with a focus on benzodiazepines and phenobarbital
- Outline the role of adjunct medications in alcohol withdrawal

Supportive Care/Adjunctive agents

- Alpha-2 agonists/beta-blockers
- Non-benzodiazepine anticonvulsants (NBACs)
- Antipsychotics
  - Cautious use in first 48 hours when seizure risk is high
- Vitamins
  - Thiamine
    - Prevention of WE: 100 mg IM/IV x 3-5 days followed by 100 mg orally daily
    - Treatment: 200-500 mg TID x 5-7 days followed by 100 mg orally 1-3 x/day
  - MVI, folate
  - TWDFNR™- prescribing upon discharge

DeFries 2021 J Hosp Med https://doi.org/10.12788/jhm.3691

Alpha-2 agonists (off label)

- Clonidine and dexmedetomidine
- MOA: inhibition of norepinephrine release via alpha-2 agonism
- Clonidine dose: 0.1-0.3 mg q6-8 hours
- Helps with autonomic hyperactivity and anxiety
- Benzodiazepine sparing effect
- ***Do not use as monotherapy!***

Jesse S, et al. Acta Neurol Scand 2017 doi: 10.1111/ane.12671
Muzyk AJ, et al. The Annals of Pharmacotherapy 2011

All OFF LABEL

NBACs

- **Carbamazepine (cbz)***
- **Gabapentin***
- **Valproic acid***
- Topiramate
- Oxcarbazepine
- Lamotrigine

*most studied

- ASAM guidelines states: cbz and gabapentin **may be used for mild to mod AWS** at minimal risk of developing severe or complicated withdrawal
- 2022 systematic review and meta-analysis states: no differences were found between AED and placebo for **mod-severe AWS**; at this time it is **suggested not to use these drugs** unless comorbid condition

American Society of Addiction Medicine 2020 ASAM CPG on Alcohol Withdrawal Management
Rojo-Mira J, et al. Alcohol and Alcoholism 2022 https://doi.org/10.1093/alcalc/agab057

Benzodiazepine-Sparing Alcohol Withdrawal Order Set in an Integrated Health Care System

Population: 22,899 patients hospitalized with AWS @Kaiser Health

Intervention: cascading order set options based on 3 risk categories using PAWSS/CIWA-Ar

1. Observation (P: <4, C<8)-supportive tx with vitamins and thiamine
2. Prevention/active withdrawal (P: ≥4, C: 8-15)-gabapentin or VA and clonidine with bzd for C ≥15
3. Severe and complex in ICU (C: ≥15)-bzd, adjuncts **+ dexmedetomidine**

Results:

- BZD requirement 78.1%→60.7% (p<0.001)
- ↓ ICU use (ARR 0.71; 95% CI 0.25-0.80; p=0.003)
- ↓ hospital LOS (ARR, 0.71; 95% CI, 0.58-0.86; p<0.001)

Smith J, et al. JAMA Network Open. 2022; 5(2): 3220158. doi:10.1001/jamanetworkopen.2022.0158

Complicated AWS

- Alcohol withdrawal seizure
  - 1st line benzodiazepines, 2nd line phenobarbital
- Alcohol withdrawal delirium
  - Benzodiazepines ± antipsychotics
- Resistant alcohol withdrawal
  - Defined in reviews as >150-200 mg diazepam or 30-40 mg lorazepam in first 3-4 hours of treatment
  - May use adjunct phenobarbital, propofol or dexmedetomidine

Mechanically ventilated/ICU

American Society of Addiction Medicine 2020 ASAM CPG on Alcohol Withdrawal Management

Special considerations

- Comorbid opioid/benzo use disorder
  - Opioids plus benzodiazepines→increased risk respiratory depression
  - Patients with benzodiazepine use disorder→risk of delayed seizure plus may need higher doses
- Pregnancy
  - BZD and barbituates should still be used for mod-severe AWS
    - Both associated with risks to fetus but appears small and likely less than if seizure were to occur
    - Late third trimester, use short acting benzos to limit fetal intoxication risk
    - Do NOT use valproic acid

American Society of Addiction Medicine 2020 ASAM CPG on Alcohol Withdrawal Management

AUD therapy initiation

- Less than 10% of adults with AUD receive treatment
- Less than 4% were prescribed a medication approved by FDA
- Medications
  - Naltrexone 50 mg daily/380 mg IM q4weeks (NNT=12)
  - Acamprosate 666 mg TID (NNT=12)
  - Disulfiram (not first line)
  - Gabapentin 900-1800 mg daily (NNT=8)
  - Topiramate dosed up to 300 mg daily

National Institute on Alcohol Abuse and Alcoholism Alcohol Facts and Statistics | National Institute on Alcohol Abuse and Alcoholism (NIAAA) (nih.gov) updated March 2022
APA 2018 AUD guidelines
Kranzler 2018 JAMA
Anton 2020 JAMA Internal Medicine

Summary

- Alcohol withdrawal remains a prevalent complication during hospital admission
- Guideline recommends benzodiazepines as first line therapy with phenobarbital as a second line option
- Many studies have shown phenobarbital is safe for use in AWS for patients in the ICU, ED and general medical floors
- More studies are needed to inform optimal dosing strategy and target serum concentration for phenobarbital in AWS
- Adjunct medications may provide a benzodiazepine sparing effect