Penn State College of Medicine
Continuing Education

Seventh Annual Neurocritical Care Conference

Thursday, Oct. 23, 2025

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Alcohol Withdrawal and Treatment in the Neurological ICU

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AHN

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Disclosures

- Mainstay Medical- Education
- Boston Scientific- Education

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Objectives

- **Review pathophysiology and timeline of alcohol withdrawal syndrome (AWS)**
- **Discuss treatment/dosing options available**
- **Assess current literature**
- **Determine appropriate strategies for the Neurological ICU population**

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Pathophysiology

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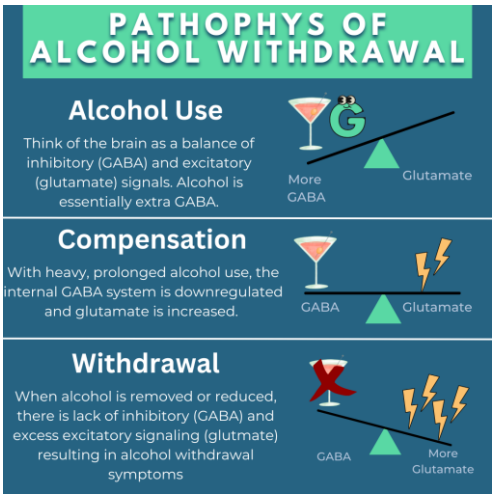
Pathophysiology of AWS



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Symptoms of AWS

Table 1. Stages of Alcohol Withdrawal Symptoms[2, 4, 8]

Stage	Time since last alcoholic drink	Signs and symptoms
1	6–24 hrs	Tremor Autonomic activity Insomnia/agitation Tachypnea/hyperventilation Headache Sweating Anorexia/nausea/vomiting
2	7–48 hrs	Distractibility, tonic-clonic seizures (10% of patients) Visual, tactile, or auditory hallucinations (30% of patients) Autonomic instability Diarrhea
3	49–96 hrs	Intense tremor → delirium tremens (5% of patients [25% mortality]) Severe autonomic instability Confusion/disorientation/extreme agitation

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Predicting/Diagnosing AWS

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Prediction of AWS

Prediction of Alcohol Withdrawal Severity Scale (PAWSS)

Maldonado et al., 2014

Part A: Threshold criteria: (1 point each)

1. Have you consumed any amount of alcohol (i.e., been drinking) within the last 30 days? OR did the patient have a "+" BAL upon admission? _____

IF the answer to either is YES, proceed with test:

Part B: Based on 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 DTs? _____
5. Have you ever undergone of alcohol rehabilitation treatment? (i.e., in-patient or out-patient treatment programs or AA attendance) _____
6. Have you ever experienced blackouts? _____
7. Have you combined alcohol with other "downers" like benzodiazepines or barbiturates during the last 90 days? _____
8. Have you 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? (e.g., HR > 120 bpm, tremor, sweating, agitation, nausea) _____

Total Score: _____

- A negative PAWSS (<4) developed moderate to severe alcohol withdrawal in 0.5% of the validation cohort
- A positive PAWSS (≥4) resulted in moderate to severe alcohol withdrawal in 93.1% of the validation cohort

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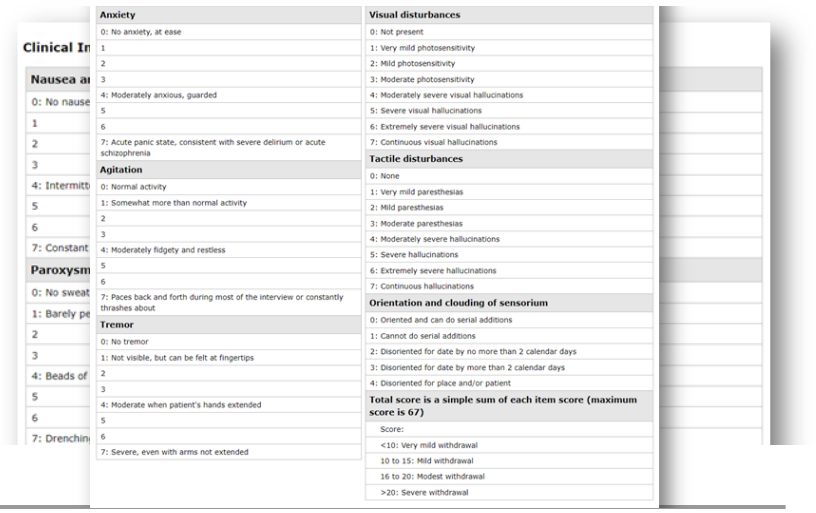
Clinical Institute Withdrawal Assessment

TABLE 2. Components of the CIWA-Ar[11,18]

Nausea and vomiting (0-7)	Tactile disturbances (0-7)
Tremor (0-7)	Auditory disturbances (0-7)
Paroxysmal sweats (0-7)	Visual disturbances (0-7)
Anxiety (0-7)	Headache (0-7)
Agitation (0-7)	Orientation and clouding of sensorium (0-4)

Score*: **<8:** Very mild withdrawal; **8-14:** Mild withdrawal; **15-20:** Modest withdrawal; **≥20** Severe withdrawal

* Interpretation of cutoff scores for mild, modest, and severe vary by source.



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Limitations to CIWA in Neurological ICU

- Patient must be able to communicate and answer questions
- Cannot be used in intubated patients
- Headache and visual disturbances may be due to neuro injury
- Not validated in Neurological ICU patients

Minnesota Detoxification Scale (MINDS)

Symptom	Score
Pulse (beats per minute)	
<90	0
90-110	1
>110	2
Diastolic blood pressure (mm Hg)	
<90	0
90-110	1
>110	2
***Tremor** – Assess with patient's arms extended and fingers spread.	
Absent	0
Slightly visible or can be felt fingertip to fingertip	2
Moderate – Noticeably visible with arms extended	4
Severe – Noticeable even with arms not extended	6
Sweat	
Absent	0
Barely; Moist palms	2
Beads visible	4
Drenching	6

Hallucinations** – Feeling crawling sensations over skin (tactile), hearing voices when no one has spoken (auditory), or seeing patterns, lights, beings, or objects that are not there (visual).	
Absent	0
Mild – Mostly lucid, sporadic/rare hallucinations	1
Moderate/Intermittent – Hallucinating at times (when first waking up or in between conversations/pt care) with moments of lucidity but able to be reoriented	2
Severe, continuous while awake	3
***Agitation** – Assess using the Richmond Agitation-Sedation Scale (RASS)	
Normal activity (RASS of 0)	0
Somewhat > normal (RASS of +1)	3
Moderately fidgety, restless (RASS of +2)	6
Pacing, thrashing (RASS of +3 or >)	9
***Orientation**	
Oriented x3 (person/place/time OR at patient's baseline)	0
Oriented x2	2
Oriented x1	4
Disoriented	6
Delusions** – Unfounded ideas that can be related to suspicions or paranoid thoughts, i.e patient believes their things have been stolen, or they are being persecuted unjustly	
Absent	0
Present	6
Seizures	
Absent	0
Present	6

*Unable to assess secondary to over sedation, score = 0.
**MINDS adapted from Decarolis D, et al. Symptom-driven lorazepam protocol for treatment of severe alcohol withdrawal delirium in the Intensive Care Unit. *Pharmacotherapy* 2007: 27(4):510-518.

Minnesota Detoxification Scale (MINDS)

- Alternative to CIWA
- Not as much patient participation
- More objective criteria included
- Alson not validated in Neurological ICU patients

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Pharmacological Management

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Goals of Treatment

- **Prevent Seizures**
- **Reduce Symptoms**
- **Prevent harm to patient/staff**

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Pharmacological Management

- **Primary Agents**
  - Benzodiazepines
  - Barbiturates
- **Secondary Agents**
  - Dexmedetomidine
  - Valproic Acid
  - Ketamine
  - Gabapentin

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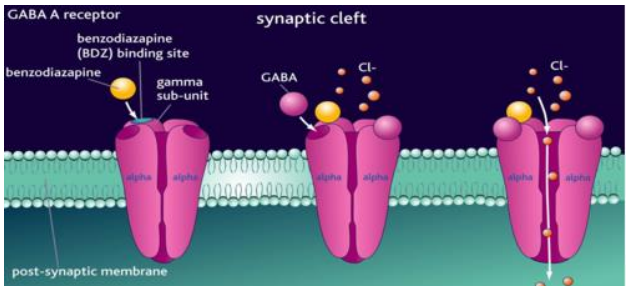
Benzodiazepines

- **Pros:**
  - Target GABA receptors
    - Requires endogenous GABA for effect
  - Effective in symptom mitigation, seizure prevention and DT prevention
  - Can use symptom triggered treatment



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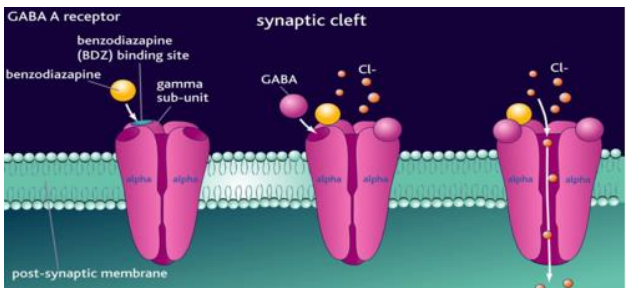
Benzodiazepines

- **Cons:**
  - Does not target the Glutamate receptors
  - Symptom trigger approach can lead to over or under treatment
  - Can heavily impact neurologic examination



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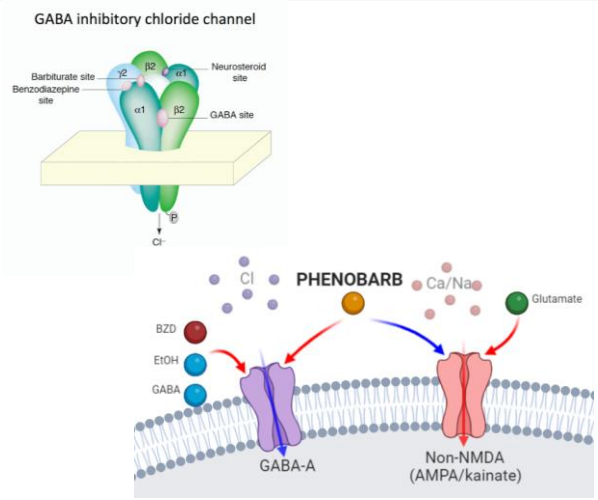
Barbiturates

- **Pros:**
  - Targets GABA and glutamate receptors
  - Decrease use of benzodiazepines in AWS
  - Data to support adjunctive use to benzodiazepines



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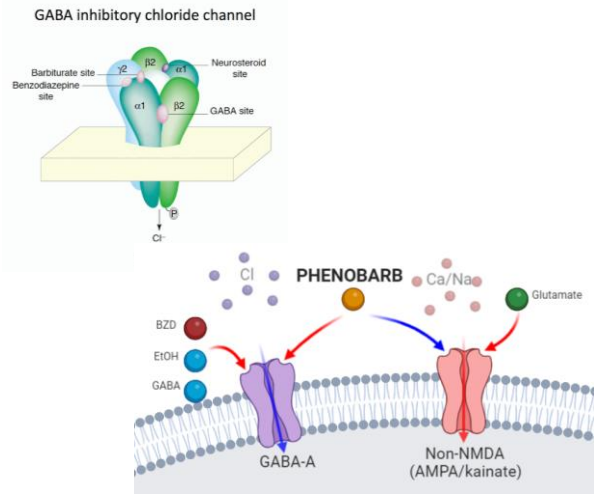
Barbiturates

- **Cons:**
  - Minimal data as a monotherapy
  - Optimal dosing not known
  - Still sedating and can cloud neurological exam
  - Strong inducer of CYP450



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Phenobarbital

- **Pharmacokinetics**
  - Onset – 5 minutes
  - Peak – 20-30 minutes
  - Half Life – 53-140 hours
- **Dosing**
  - 30-120 mg PO
  - 32.5-130 mg IV
  - 130 mg is max IVP dose

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Phenobarbital

- **Pharmacokinetics**
  - Onset – 5 minutes
  - Peak – 20-30 minutes
  - Half Life – 53-140 hours
- **Dosing**
  - 30-120 mg PO
  - 32.5-130 mg IV
  - 130 mg is max IVP dose

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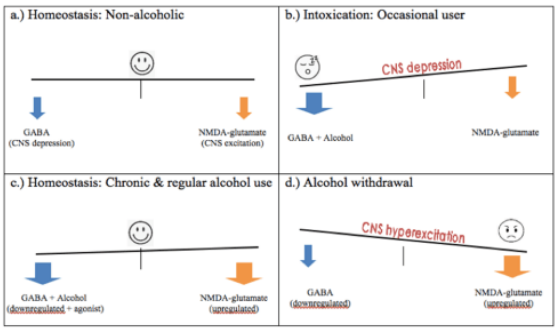
Phenobarbital

- **Agonist at GABA receptor**
  - Of note, does not require endogenous GABA
- **Inhibits Glutamate receptors**

Figure 1. Neurochemistry of AWS[13,20]



American Society of Addiction Medicine

- **When to treat**
  - CIWA < 10 (Mild) – Supportive Care
  - CIWA 10-18 (Moderate) – Benzodiazepines are first line
  - CIWA ≥ 19 (Severe) – Benzodiazepines are first line

D. Pharmacotherapy

(1) Prophylaxis

Recommendation V.13: For patients at risk of developing severe or complicated alcohol withdrawal or complications of alcohol withdrawal, preventative pharmacotherapy should be provided. Benzodiazepines are first-line treatment because of their well-documented effectiveness in reducing the signs and symptoms of withdrawal including the incidence of seizure and delirium. For patients with a contraindication for benzodiazepine use, phenobarbital can be used by providers experienced with its use. In settings with close monitoring, phenobarbital adjunct to benzodiazepines is also appropriate.

Recommendation V.14: A front loading regimen is recommended for patients at high risk of severe withdrawal syndrome. Providing at least a single dose of preventative medication is appropriate for patients at lower levels of risk who have:

Phenobarbital v. CIWA-Ar

- **Medical ICU patients**
- **Retrospective Cohort**
- **Suspected or diagnosed AWS**
- **Primary Endpoint: ICU LOS**

TREATMENT OF ALCOHOL WITHDRAWAL SYNDROME: PHENOBARBITAL VS CIWA-AR PROTOCOL

By William P. Tidwell, PharmD, Tonya L. Thomas, PharmD, Jonathon D. Pouliot, PharmD, MS, BCPS, Angelo E. Canonico, MD, and Angus J. Webber, MD

Phenobarbital v. CIWA-Ar

Table 2
Baseline patient demographics

Demographics	CIWA-Ar arm (n=60)	Phenobarbital arm (n=60)	P
Age, mean (SD), y	52 (15.5)	45 (11.4)	.003
Race, No. (%) of patients			>.99
White	57 (95)	57 (95)	
Black or African American	2 (3)	1 (2)	
Other	1 (2)	2 (3)	
Male sex, No. (%) of patients	43 (72)	44 (73)	.84
Left against medical advice, No. (%) of patients	1 (2)	3 (5)	
Comorbid conditions			
Psychiatric disorder	29	29	>.99
Polysubstance abuse	10	10	>.99
Seizure disorder	5	8	.41
Reactive airway disorder	8	6	.59
Liver disease	14	16	.68
Previous delirium tremens or withdrawal seizures	27	32	.92
Clinical presentation on admission			
Abnormal liver laboratory values	30	38	.17
Active alcohol withdrawal/delirium tremens	20	28	.46

Abbreviation: CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol, revised.

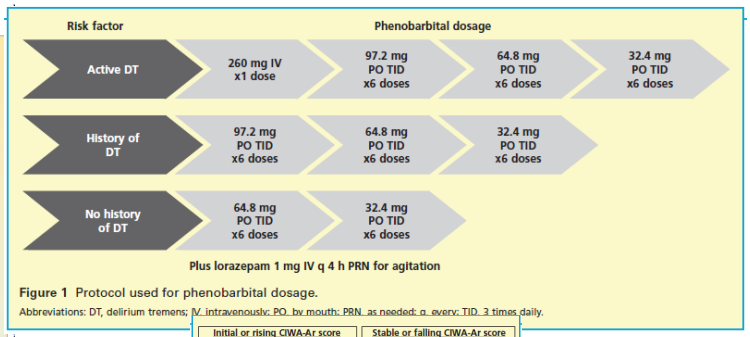


Figure 1 Protocol used for phenobarbital dosage.

Abbreviations: DT, delirium tremens; IV, intravenously; PO, by mouth; PRN, as needed; q, every; TID, 3 times daily.

Initial or rising CIWA-Ar score	Stable or falling CIWA-Ar score
5-9: lorazepam 1 mg IV q 4 h	5-9: lorazepam 1 mg IV q 8 h
10-14: lorazepam 2 mg IV q 2 h	10-14: lorazepam 2 mg IV q 4 h
15-19: lorazepam 3 mg IV q 1 h	15-19: lorazepam 3 mg IV q 2 h
20-24: lorazepam 4 mg IV q 30 min	20-24: lorazepam 4 mg IV q 1 h
25-29: lorazepam 5 mg IV q 15 min	25-29: lorazepam 5 mg IV q 30 min
30-34: lorazepam 6 mg IV q 10 min	30-34: lorazepam 6 mg IV q 10 min
≥ 35: lorazepam 6 mg IV x 1 dose, lorazepam infusion at 4 mg/h, increase by 2 mg/h q 30 min until score stabilizes or falls	

Figure 2 CIWA-Ar protocol.

Abbreviations: CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol, revised; IV, intravenously; q, every.

Phenobarbital v. CIWA-Ar

Table 3
Outcomes and clinical characteristics

Outcome or clinical characteristic	CIWA-Ar arm (n=60)	Phenobarbital arm (n=60)	P
ICU stay (midnights), mean (SD)	4.4 (3.9)	2.4 (1.5)	<.001
Hospital stay (midnights), mean (SD)	6.9 (6.6)	4.3 (3.4)	.004
Total lorazepam equivalents, mean (SD), mg	35.2 (48.5)	11.3 (18)	<.001
Ventilator use, No. of patients	14	1	<.001
Dexmedetomidine use, No. of patients	17	4	.002
Olanzapine use, No. of patients	7	5	.54
Haloperidol use, No. of patients	10	4	.08
Quetiapine use, No. of patients	5	2	.24

Abbreviations: CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol, revised; ICU, intensive care unit.

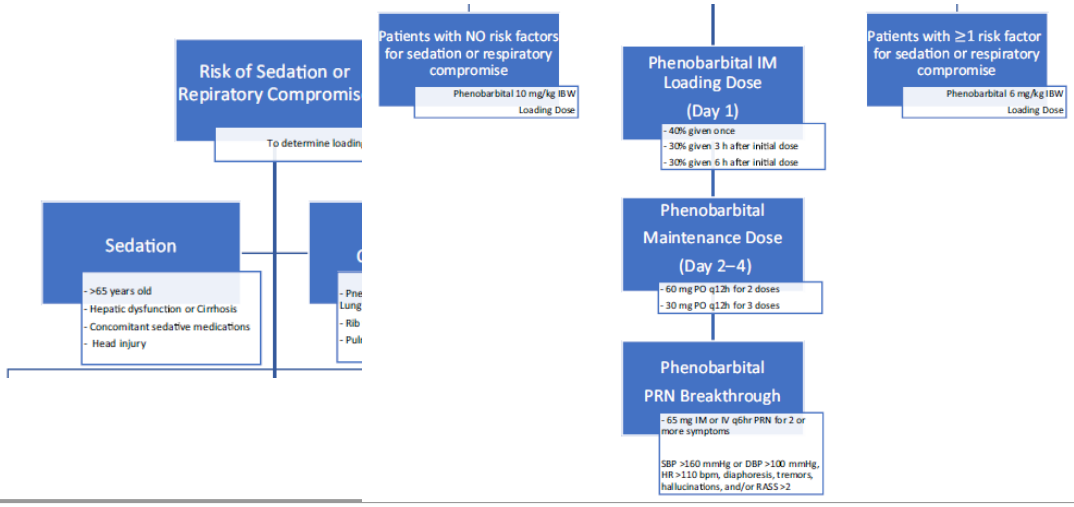
Phenobarbital v. Benzodiazepines

Phenobarbital versus benzodiazepines in alcohol withdrawal syndrome

Deanna Malone[1] | Blair N. Costin[1,2] | Dawn MacElroy[1] | Mashael Al-Hegelan[1,2] | Julie Thompson[3] | Yuriy Bronshteyn[2,4]

- Assess safety and efficacy of phenobarbital for treatment of moderate to severe AWS
  - ICU patients
  - PAWSS≥4, CIWA>15, prior hospitalization for AWS, history of alcohol withdrawal seizures, admission blood alcohol level ≥200, or clinical judgement
  - Excluded patients with history of epilepsy
- Medication comparisons
  - Phenobarbital dosing protocol
  - Benzodiazepine symptom-based dosing strategy

Phenobarbital v. Benzodiazepines



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Phenobarbital v. Benzodiazepines

Clinical Outcomes	Phenobarbital; *n* = 76	Benzodiazepine; *n* = 71	*p*-Value
Primary outcome			
Intubation (after initiation of AWS protocol); *n* (%)	15 (20)	36 (51)	<0.001
≥6 L of oxygen; *n* (%)	10 (13)	28 (39)	<0.001
Secondary outcomes			
Pneumonia incidence; *n* (%)	15 (20)	33 (47)	<0.001
Seizure incidence; *n* (%)	5 (7)	6 (9)	0.759
Median seizures; (min; max)	0 (0; 3)	0 (0; 6)	0.677
Median LOS in days (min; max)			
ICU	2 (0; 11.2)	4.2 (0.7; 30)	<0.001
Hospital	5.3 (0.3; 20.7)	9.9 (1.4; 63.7)	<0.001
Median additional medications for delirium; (min; max)	0 (0; 3)	1 (0; 3)	<0.001

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Phenobarbital v. Benzodiazepines

Dexmedetomidine	12 (16)	40 (56)	<0.001
Haloperidol	16 (21)	28 (39)	0.019
Quetiapine	8 (11)	18 (25)	0.029
Mode RASS			
0–9 h (min; max)	0 (−4; 3)	-1 (−5; 4)	0.525
9–24 h (min; max)	0 (−5; 3)	−2 (−5; 4)	0.002
24–48 h (min; max)	0 (−5; 1)	−1 (−5; 3)	<0.001
48–96 h (min; max)	0 (−5; 1)	0 (−5; 3)	0.357
Discharge type; *n* (%)			
Against medical advice	16 (21)	3 (4)	0.01
Planned	55 (72)	62 (87)	
Death from any cause/hospice	5 (7)	6 (9)	

Note: Phenobarbital treatment was associated with a statistically significant decreased occurrence of respiratory complications including intubation (15/76 [20%] vs. 36/71 [51%] patients; $p < 0.001$). Phenobarbital treatment was also associated with a statistically significant lower occurrence of 6 or greater liters of oxygen (10/76 [13%] vs. 28/71 [39%] $p < 0.001$). Of note; intubation refers to any time after the initiation of treatment for AWS with either phenobarbital or benzodiazepines.

Abbreviations: ICU, intensive care unit; LOS, length of stay; Max, maximum; Min, minimum; Planned: home, skilled nursing facility, rehabilitation, other hospitals; RASS, Richmond Agitation Sedation Scale.

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Phenobarbital in Surgical-Trauma Patients

Phenobarbital Monotherapy for the Management of Alcohol Withdrawal Syndrome in Surgical-Trauma Patients

Annals of Pharmacotherapy
2021, Vol. 55(3) 294–302

DOI: 10.1177/1060028020949137
journals.sagepub.com/home/aop
SAGE

Table 1. Criteria for High and Medium Risk for Alcohol Withdrawal Syndrome.

High risk for alcohol withdrawal syndrome	Medium risk for alcohol withdrawal syndrome
Previous history of delirium tremens with or without history of alcohol withdrawal seiz alcohol use (≤2 weeks) with eith • Positive BAL greater than 0.1 g • Elevated MCV (>90 fL) • Elevated AST to ALT ratio ≥1.	Active alcohol dependence per patient's

Abbreviations: ALT, alanine aminotrans

Table 2. Risk Factors for Sedation and Respiratory Compromise.

Risk factors for sedation	Risk factors for respiratory compromise
• Age >65 years • Hepatic dysfunction (AST and ALT 2-3 times ULN) • Liver cirrhosis • Head injury • Recent administration of any opioids within past 6 hours • Recent administration of any benzodiazepines within past 6 hours • Recent administration of sedatives	• Pneumonia • Rib fracture(s) • Chest tube(s) • Pulmonary contusion(s) • Cervical collar/spinal brace

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper lower limit of normal.

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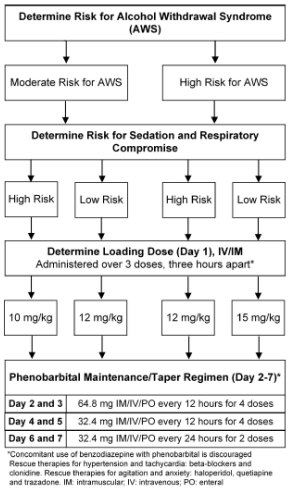
Phenobarbital in Surgical-Trauma Patients



- **Loading dose 10-15 mg/kg**
- **Based on risk factors identified**
- **3 consecutive doses**
  - 40%, 30%, 30%
  - 3 hours between dosage

Phenobarbital in Surgical-Trauma Patients

- **31 patients included**
  - All with history of AWS
  - 35% with history of DTs
  - 77% intoxicated on admission
- **No severe AWS related symptoms (i.e. seizures, hallucinations, delirium)**

Table 4. Patient Outcomes.[a]

Outcome		n = 31
Hospital LOS, days		6 (4-15)
ICU LOS, days		2 (1-4)
Hospital/ICU mortality		0
Highest hemodynamic parameters 6 hours post–PHB administration	SBP, mm Hg	139 ± 17
	DBP, mm Hg	77 ± 15
	HR, bpm	92 ± 18
RASS score 6 hours post–PHB administration[b]		−1 (−1-0)
Hypotension		3 (10)[c]
Intubated during PHB administration		3 (10)[d]
Respiratory depression		0
Oversedation		0

Abbreviations: bpm, beats per minute; DBP, diastolic blood pressure; HR, heart rate; ICU, intensive care unit; LOS, length of stay; PHB, phenobarbital; RASS, Richmond Agitation and Sedation Scale; SBP, systolic blood pressure.
[a]Data are presented as median (interquartile range), n (%), and mean ± SD, as appropriate.
[b]Evaluable patients = 22.

Phenobarbital Protocol in Medical ICU

- **MICU patients with primary diagnosis of AWS**
- **102 patients**
- **51 in benzodiazepine protocol group**
- **51 in phenobarbital monotherapy group**
  - Phenobarbital protocol included 260 mg IV loading dose with repeated doses of 130 mg IV doses as needed every 15-30 minutes up to 15 mg/kg IBW to achieve a CIWA < 10
- **Primary Outcome: ICU LOS**
- **Secondary Outcomes: Hospital LOS, Intubation, Adjunct Medications, ICU readmission, sitter, restraints, hypotension**

Phenobarbital Protocol in Medical ICU

TABLE 2.
Primary and Secondary Outcomes

Outcomes	Phenobarbital (n = 51)	Benzodiazepines (n = 51)	p[d]
Primary outcome			
ICU LOS[a] (d)	1.5 (1.2–2.4)	2.3 (1.4–4.8)	**0.009**
Secondary outcome			
Hospital LOS[a] (d)	3 (2.7–4)	6 (4–10)	**< 0.001**
Clinical Institute Withdrawal Assessment Alcohol Scale-Revised score control			
Maximum during MICU stay[a]	16 (12–22)	21 (15–27)	**0.009**
MICU discharge[a]	3 (2–5)	5 (3–8)	**0.010**
Safety			
Hypotension[b]	0 (0)	1 (2)	1.000
Agranulocytosis[b]	0 (0)	1 (2)	1.000
Sitter[b]	16 (31.4)	13 (25.5)	0.510
Restrain[b]	19 (37.3)	29 (56.9)	**0.047**
Need for mechanical ventilation[b]	1 (2)	10 (19.6)	**0.023**
MICU readmission[b]	3 (5.9)	3 (5.9)	1.000
Adjunct medications[c]	0.7 (0.5–1)	2.5 (2–3)	**< 0.001**
Dexmedetomidine[b]	13 (25.5)	24 (47.1)	**0.023**
Gabapentin[b]	6 (11.8)	39 (76.5)	**< 0.001**
Haloperidol[b]	11 (21.6)	31 (60.8)	**< 0.001**
Clonidine[b]	8 (15.7)	27 (52.9)	**< 0.001**
Valproic acid[b]	0 (0)	6 (11.8)	**0.027**

LOS = length of stay, MICU = medical ICU.

Current Protocol

- **Step 1**
  - Risk Assessment (PAWSS ≥ 4)
  - Score CIWA without PRN benzodiazepines
- **Step 2**
  - Phenobarbital Monotherapy
  - 130 mg loading dose then 65 mg q8h (start 3 hours after LD) x 6 doses
  - If scoring >20 CIWA, discuss options with provider
    - Give additional 130 mg loading dose
    - Increase dose after first maintenance dose
  - Weaning plan
    - Further weaning based on patient response
    - Anticipated duration of withdrawal also considered
- **Step 4**
  - Adjunctive Agents

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Current Protocol

	If able to take PO	If unable to take PO or IV preferred
Low-dose taper • Scheduled therapy is necessary • High-risk of respiratory compromise/over-sedation	Pb 60 mg PO Q6H x 1 dose, Pb 30 mg PO Q6H x 8 doses (2 days) Pb 30 mg PO Q8H x 6 doses (2 days)	Pb 65 mg IV Q6H x 1 dose, Pb 32.5 mg IV Q6H x 8 doses (2 days) Pb 32.5 mg IV Q8H x 6 doses (2 days)
Standard-dose taper • No history of DTs/severe withdrawal or exceedingly high daily consumption • Low/moderate risk of respiratory compromise/over-sedation	Pb 60 mg PO Q6H x 4 doses (1 day), Pb 60 mg PO Q8H x 3 doses (1 day), Pb 30 mg PO Q8H x 6 doses (2 days)	Pb 65 mg IV Q6H x 4 doses (1 day), Pb 65 mg IV Q8H x 3 doses (1 day), Pb 32.5 mg IV Q8H x 6 doses (2 days)
High-dose taper with loading dose • *Very high-risk* withdrawal (Hx DTs/severe withdrawal or exceedingly high daily consumption) • Low/moderate risk of respiratory compromise/over-sedation	Pb 130 mg IV Q30min x 2 doses, Pb 90 mg PO Q8H x 6 doses (2 days), Pb 60 mg PO Q8 x 6 doses (2 days), Pb 30 mg PO Q8H x 6 doses (2 days)	Pb 130 mg IV Q30min x 2 doses, Pb 65 mg IV Q6H x 8 doses (2 days), Pb 65 mg IV Q8 x 6 doses (2 days), Pb 32.5 mg IV Q8H x 6 doses (2 days)
High-dose taper without loading dose • High-dose taper is desired, but omit 260 mg loading dose due to clinical judgement, previous loading dose given, or individualized loading dose desired	Pb 90 mg PO Q8H x 6 doses (2 days), Pb 60 mg PO Q8 x 6 doses (2 days), Pb 30 mg PO Q8H x 6 doses (2 days)	Pb 65 mg IV Q6H x 8 doses (2 days), Pb 65 mg IV Q8 x 6 doses (2 days), Pb 32.5 mg IV Q8H x 6 doses (2 days)

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Adjunctive Agents

- **Dexmedetomidine**
  - Central-acting alpha-2 receptor agonist
  - Will mask symptoms of AWS
  - SHOULD NOT be used alone in AWS
- **Valproic Acid**
  - Broad mechanism of action
  - Antiepileptic and mood stabilizer
  - Could minimize benzodiazepine and phenobarbital use
- **Ketamine**
  - NMDA receptor antagonist
  - Minimal respiratory depression
  - Great option in hemodynamically unstable patients

Downsides

- **No data available for Neurological ICU patients**
  - Concern for sedation
  - Concern for impaired neurologic examination
- **Optimal dose unknown**
  - Magnitude of loading dose
  - Frequency of maintenance dose
- **Drug Interactions**
  - CYP34 Inducer
  - Nimodipine – significant reduction in Cmax and AUC noted
  - Ticagrelor – reduced exposure and decreased efficacy noted

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Questions?

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