Phenobarbital in Severe Alcohol Withdrawal Syndrome

Jordan Rowe
Pharm.D. Candidate
UAMS College of Pharmacy

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No relevant financial relationship exists.

Objectives

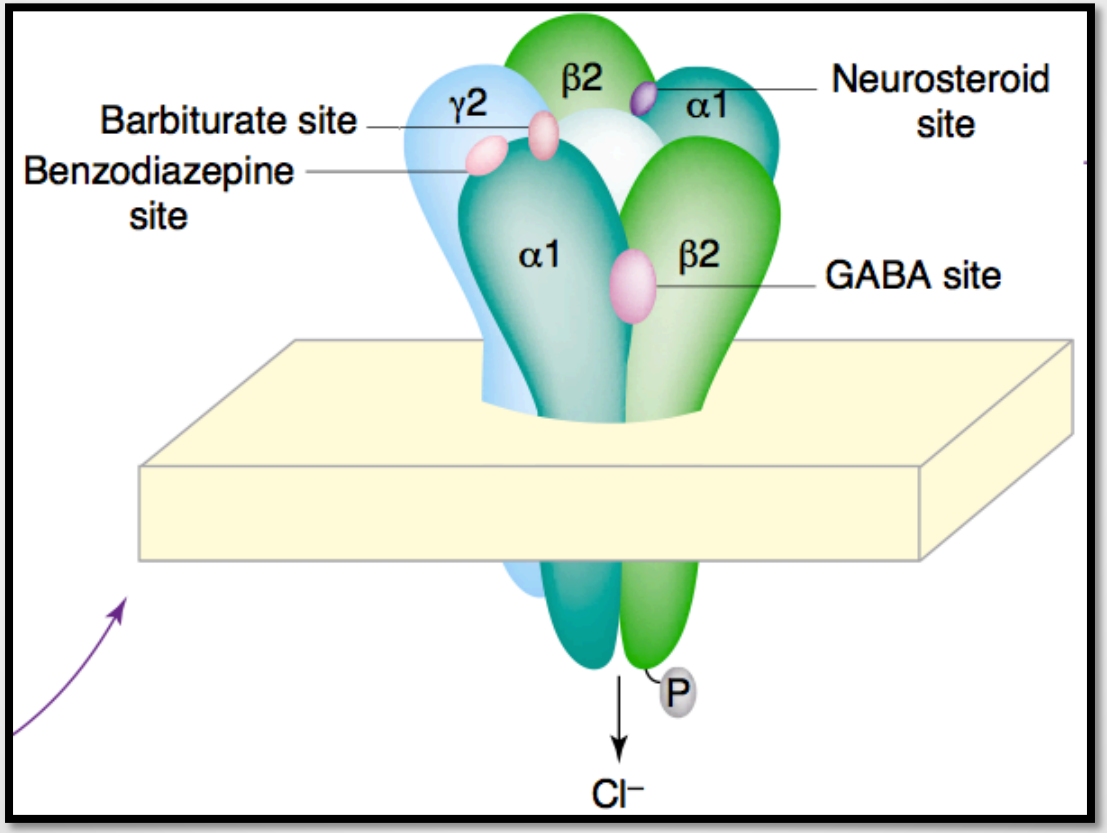
1. Describe the pathophysiology and clinical presentation of alcohol withdrawal syndrome (AWS).

2. Evaluate the role for phenobarbital in adult patients at risk for developing AWS.

Patient Case

A 32 year old male arrives at the ED by ambulance. His spouse called 911 after the patient reported that he felt like bugs were crawling under his skin. The patient also reported constant nausea, moderate anxiety, and slight tremor. He was given a bolus dose of lorazepam upon arrival as his spouse said he recently decided to quit drinking alcohol.

Pathophys of AWS - GABA Receptor



Clinical Institute Withdrawal Assessment for Alcohol Revised (CIWA-Ar)

	Response (0)	Response (7)
Nausea and Vomiting	None	Constant nausea, frequent dry heaves and vomiting
Tremor	None	Sever, even with arms not extended
Paroxysmal Sweats	No sweat visible	Drenching sweats
Anxiety	No anxiety, at ease	Acute panic state
Agitation	Normal activity	Pacing back and forth, or constant thrashing
Tactile Disturbances	None	Continuous hallucinations
Auditory Disturbances	None	Continuous hallucinations
Visual Disturbances	None	Continuous Hallucinations
Headache/Fullness in Head	None	Extremely Severe
Orientation and Clouding Sensorium	Oriented	Disoriented for place or person

Self-assessment question

TW, a 32 year old male arrives at the ED by ambulance. His spouse called 911 after the patient reported that he felt like bugs were crawling under his skin. The patient also reported constant nausea, moderate anxiety, and slight tremor. He was given a bolus dose of lorazepam upon arrival as his spouse said he recently decided to quit drinking alcohol.

What is TW's CIWA score?

Tactile Disturbance: 7
Nausea: 5
Anxiety: 4
Tremor: 2

Total Score: 18

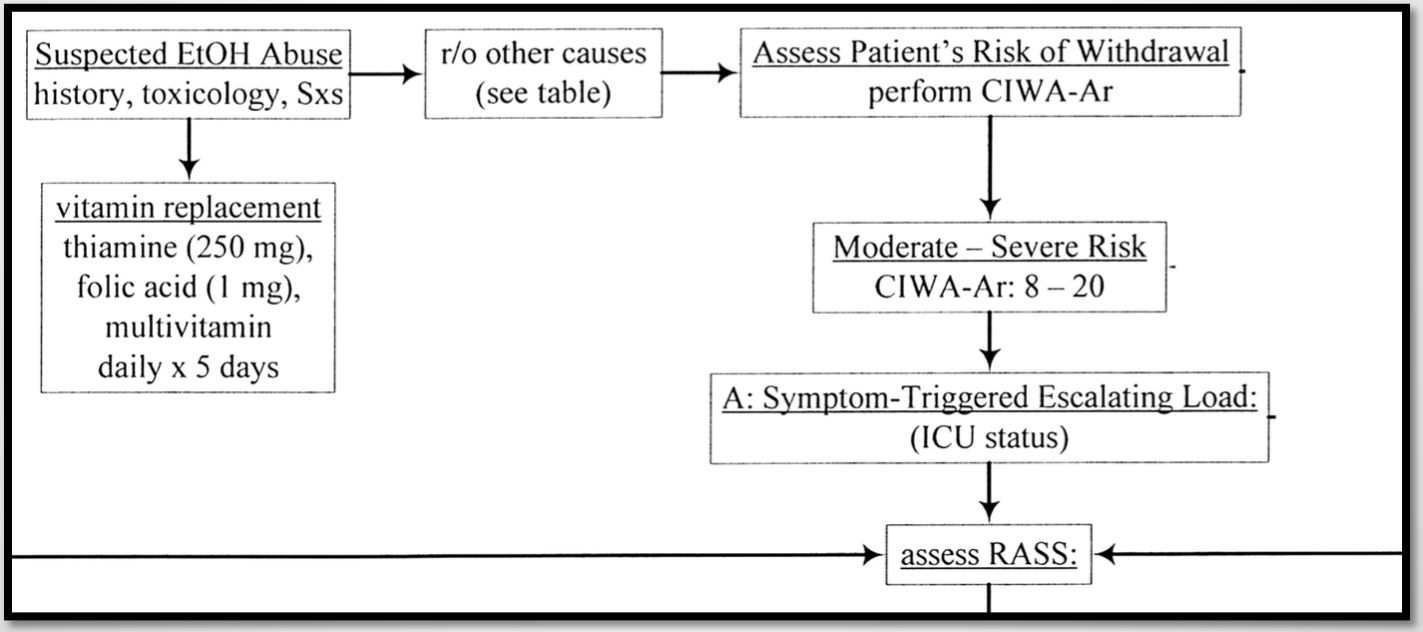
Treating Alcohol Withdrawal

Benzodiazepines have become the standard for treatment

New evidence suggests that phenobarbital could play a successful role of an AWS protocol

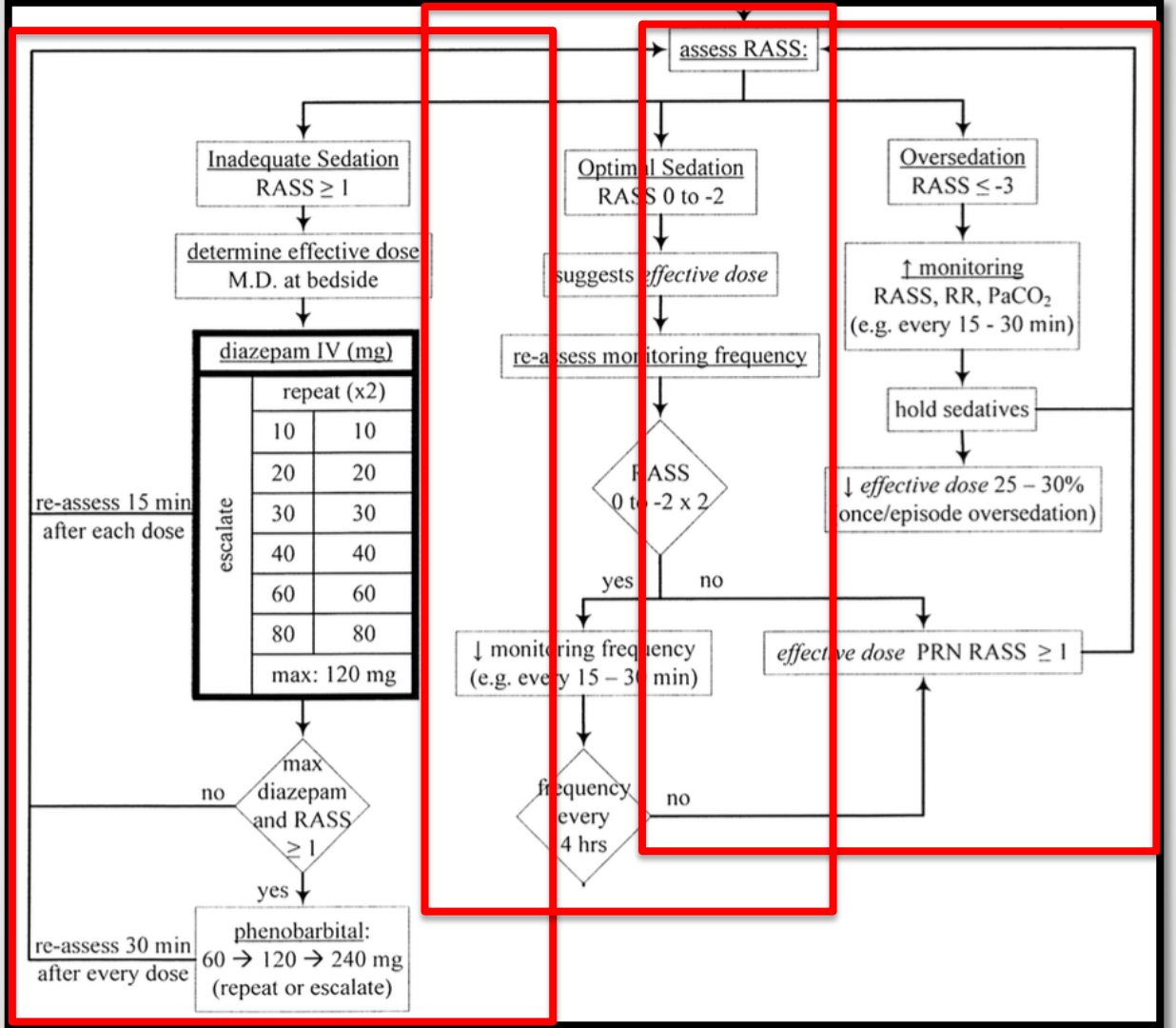
Duby: Protocolized vs. Non-protocolized

- Population: 132 adult ICU admittants with diagnosed AWS



Richmond Agitation and Sedation Scale

Score	Term	Description
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent non-purposeful movements, fights ventilator
+1	Restless	Anxious but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained awakenings (eye contact) to voice (≥10 s.)
-2	Light sedation	Briefly awakens with eye contact to voice (<10 s.)
-3	Moderate sedation	Movement/eye opening to voice (no eye contact)
-4	Deep sedation	No response to voice; movement/eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation


assess RASS:
Inadequate Sedation
RASS ≥ 1
determine effective dose
M.D. at bedside
diazepam IV (mg)
repeat (x2)
escalate
10 10
20 20
30 30
40 40
60 60
80 80
max: 120 mg
re-assess 15 min
after each dose
max diazepam and RASS ≥ 1
no
yes
phenobarbital:
60 → 120 → 240 mg
(repeat or escalate)
re-assess 30 min
after every dose
Optimal Sedation
RASS 0 to -2
suggests effective dose
re-assess monitoring frequency
RASS 0 to -2 x 2
yes
no
↓ monitoring frequency
(e.g. every 15 – 30 min)
frequency every 4 hrs
no
Oversedation
RASS ≤ -3
↑ monitoring
RASS, RR, PaCO2
(e.g. every 15 - 30 min)
hold sedatives
↓ effective dose 25 – 30%
once/episode oversedation)
effective dose PRN RASS ≥ 1

Decreased Mean Dosing

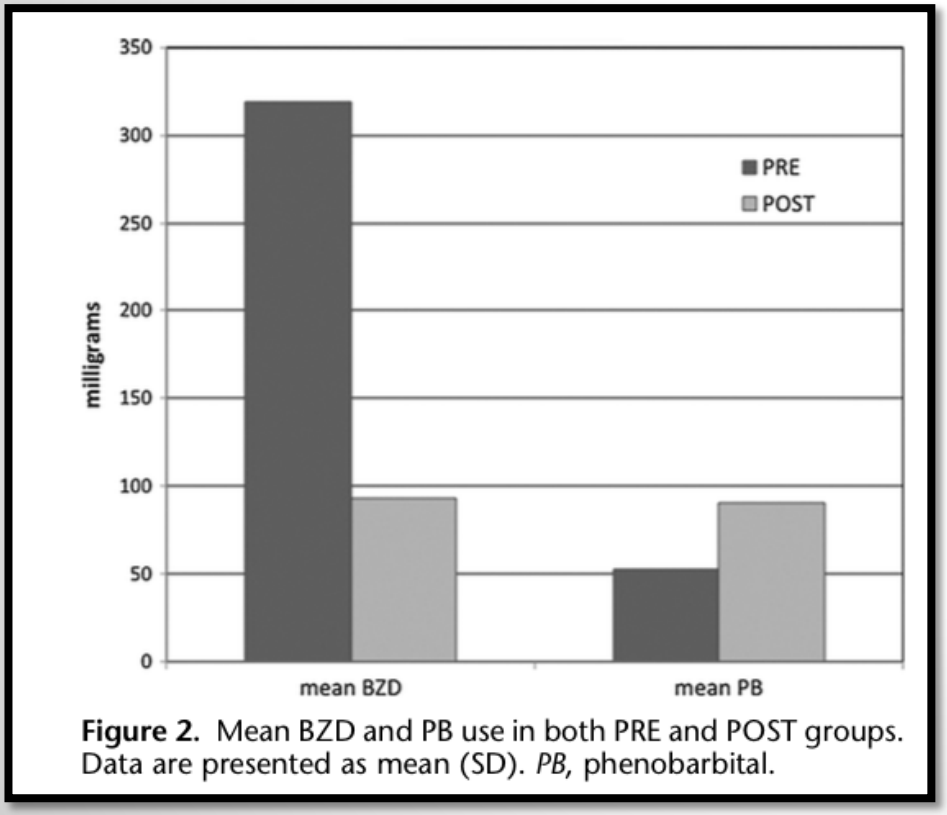


Figure 2. Mean BZD and PB use in both PRE and POST groups. Data are presented as mean (SD). *PB*, phenobarbital.

- Decreased ICU LOS, intubation due to AWS, time on ventilator, and duration of sedation (all $p<0.001$)
- Trend toward decreased mortality

Big Take Away

- Protocolized administration
  - Decreased overall dose necessary
  - Decreased ICU LOS and ventilator time
  - Dependant on RASS - close monitoring is necessary with this approach

Michaelsen - Phenobarbital vs. Diazepam for DT

- Population: patients receiving treatment for DT at two psychiatric departments over 8 years
- Phenobarbital dose: 100-200 mg IV or PO hourly
- Diazepam dose: initially 10-20 mg IV hourly, up to 4 times an hour

Efficacy and Complications

	PB Rigshospitalet	PB Bispebjerg	DZP Bispebjerg
Length of Delirium	5.85 +/- 6.3 days	5.30 +/- 2.6 days	6.64 +/- 4.2 days
Length of Hospitalization	13.0 +/- 13 days	12.2 +/- 10 days	12.3 +/- 11 days
Mortality	2 (4%)	1 (2%)	1 (4%)
Respiratory Complications	18 (34%)	21 (40%)	38 (43%)
Pneumonia	11 (20%)	15 (28%)	24 (27%)
ICU admission	8 (16%)	5 (9%)	12 (14%)

Big Take Away

- Phenobarbital is a relatively safe and equipotent alternative to benzodiazepines for treatment of DT.
- No significant differences in length of DT and hospitalization between PB and DZP.
- No significant differences in complications between PB and DZP.

Rosenson – Phenobarbital for Acute AWS

- Phenobarbital vs. placebo control
- Prospective randomized double-blind placebo controlled study
- Population: ED patients with suspected acute AWS
- Hypothesized PB will decrease ICU admission

Protocol

- Single dose of phenobarbital (10mg/kg in NS) or placebo (100 mL NS)

- PB/placebo given in addition to symptom-guided lorazepam AWS protocol

Clinical Outcomes

Table 2. Clinical Outcomes

Clinical Outcome*	Phenobarbital (n = 51)	Placebo (n = 51)	Difference (95% CI)
ICU admission: n (%)	4 (8)	13 (25)	17 (4–32)
TCU admission, number: n (%)	23 (45)	20 (39)	−6 (−25–13)
Floor admission: n (%)	24 (47)	18 (35)	−12 (−31–7)
Maximum AWCA score: median (IQR)	8 (5–10)	10 (5–14)	2 (−0.2–3)
Continuous lorazepam infusion: n (%)	2 (4)	16 (31)	27 (14–41)
Total length of stay, hours: median (IQR)	76 (54–114)	118 (47–190)	42 (−4–82)
ICU length of stay, hours: median (IQR)	34 (30–276)	94 (43–134)	60 (−170–434)
Intubation: n (%)	1 (2)	1 (2)	0 (−0.05–0.05)
Seizure: n (%)	1 (2)	2 (4)	2 (−5–9)
Restraints: n (%)	15 (29)	23 (45)	16 (−3–34)
Bedside sitter: n (%)	14 (28)	11 (22)	−6 (−11–23)

CI = confidence interval; ICU = intensive care unit; TCU = transitional care unit; AWCA = Alcohol Withdrawal Clinical Assessment; IQR = interquartile range.

* No falls nor mortalities were observed in any study subjects.

Possible Implications

- Provides evidence of synergistic clinical effects of phenobarbital and lorazepam in AWS

- Cost: ~ $18.00/patient for phenobarbital vs. additional cost of ICU admission

Big Take Away

- A single IV PB dose decreased ICU admission rate, use of continuous lorazepam infusions, and total lorazepam administered
- No differences in incidence of adverse effects between the two groups
- Possible synergistic effect between phenobarbital and lorazepam in acute AWS

Further Avenues for Investigation

- Cost-benefit analysis of incorporation of phenobarbital into AWS protocol

- Comparison of phenobarbital and benzodiazepines as monotherapy for AWS using escalation of dosing strategy

Addressing Concerns for Phenobarbital Use

- In-service or other education opportunities explaining the available literature
- Adverse effects: Most with PB are seen with prolonged use and at very high doses
- Utilize interprofessional teams to build protocols to decrease error at all levels of care

Patient Case

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What dose of IV lorazepam is appropriate for this patient?

What options are available for this patient?

Single dose of IV lorazepam

Continue to monitor sedation and use lorazepam as needed

Conclusions:

Phenobarbital shows great evidence in improving outcomes in patients with AWS.

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References

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