EMPoweRx
conference

A conference that is for us and by us

Emergency Medicine Pharmacotherapy with Resuscitation (EMPoweRx) Conference

The Pharmacologic Approach to Severe Alcohol Withdrawal: A Focus on Phenobarbital vs Benzodiazepines

Jimmy L. Pruitt III, Pharm.D., BCPS, BCCCP

Emergency Medicine Clinical Pharmacy Specialist

EM PoweRx conference

A conference that is for us and by us

Disclosure

- I have no real or apparent conflicts of interest to disclose
- I will not be discussing off-label or investigational uses of medications

Objectives

- Review pathophysiology and assessment of acute alcohol withdrawal syndrome
- Discuss the pharmacology and pharmacokinetics of common medications used in alcohol withdrawal
- Analyze the clinical literature regarding management of alcohol withdrawal using phenobarbital
- Apply clinical literature to patient case

Background on Alcohol Withdrawal

An estimated 76.3 million people worldwide have alcohol use disorders (AUDs), and these account for 1.8 million deaths each year

Greater than 30% of emergency department presentations are alcohol related

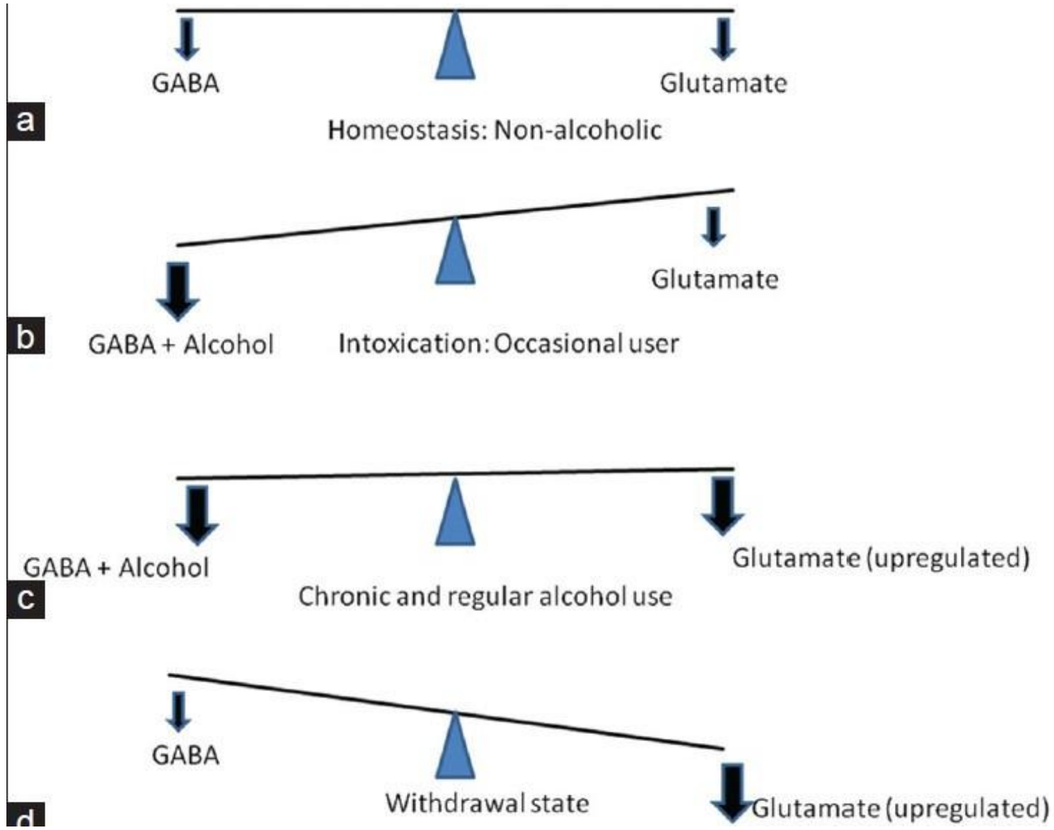
Severe alcohol withdrawal syndrome (AWS) more than doubles the length of stay and frequently requires treatment at the ICU

A complicated AWS includes epileptic seizures and/or delirium tremens (DT), the occurrence of which may be as high as 15% in AUD patients

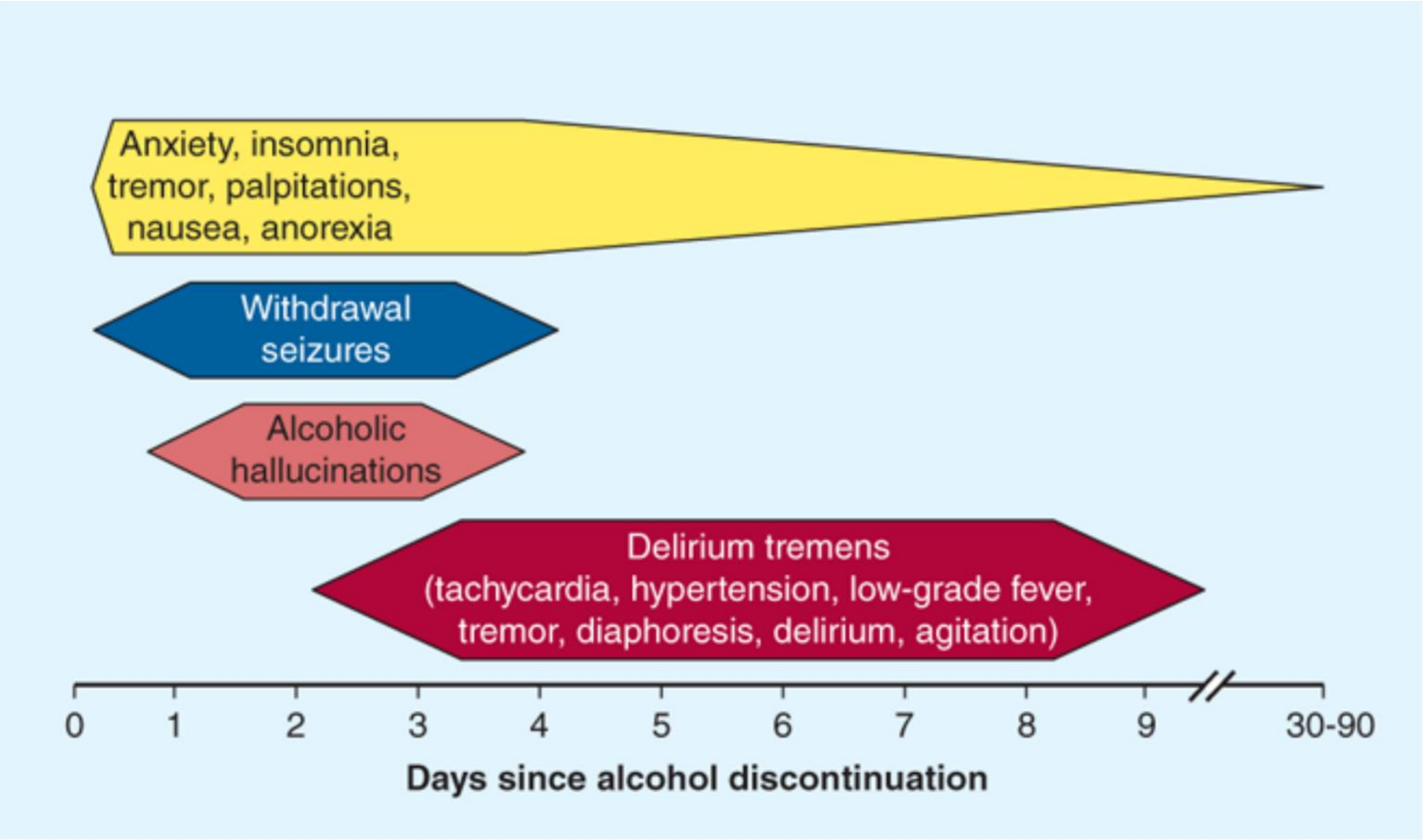
1. World Health Organization. Management of substance abuse: alcohol
2. Mennecier D. Gastroenterol Clin Biol. 2008;32:792–797. Epub 2008/09/02.
3. Chan GM, J Med Toxicol. 2009;5:8–14. Epub 2009/02/05.

Alcohol use disorders (AUDs)
Alcohol withdrawal syndrome (AWS)
Delirium tremens (DT)

Pathophysiology



Kattimani et al. Ind Psychiatry J. 2013 Jul-Dec; 22(2): 100–108.



The Alcohols, Katzung BG. Basic & Clinical Pharmacology, 14e; 2017.

DSM-5 Diagnostic Criteria for Alcohol Withdrawal

Diagnostic and Statistical Manual of Mental Disorders (DSM-5) Diagnostic 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 criterion A:
1. Autonomic hyperactivity
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

American Psychiatric Association. 2013. American Psychiatric Publishing.

CIWA-Ar

The Clinical Institute Withdrawal Assessment for Alcohol scale in its revised version (CIWA-Ar) is the most widely used tool in US

Used to determine the severity of the withdrawal symptoms as they are actively experienced

Validated 10-item Assessment tool

- Examines: Agitation, anxiety, auditory disturbances, clouding of sensorium, headache, paroxysmal sweats, tactile disturbances, tremor, and visual impairment

Score 8-15 indicates mild alcohol withdrawal

Scores >20 indicate severe alcohol withdrawal

Schmidt KJ. Ann Pharmacother. 2016 May;50(5):389-401

CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol Scale

MINDS

MINDS Alcohol Withdrawal Scale
(0-46 points)

Table 1. Minnesota Detoxification Scale

Symptom	Score
Pulse (beats/min)	
< 90	0
90–110	1
> 110	2
Diastolic blood pressure (mm Hg)	
< 90	0
90–110	1
> 110	2
Tremor	
Absent	0
Visible	2
Moderate	4
Severe	6
Sweat	
Absent	0
Barely; moist palms	2
Beads visible	4
Drenching	6

MINDS Alcohol Withdrawal Scale
(0-46 points)

Table 1. Minnesota Detoxification Scale

Symptom	Score
Hallucinations	
Absent	0
Mild	1
Moderate, intermittent	2
Severe, continuous	3
Agitation	
Normal activity	0
Somewhat > normal	3
Moderately fidgety, restless	6
Pacing, thrashing	9
Orientation	
Oriented x 3 (person, place, time)	0
Oriented x 2 (person, place)	2
Oriented x 1 (person)	4
Total disorientation	6
Intubated	0
Delusions	
Absent	0
Present	6
Seizures	
Absent	0
Present	6

DeCarolis DD, et al. Pharmacotherapy. 2007

CIWA-Ar

	Saitz et al. Individualized Treatment for Alcohol Withdrawal: A Randomized Double-blind Controlled Trial
Objective	To assess the effect of an individualized treatment regimen on the intensity and duration of medication treatment for alcohol withdrawal.
Design	A randomized double-blind, controlled trial
Setting	An inpatient detoxification unit in a Veterans Affairs medical center.
Intervention Control	Fixed-schedule: Chlordiazepoxide four times daily +PRNs vs Symptom triggered therapy: Chlordiazepoxide only in response to signs and symptoms of alcohol withdrawal
Results	• The median duration of treatment in fixed-schedule 68 hr vs 9 hr in symptom-triggered group (P<.001) • Mean dose 425 mg vs 100 mg (P<.001) • No significant differences in the severity of withdrawal, incidence of seizures, or delirium tremens.
Conclusion	Symptom-triggered therapy individualizes treatment, decreases both treatment duration and the amount of benzodiazepine used, and is as efficacious as standard fixed-schedule therapy for alcohol withdrawal.

Saitz R. JAMA. 1994 Aug 17;272(7):519-23.

CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol Scale

American Society of Addiction Medicine

Sedative hypnotic drugs are recommended as the primary agents for managing AWD (grade A recommendation)

- There isn’t evidence that one sedative-hypnotic agent that is superior to others or that switching from one to another is helpful.

Dose agents to achieve light sedation (grade C recommendation).

- The patient is awake but tends to fall asleep unless stimulated

Adrenergic antagonists may be considered as adjunction (grade C recommendation)

- For control of persistent hypertension or tachycardia

Mayo-Smith MF. Arch Intern Med. 2004 Jul 12;164(13):1405-12.

Objectives

- Review pathophysiology and assessment of acute alcohol withdrawal syndrome
- Discuss the pharmacology and pharmacokinetics of common medications used in alcohol withdrawal
- Analyze the clinical literature regarding management of alcohol withdrawal using phenobarbital

Benzodiazepines

MOA

- Binds to GABAA enhancing GABA activity (requires GABA to be present)
  - Increases the frequency of GABAA receptor channel opening
- Common agents: lorazepam, chlordiazepoxide, diazepam

Dose*

- Depends on agent, higher doses than used for sedation

PK/PD

- Onset: 2-10 minutes
- Metabolism: Hepatic and substrate of CYP isoenzymes
- Elimination: primary through urine as metabolites

Adverse Effects

- Hypotensive
- Respiratory depression

* Individual agents on summary chart

Mechanism of action (MOA)
Pharmacokinetic/dynamics (PK/PD)

Micromedex [Electronic version].Greenwood Village, CO: Truven Health Analytics. Retrieved September 28, 2019, from http://www.micromedexsolutions.com/

Benzodiazepines

Agent	Equivalent Dose (mg)	Onset of Action	Duration	Active Metabolites
Chlordiazepoxide	10	Intermediate	Long	Yes
Clonazepam	0.25	Fast	Intermediate	Yes
Diazepam	5	Fast	Long	Yes
Lorazepam	1	Fast	Intermediate	No
Alprazolam	0.5	Fast	Short	Yes (Minimal)
Midazolam	1.25-1.7	Fast	Short	Yes
Oxazepam	15	Slow	Intermediate	No

Micromedex [Electronic version].Greenwood Village, CO: Truven Health Analytics. Retrieved September 28, 2019, from http://www.micromedexsolutions.com/

Mechanism of action (MOA)
Pharmacokinetic/dynamics (PK/PD)

Phenobarbital

MOA

- Enhances the binding of GABA to the receptor and through increasing the duration of GABAA-mediated inhibitory currents
- Barbiturates at high concentrations may also be GABA mimetic and inhibit stimulatory AMPA Glutamate receptors

Dose

- Weight-based and fixed doses
- IV: 65 to 260 mg of phenobarbital up to 10-20 mg/kg
- Oral: 60 mg 4 times daily on day 1, followed by 60 mg 3 times daily on day 2, 60 mg twice daily on day 3, and 30 mg twice daily on day 4.

PK/PD

- Onset: IV: 5 min, Oral: 30 min
- Metabolism: Substrate of CYP2C19 (major); major CYP450 inducer
- Elimination: 25-50% eliminated unchanged in the urine

Adverse Effects

- Hypotensive
- Respiratory depression

Mechanism of action (MOA)
Pharmacokinetic/dynamics (PK/PD)

Micromedex [Electronic version].Greenwood Village, CO: Truven Health Analytics. Retrieved September 28, 2019, from http://www.micromedexsolutions.com/

Pharmacology and Pharmacokinetics

Agent	Routes of Administration	Dose	Onset (minutes)	Metabolism
Lorazepam	PO, IV, IM	IV 1-4 mg q 5-15 min	IV: 15-20	Hepatic (inactive)
Diazepam	PO, IV, IM, rectal	IV: 5-10 mg q 10-15 minutes	IV: 2-5	Hepatic (active)
Chlordiazepoxide	PO	Initial: 50-100 mg q Max 300 mg per 24 hr	Oral: 30-120	Hepatic (active)
Phenobarbital	PO, IV, IM	10 mg/kg or 130-260 mg	IV: 5 Oral: 30	Hepatic (inactive)
Dexmedetomidine	IV	0.1-0.7 mcg/kg/hr	IV: 15-30	Hepatic (inactive)
Ketamine	IV,IM,PO,IN	0.15–0.3mg/kg/hr	IV: 1-5	Hepatic (active)

Micromedex [Electronic version].Greenwood Village, CO: Truven Health Analytics. Retrieved September 28, 2019, from http://www.micromedexsolutions.com/

Objectives

- Review epidemiology, pathophysiology, assessment of acute alcohol withdrawal syndrome
- Discuss the pharmacology and pharmacokinetics of common medications used in alcohol withdrawal
- Analyze the clinical literature regarding management of alcohol withdrawal using phenobarbital

Author, Year	Design	Sample Size	PB Dose/ comparator	Outcome
Robeson, 2013	Prospective, randomized, double-blind, placebo controlled trial	102	10 mg/kg IV x1 + PRN benzodiazepines Placebo + PRN benzodiazepines	PB decreased ICU admission PB decreased continuous infusion lorazepam PB decreased total lorazepam requirements No difference in ICU or hospital LOS
Duby, 2014	Retrospective, cohort study	135	<u>Post-guideline</u> -PB 60 mg, 120 mg, and 240 mg after max + diazepam (120 mg) based on RASS <u>Pre-guideline</u> Physician preference	Post-guideline care associated with: Decreased ICU LOS (9.6 d vs 5.2 d) Decreased ventilator days (5.6 d vs 1.31 d) Decreased need for continuous sedation (33 [55%] vs 18 [24%] Decreased intubation (13 [22%] vs 4 [5
Hendey, 2011	Prospective, randomized, double-blind trial	44	PB 260 mg IV ×1, 130 mg IV PRN Lorazepam 2 mg IV PRN + PRN chlordiazepoxide	PB and LZ both reduced the average CIWA-Ar score from baseline to discharge No difference in ED LOS and hospital LOS
Young, 1987	Prospective, uncontrolled trial	62	260 mg IV ×1 then 130 mg IV until clinical end point of light sedation	Safe discharge from ED was achieved in 92% of patients Average ED LOS was 3 h, 47 min No discharged patients returned to ED during the following week Adverse effect in 6% of patients (none were admitted to hospital

Phenobarbital for acute alcohol withdrawal: prospective randomized double-blind placebo-controlled study.

Objective	To investigate if a single dose of intravenous (i.v.) phenobarbital combined with a standardized lorazepam-based alcohol withdrawal protocol decreases intensive care unit (ICU) admission in ED patients with acute alcohol withdrawal
Design	Prospective, randomized, double blind, placebo-controlled study.
Population	198 patients with suspected acute alcohol withdrawal syndrome

Rosenson et al. J Emerg Med. 2013 Mar;44(3):592-598

Design

Inclusion/ Exclusion	I: > 18 year old with suspected acute alcohol withdrawal syndrome E: Allergy to study drugs, hepatic impairment, no IV access, and other primary diagnosis
Intervention	IV phenobarbital (10 mg/kg) in 100 mL normal saline over 30 mins
Outcomes	Primary: Initial level of hospital admission from the ED Secondary: Use of continuous lorazepam infusion, hospital length of stay, total amount of lorazepam used, and incidence of adverse events

Rosenson et al. J Emerg Med. 2013 Mar;44(3):592-598

Baseline Characteristics

	Phenobarbital (n = 51)	Placebo (n = 51)
Male	46 (90)	45 (88)
Age, years: median (IQR)	46 (40–52)	48 (37–54)
Initial AWCA score: median (IQR)	6 (4–10)	7 (4–10)
Initial heart rate: median (IQR)	106 (100–123)	112 (108–120)
Initial tremor: n (%)	48 (95)	48 (95)
Initial sweats: n (%)	25 (49)	32 (63)
Initial agitation: n (%)	20 (40)	21 (41)
Initial anxiety: n (%)	35 (68)	43 (84)
Altered level of consciousness: n (%)	30 (58)	35 (68)
Auditory/visual disturbances: n (%)	20 (40)	21 (41)
Time to initial lorazepam administration, minutes: median (IQR)	84 (48–146)	84 (40–312)
Time to study medication administration, minutes: median (IQR)	144 (103–263)	150 (100–26
Patients with prior alcohol withdrawal admissions to study institution: n (%)	21 (41)	25 (49)

Rosenson et al. J Emerg Med. 2013 Mar;44(3):592-598

Results

Primary Outcome	ICU admission rate: Phenobarbital vs Placebo • 8% vs. 25% • Difference 17% [95% confidence interval (CI) 4–32%])

Secondary Outcomes	Use of continuous lorazepam infusion
	• 4% vs. 31%
	  • Difference 27% [95% CI 14–41%]
	Total lorazepam required
	• 26 vs. 49 mg
	  • Difference 23 mg [95% CI 7–40]
	
	• There were no differences in telemetry admission or floor ward admission
	• Trend toward lower median ICU or total hospital
	  • Hospital LOS: 76 hr (54–114) vs 118 hr (47–190)
	  • ICU LOS: 34 hr (30-276) vs 94 hr (43–134)

Adverse Effects	• No differences in incidence of intubation, seizure, mechanical restraints, and bedside sitter. • There were no falls or mortality reported in either group.

Rosenson et al. J Emerg Med. 2013 Mar;44(3):592-598

Discussion

Strengths

- Randomized
- Prospective
- Clinical relevant study outcomes

Limitations

- Formal sample size analysis was not done
- Small sample
- Single Center
- Delirium, respiratory depression, EtOH level, and hypotension were missing from analysis

Takeaways

- Phenobarbital is an option as adjunct to benzodiazepine for AAWS
- 10 mg/kg did not lead to significant increase in adverse effects compared to standard of care

Alcohol withdrawal syndrome in critically ill patients: Protocolized versus Nonprotocolized management.

Objective	to compare patient outcomes in critically ill patients with AWS, regardless of their admission ICU diagnosis, that were treated with this protocolized approach versus a non-protocolized approach.
Design	Retrospective pre-post study.
Population	135 patients with suspected acute alcohol withdrawal syndrome admitted to the ICU

Duby JJ et al. J Trauma Acute Care Surg. 2014 Dec;77(6):938-43

Design	
Inclusion/ Exclusion	I: > 18 year old with suspected acute alcohol withdrawal syndrome admitted to ICU E: Patients with severe brain injury—defined as persistent Glasgow Coma Score < 8
Intervention	Pre-Protocol: • Typically received continuous infusions or scheduled doses of BZDs per physician preference Post-Protocol • Escalating doses of diazepam and phenobarbital according to an AWS protocol
Outcomes	Primary: • ICU length of stay Secondary: • Mean and median BZD use, mean and median phenobarbital use, duration of sedation, requirement for mechanical ventilation (MV), ventilator-free days, and requirement for MV due to AWS

Duby JJ et al. J Trauma Acute Care Surg. 2014 Dec;77(6):938-43

Baseline Characteristics			
	Pre (n = 60)	Post (n = 75)	P Value
Age	55.7 ± 8.7	50.7 ± 13.8	0.03
Male	81.6%	81.3%	1.0
History of Alcohol Withdrawal	40%	30.6%	0.28
History of Psychosis	10%	12%	0.78
History of Delirium Tremens	10%	4%	0.19
History of Seizure	18.3%	21%	0.83
Mean SOFA score on admit	6.1 ± 3.7	3.9 ± 2.9	0.0004
Mean blood alcohol level on admit (mg/dL)	135 ± 156	134 ± 140	0.56

Duby JJ et al. J Trauma Acute Care Surg. 2014 Dec;77(6):938-43

Results	
Primary Outcome	ICU LOS: Pre vs Post Protocol • 9.6 ± 10.5 vs 5.2 ± 6.4 (P-value 0.0004)
Secondary Outcomes	Time on Ventilator (days) 5.6 ± 13.9 vs 1.31 ± 5.6 (P-value < 0.0001) Ventilator-free days • 21.3 ± 9.5 vs 26.3 ± 5.6 (P-value 0.0004) Intubation due to AWS • 13 (22%) vs 4 (5%) (P-value < 0.001) Need for continuous sedation • 33 (55%) vs 18 (24%) (P-value < 0.001) Duration of sedation (days) • 10.8 ± 8.9 vs 3.5 ± 3.5 (P-value < 0.001)
Adverse Effects	Death • 7 (12%) vs 2 (3%) (P-value 0.07)

Duby JJ et al. J Trauma Acute Care Surg. 2014 Dec;77(6):938-43

Discussion

Strengths

- Clinical relevant study outcomes
- Provided protocol

Limitations

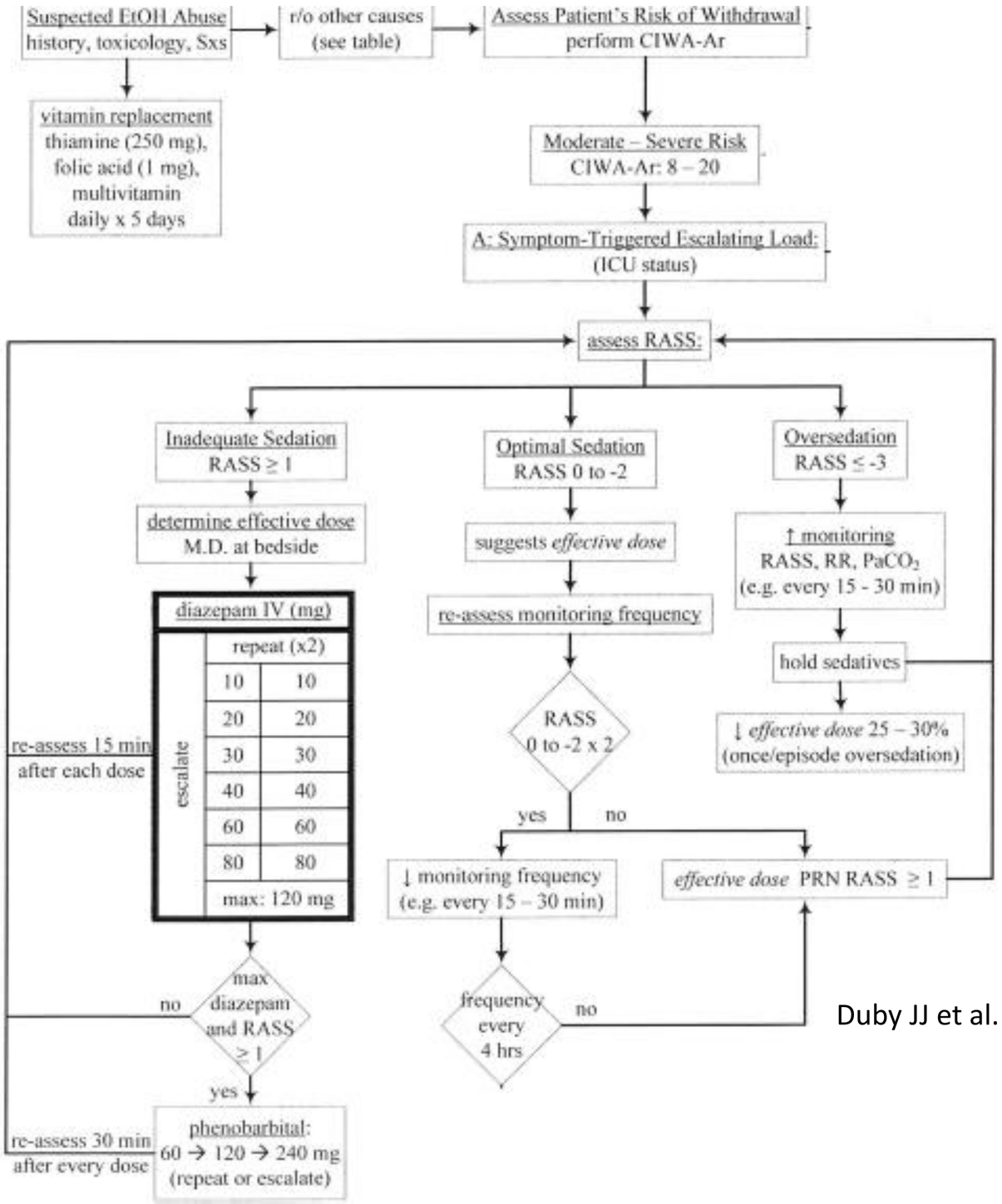
- Retrospective
- Small sample
- Single Center
- Delirium, respiratory depression, and hypotension were missing from analysis

Takeaways

- Phenobarbital is an option as adjunct to benzodiazepine for AAWS
- Protocol utilizing adjunct phenobarbital may reduce ICU LOS

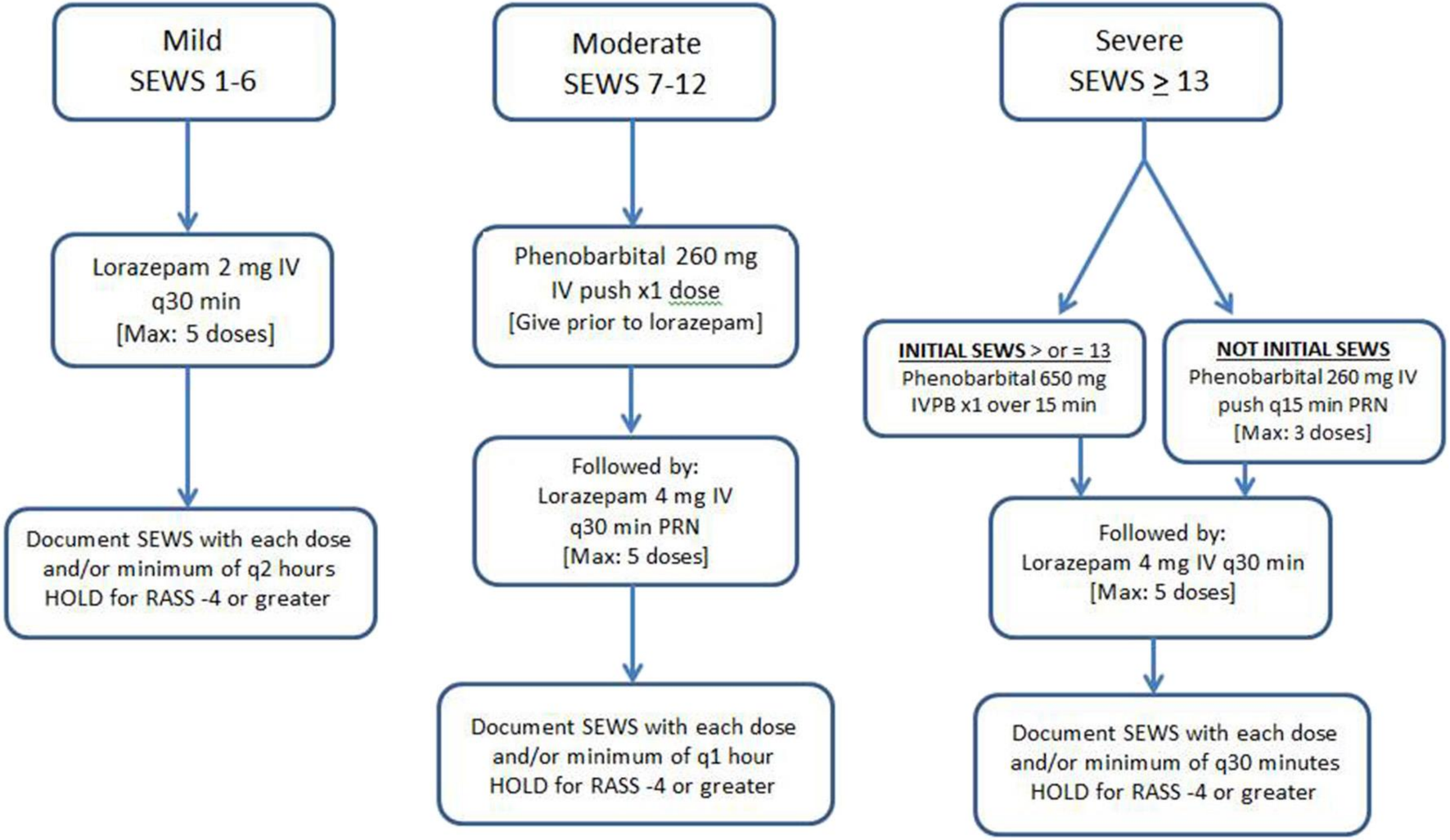
Duby JJ et al. J Trauma Acute Care Surg. 2014 Dec;77(6):938-43

Author, Year	Design	PB Dose/ comparator	Outcome
Ibarra, 2019	Retrospective observational/ n=78	Lorazepam protocol only (LZP) PB x 1 + LZP protocol (PB+LZP)	No difference in daily lorazepam requirements or hospital LOS PB+LZP group had ↑ pts d/c within 72 hrs No patient in PB group experience intubation or hypotension
Nisavic, 2019	Retrospective observational/ n=562	BZD only fixed dosing PB- Based Protocol (IM load + PO taper)	No difference in AWS-related seizures , ICU admission, over-sedation, LOS, and hallucinations ↑ Delirium in BZP group In BZP PB crossover pts, PB led to rapid improvement of BZP resistant AWS Symptoms
Nelson, 2019	Pre-post observational/ n=300	IV diazepam alone (DZP) IV LZP + IV PB (LZP + PB) IV PB alone (PB)	No difference in ICU admission, ICU LOS, and need for intubation. PB associated with ↑ ED LOS but ↓ BZP Requirements
Tidwell, 2019	Pre-post observational/ n=120	BZD only CiWA- Protocol PB Taper ± Benzo PRN	PB ↓ ICU+ Hospital LOS PB↓ total lorazepam requirements PB had less patient intubated



Duby JJ et al. J Trauma Acute Care Surg. 2014 Dec;77(6):938-43

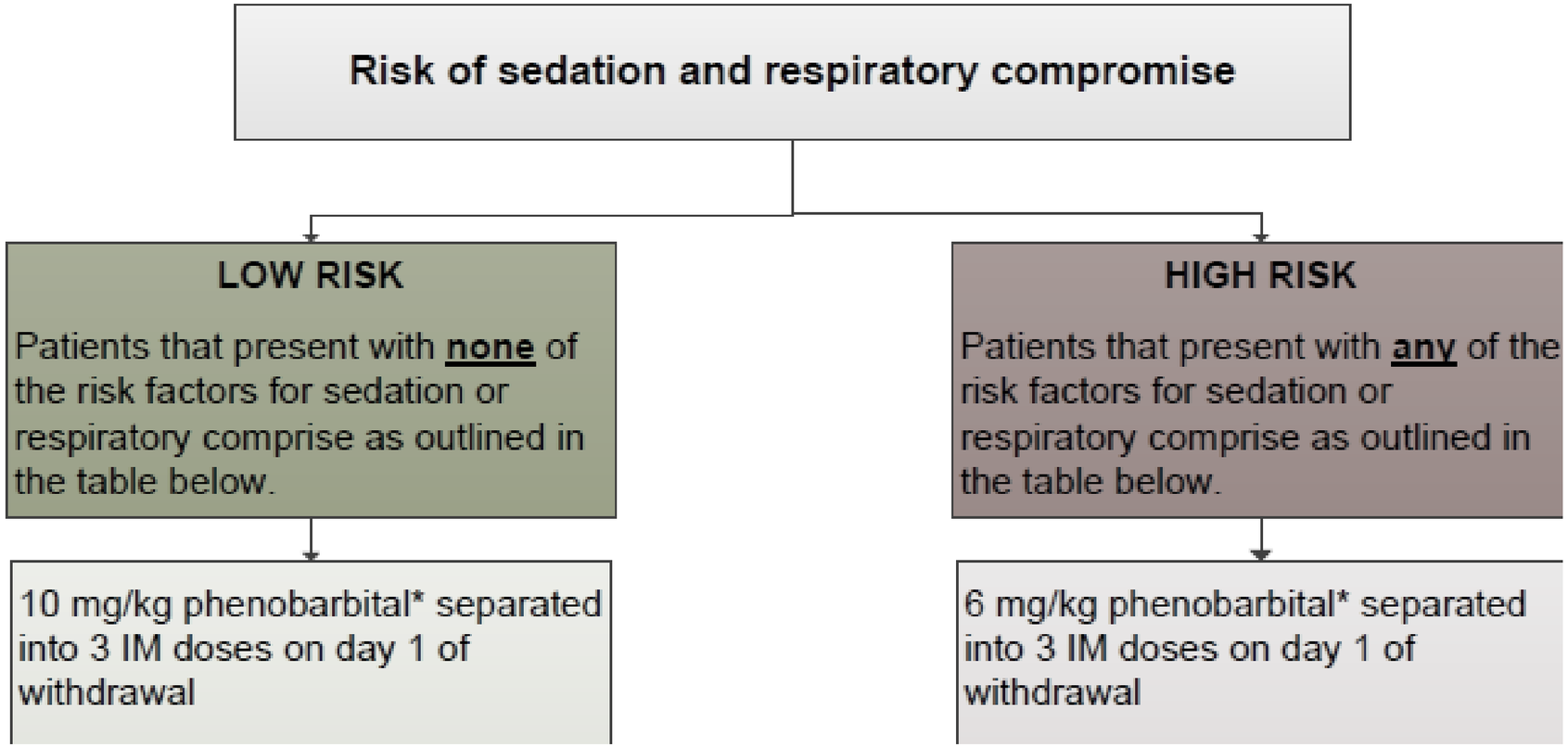
Phenobarbital Protocols



Severity of Ethanol Withdrawal Scale (SEWS)

Nelson AC et al. Am J Emerg Med. 2018 Mar 21. pii: S0735-6757(18)30241-9.

Ohio State Alcohol Withdrawal Protocol



Questions

- True or False. Do symptom-triggered therapy with benzodiazepines lead to equal efficacy outcomes without compromising safety?

Questions

- True or False. Do symptom-triggered therapy with benzodiazepines lead to equal efficacy outcomes without compromising safety?
  - True, based on Saitz et al, when displayed that there was no significant differences in the severity of withdrawal, incidence of seizures, or delirium tremens.

Questions

- True or false. In the studies presented, is there a reduction in ICU length of stay and benzodiazepine requirements with the use of phenobarbital?

Questions

- True or false. In the studies presented, is there a reduction in ICU length of stay and benzodiazepine requirements with the use of phenobarbital?
  - Darby et al displayed that a protocolized treatment approach of AWS in critically ill patients involving symptom-triggered, dose escalations of diazepam and phenobarbital lead to a decreased ICU length of stay, decreased time spent on mechanical ventilation, and decreased BZD requirements.

Summary

- Severe alcohol withdrawal presents a unique set of problems for patients in the ED
- Phenobarbital-based treatment of AWS seems to provide comparable benefit to traditional benzodiazepine-based treatment
- More studies are needed to find the most favorable dosing regimen and patient population that phenobarbital is preferred compared to benzodiazepines

The Pharmacologic Approach to Severe Alcohol Withdrawal: A Focus on Phenobarbital vs Benzodiazepines

Jimmy L. Pruitt III, Pharm.D., BCPS, BCCCP

Emergency Medicine Clinical Pharmacy Specialist

EM PoweRx conference

A conference that is for us and by us