Beyond Benzodiazepines for Severe Alcohol Withdrawal

John Radosevich, PharmD, BCCCP, BCPS
Clinical Pharmacy Specialist – Medical/Surgical/Trauma ICU
St. Joseph's Hospital and Medical Center
Phoenix, Arizona

February 15th, 2019

Dignity Health

Objectives

- Evaluate the literature supporting non-benzodiazepine therapies for severe alcohol withdrawal

- Develop a pharmacotherapy plan for treatment of severe alcohol withdrawal refractory to benzodiazepines

Outline

- Pathophysiology
- Presentation of acute alcohol withdrawal
- Assessment Tools
- Pharmacotherapy
  - Benzodiazepine
  - Non-benzodiazepine
    - (e.g. barbiturates, dexmedetomidine, ketamine, haloperidol)

Introduction

- Alcohol withdrawal in the hospital setting
  - Often happens in conjunction with critical illness from other causes
    - **Trauma**
    - Infection
    - Surgery
  - Assessment of withdrawal can be challenging in this population
    - Ability to communicate
    - Confounding comorbidities (delirium, pain, intoxication vs withdrawal)

Dignity Health.

Jawa RS et al. *Am J Emerg Med*. 2013.

Pathophysiology

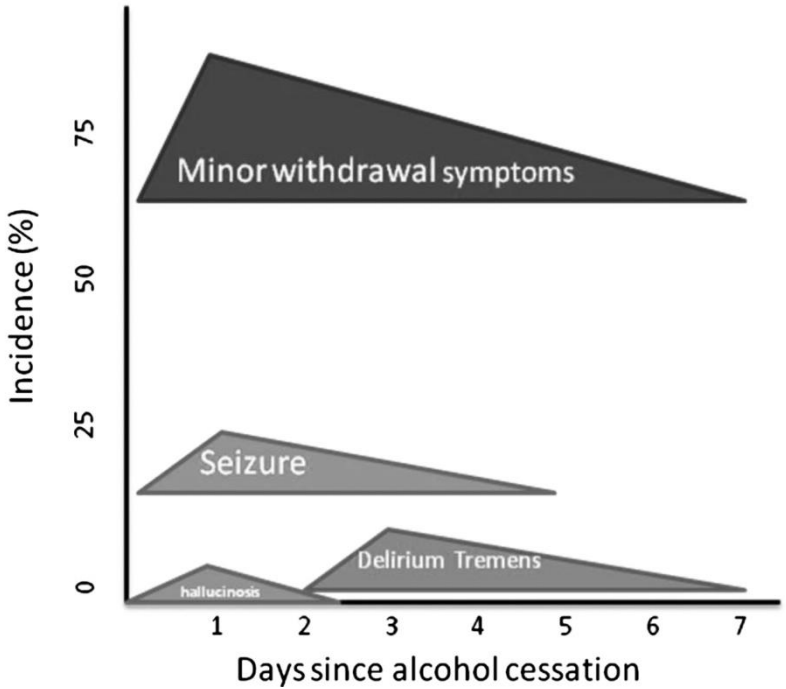
- Ethanol acts to **increase gamma aminobutyric acid (GABA)** receptor mediated inhibition
  - No specific binding site has been identified
  - May also reduce excitatory activity at N-methyl-D-aspartate (NMDA) receptors
- Long term alcohol intake results in *adaptive changes*
  - **↓ GABA receptors, ↓ GABA & sensitivity @ receptors**
  - **↑ NMDA receptors, ↑ sensitivity of Glutamate @ receptors**

Dignity Health.

Schmidt KJ et al. *Ann Pharmacother*. 2016.
Stehman CR et al. *Am J Emerg Med*. 2013.

Stages of Alcohol Withdrawal Symptoms

Stage	Time Sir Alcoholi	
1	6-2	nnia, Agitation, Anorexia, N/V
2	7-4	ual/auditory/tactile), eizures
3	49-9	mic Instability, e Agitation



Dignity Health.

Walker B et al. *J Trauma Acute Care Surg*. 2013.
Stehman CR et al. *Am J Emerg Med*. 2013.

Risk Assessment

- **AUDIT** (10 questions; 3 about quantity and frequency of drinking)
- **CAGE** (focuses on signs of impaired control, use of alcohol despite consequences)
- **Symptoms** (high risk – delirious, hx of withdrawal/seizures/DTs)

Monitoring Withdrawal Symptoms

- **CIWA-Ar (Clinical Institute Withdrawal Assessment)**
  - Most widely cited
  - **Not validated in the following populations**
    - **ICU patients**
    - **Non-communicative patients**
    - **Delirious patients/hx of alcohol withdrawal seizures**
- **MINDS (Minnesota Detoxification Scale)**
  - Limited published data
  - Targeted to ICU patients
  - **Not validated**

Sullivan JT et al. *J Clin Psychopharmacol*. 1991.
Jaeger TM et al. *Mayo Clin Proc*. 2001.
Stanely KM et al. *Pharmacotherapy*. 2003.
Reoux JP et al. *Am J Addict*. 2006.
Decarolis DD et al. *Pharmacotherapy*. 2007.

Alcohol Withdrawal Assessment Scoring Guidelines (CIWA - Ar)

Nausea/Vomiting - Rate on scale 0 - 7

0 - None
1 - Mild nausea with no vomiting
2
3
4 - Intermittent nausea
5
6
7 - Constant nausea and frequent dry heaves and vomiting

Tremors - have patient extend arms & spread fingers. Rate on scale 0 - 7.
0 - No tremor
1 - Not visible, but can be felt fingertip to fingertip
2
3
4 - Moderate, with patient's arms extended
5
6
7 - severe, even w/ arms not extended

Anxiety - Rate on scale 0 - 7
0 - no anxiety, patient at ease
1 - mildly anxious
2
3
4 - moderately anxious or guarded, so anxiety is inferred
5
6
7 - equivalent to acute panic states seen in severe delirium or acute schizophrenic reactions.

Agitation - Rate on scale 0 - 7
0 - normal activity
1 - somewhat normal activity
2
3
4 - moderately fidgety and restless
5
6
7 - paces back and forth, or constantly thrashes about

Paroxysmal Sweats - Rate on Scale 0 - 7.
0 - no sweats
1- barely perceptible sweating, palms moist
2
3
4 - beads of sweat obvious on forehead
5
6
7 - drenching sweats

Orientation and clouding of sensorium - Ask, "What day is this? Where are you? Who am I?" Rate scale 0 - 4
0 - Oriented
1 – cannot do serial additions or is uncertain about date

2 - disoriented to date by no more than 2 calendar days

3 - disoriented to date by more than 2 calendar days
4 - Disoriented to place and / or person

Tactile disturbances - Ask, "Have you experienced any itching, pins & needles sensation, burning or numbness, or a feeling of bugs crawling on or under your skin?"
0 - none
1 - very mild itching, pins & needles, burning, or numbness
2 - mild itching, pins & needles, burning, or numbness
3 - moderate itching, pins & needles, burning, or numbness
4 - moderate hallucinations
5 - severe hallucinations
6 - extremely severe hallucinations
7 - continuous hallucinations

Auditory Disturbances - Ask, "Are you more aware of sounds around you? Are they harsh? Do they startle you? Do you hear anything that disturbs you or that you know isn't there?"
0 - not present
1 - Very mild harshness or ability to startle
2 - mild harshness or ability to startle
3 - moderate harshness or ability to startle
4 - moderate hallucinations
5 - severe hallucinations
6 - extremely severe hallucinations
7 - continuous hallucinations

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
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

Pharmacotherapy

Dignity Health.

Goals of Treatment

- Provide symptomatic relief

- Prevent progression to more severe symptoms
  - i.e. delirium tremens, seizures

Treating Withdrawal Symptoms

- **GABA Receptor Agonists**
  - Benzodiazepines (lorazepam, diazepam, chlordiazepoxide)
  - Barbiturates (phenobarbital)
- **Adjunctive Agents**
  - Adrenergic symptoms
    - Clonidine, Dexmedetomidine, Ketamine
  - Delirium/Hallucinations
    - Antipsychotics (haloperidol)

Pharmacotherapy – Benzodiazepines

Benzodiazepines

- The foundation of alcohol withdrawal pharmacotherapy
- Mechanism
  - Function **allosterically** at GABA receptors **to enhance** GABA activity
    - Requires endogenous GABA to be present to be effective
- Lorazepam, diazepam, and chlordiazepoxide are the most commonly utilized agents
  - No study has shown clear superiority of one agent over another

Dignity Health.

Schmidt KJ et al. *Ann Pharmacother*. 2016.
Stehman CR et al. *Am J Emerg Med*. 2013.

Benzodiazepines

Drug	Onset	Half-life	Dosing	Metabolism
Lorazepam*	5-10 min	12 hrs	1-10 mg; repeat as needed every 10-15 min	Hepatic (*Inactive*)
Chlordiazepoxide	30-120 min	24-48 hrs	50-100 mg; repeat as needed up to 300 mg/24 hrs	Hepatic *(Active)*
Diazepam*	2-5 min	48 hrs	5-40 mg; repeat as needed every 5-15 min	Hepatic *(Active)*

*Contain propylene glycol

Schmidt KJ et al. *Ann Pharmacother*. 2016.

Benzodiazepines - Literature

- *Symptom triggered therapy (prn dosing)*
  - 1994 Saitz R *et al*. *JAMA* – Individualized treatment for AWS
    - **Reduced duration of treatment 9 hrs vs 68 hrs (p<0.001), < chlordiazepoxide use**
  - 2001 Jaeger TM *et al*. *Mayo Clin Proc* – Symptom triggered therapy for AWS in medical inpatients
    - **Decreased occurrence of delirium tremens 6.9 % vs 20.5 % (p=0.04)**
  - 2012 Cassidy EM *et al*. *Emerg Med J* – Symptom-triggered benzodiazepine therapy for AWS in the ED
    - **Reduced duration of treatment 2 days vs 3 days (p=0.006), < benzodiazepine use**

Saitz Ret al. *JAMA*. 1994.
Jaeger TM et al. *Mayo Clin Proc*. 2001.
Cassidy EM et al. *Emerg Med J*. 2012.

Benzodiazepines

- ***Symptom triggered therapy (prn dosing)***
  - Individualized therapy (CIWA-Ar scoring guided dosing)
  - Benefits may include:
    - Reduced benzodiazepine dosage and duration
    - Reduced ICU/hospital length of stay
    - Reduced need and duration for mechanical ventilation
- ***Fixed dose strategy (scheduled dosing)***
  - Worse patient outcomes in most studies

Stehman CR et al. *Am J Emerg Med*. 2013.
Schmidt KJ et al. *Ann Pharmacother*. 2016.

Pharmacotherapy – Phenobarbital

Dignity Health™

Phenobarbital

- Role in therapy is not well defined

- Mechanism
  - Function at GABA receptors, **independent** of GABA activity
    - **Does NOT require** endogenous GABA to be present to be effective

Dignity Health.

Stehman CR et al. *Am J Emerg Med*. 2013.

Phenobarbital

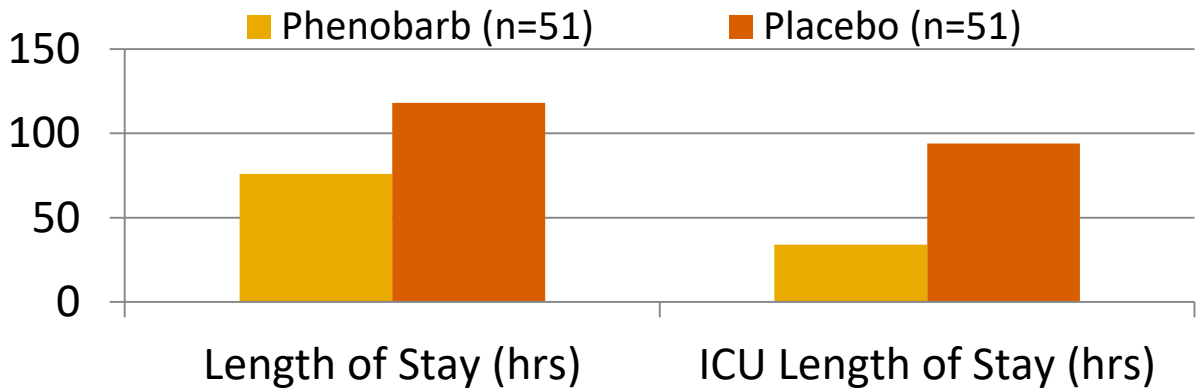
Onset	Half-life
5-10 min	50-120 hrs
Dosing	**Adverse Effects**
130-260 mg; repeat as needed every 15-60 min	Somnolence

Dignity Health

Stehman CR et al. *Am J Emerg Med*. 2013.

Phenobarbital – Literature

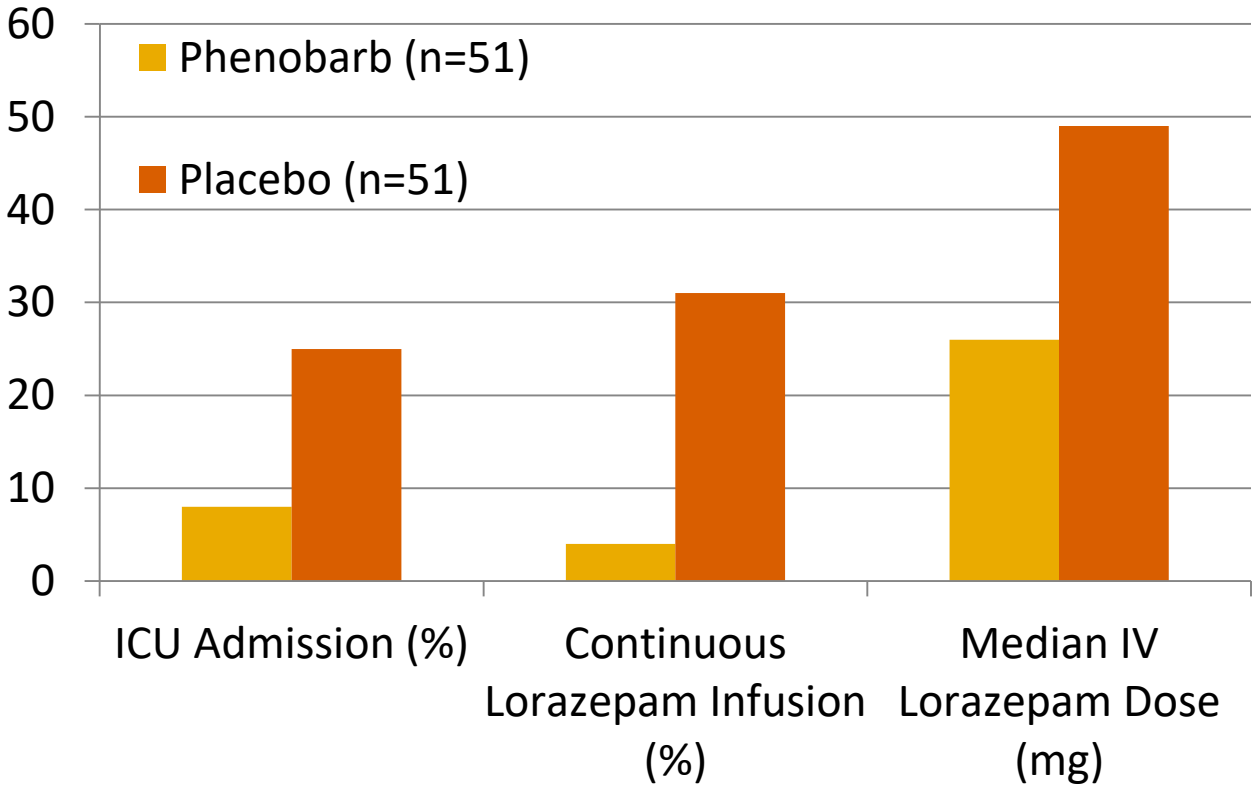
- Weight based phenobarbital in the ED
  - Prospective, randomized, double-blind placebo controlled study
    - All patients received hospital symptom triggered **lorazepam** protocol
      - Phenobarbital 10 mg/kg IV x 1 or placebo over 30 min



Dignity Health

Rosenson J et al. *J Emerg Med*. 2013.

Phenobarbital – Literature



Dignity Health.

Rosenson J et al. *J Emerg Med*. 2013.

Phenobarbital – Literature

- ICU patients admitted with AWS
  - Retrospective, single center study
    - *Pre-intervention* (n=60)
      - No protocolized care; typically scheduled or continuous infusion benzodiazepines
    - *Post-intervention (n=75)*
      - Protocolized care with escalating doses of diazepam and phenobarbital
      - Target RASS 0 to -2

Duby J et al. *J Trauma Acute Care Surg*. 2014.

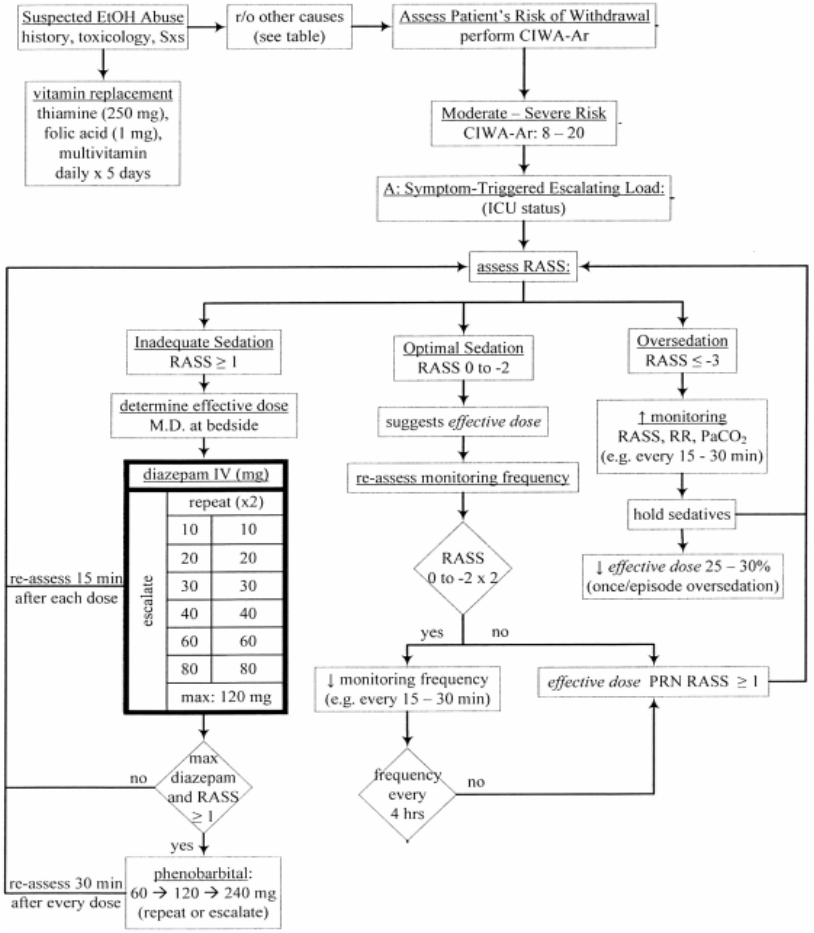


Figure 1. Alcohol withdrawal protocol based on a symptom-triggered, dose escalation approach using BZDs and phenobarbital. RASS is used for monitoring and administering sedation.

Duby J et al. *J Trauma Acute Care Surg*. 2014.

Phenobarbital – Literature

- 135 patients included in the study (50% MICU, 30% TSICU)

Outcom	tion	p-value
ICU Length of St (Days)		0.0004
Time on the ven (days)		<0.0001
Need for continu sedation (%)		<0.0001

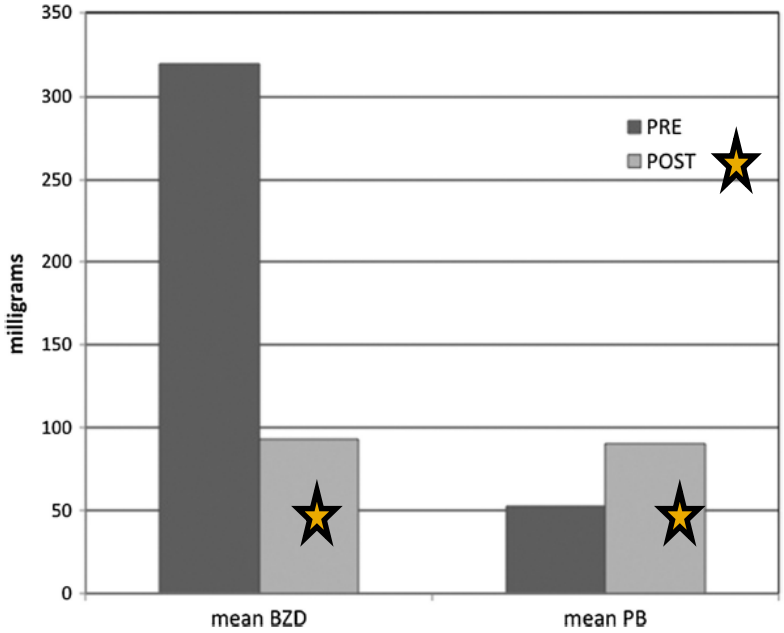


Figure 2. Mean BZD and PB use in both PRE and POST groups. Data are presented as mean (SD). *PB*, phenobarbital.

Dignity Health

Duby J et al. *J Trauma Acute Care Surg*. 2014.

Phenobarbital – Literature

- MICU patients admitted with severe AWS
  - Retrospective, single center study (n=86)
  - 130 mg IV every 15 min prn symptoms of withdrawal

- Mean total phenobarbital utilized during stay
  - **1977 mg ± 1531 mg = 25 mg/kg ± 17 mg/kg**

Dignity Health.

Oks J et al. *J Intensive Care Med* 2018.

Phenobarbital – Review of Dosing

- Dosing in studies as been highly variable

Study	Sample Size	Dosing
Gold et al. 2007	95	65 mg, 130 mg, 260 mg
Roseman et al. 2013	102	10 mg/kg IV x 1
Duby et al. 2014	135	60 mg, 120 mg, 240 mg
Gashlin et al. 2015	28	65 mg, 130 mg, 260 mg

Hammond DA et al. *Hosp Pharm*. 2017.

Phenobarbital – Review of Dosing

- Dosing in studies as been highly variable

Study	Sample Size	Dosing
Hendey et al. 2011	44	260 mg IV x 1, then 130 mg prn
Young et al. 1987	62	260 mg IV x 1, then 130 mg prn
Hjermo et al. 2010	194	100-200 mg PO or IV up to 4x/day
Rosenthal et al. 1998	42	60 mg 4x/day, then 60 mg 3x/day, then 60 mg 2x/day, then 30 mg daily
Mariani et al. 2006	21	60 mg 4x/day, then 60 mg 3x/day, then 60 mg 2x/day, then 30 mg BID, with 60 mg prn

Hammond DA et al. *Hosp Pharm*. 2017.

Phenobarbital – Summary

- Phenobarbital may have a role in AWS treatment along side of benzodiazepines, or as monotherapy
  - Benzodiazepine refractory AWS – Not clearly defined…
    - > 20-40 mg **lorazepam** in 1st 24 hrs OR > 100-200 mg **diazepam** in 1st 24 hrs
- May **improve outcomes** in patients with moderate to severe withdrawal
  - Less frequent ICU admissions
  - Decreased length of stay (ICU and Hospital)
  - Reduced duration of mechanical ventilation

Rosenson J et al. *J Emerg Med*. 2013.
Duby J et al. *J Trauma Acute Care Surg*. 2014.
Hammond DA et al. *Hosp Pharm*. 2017.
Oks J et al. *J Intensive Care Med* 2018.

Pharmacotherapy – Dexmedetomidine

Dignity Health™

Dexmedetomidine

- Role in therapy is not well defined
- Mechanism
  - Centrally acting alpha-2 adrenergic agonist
    - Blunts sympathetic outflow
      - In AWS, may reduce tremor, tachycardia, hypertension, anxiety, and agitation
- **Does NOT have activity at GABA receptors**
  - Does not treat the underlying pathophysiology of AWS
    - **Will not prevent seizures associated with severe AWS**

Dexmedetomidine - Literature

Study	Design	Number of Patients	Outcomes
Mueller et al. 2014	RTC, DB, PC	24	Less benzodiazepine use*
Bielka et al. 2015	RTC, DB, PC	72	Less benzodiazepine use*
VanderWeide et al. 2016	Retrospective	42	Less benzodiazepine use*

*More bradycardia was noted in the patients receiving dexmedetomidine

Linn DD et al. *Ann Pharmacother*. 2015.

Dexmedetomidine - Literature

Study	Design*	Number of Dexmedetomidine Patients
Tolonen et al. 2013	Prospective	18
Lizotte et al. 2014	Retrospective	34
Frazee et al. 2014	Retrospective	33
Crispo et al. 2014	Retrospective	28
Ludtke et al. 2015	Retrospective	15
Rayner et al. 2016	Retrospective	20

*Cohort studies

Linn DD et al. *Ann Pharmacother*. 2015.

Dexmedetomidine

- Role in therapy…..
  - Consider as an adjunct to benzodiazepines for patients in the ICU
    - Dosing
      - Per SJHMC hospital protocol: 0-1.4 mcg/kg/hr
        - **Consider modified dosing protocol: 0-0.5 mcg/kg/hr**
        - **Consider adding low dose scheduled benzodiazepine…?**
- Monitoring…
  - Heart rate, blood pressure, seizures

Pharmacotherapy – Ketamine

Dignity Health™

Ketamine

- Role in therapy is not well defined
- Mechanism
  - Inhibits NMDA receptors
    - In AWS, may reduce tremor, tachycardia, hypertension, anxiety, and agitation
- **Does NOT have activity at GABA receptors**
  - Unlike dexmedetomidine, it **DOES treat** the underlying pathophysiology of AWS

Ketamine - Literature

Study	Design	Number of Patients	Outcomes
Wong et al. 2015	Retrospective	23	Reduced benzodiazepine use
Shah et al. 2018	Retrospective	30	Reduced benzodiazepine use
Pizon et al. 2018	Retrospective	63	Reduced benzodiazepine use and ICU length of stay

Wong A et al. *Ann Pharmacother*. 2015.
Shah P et al. *J Med Tox*. 2018.
Pizon AF et al. *Crit Care Med*. 2018.

Ketamine - Dosing

2015 Wong et al.
- 0.2 mg/kg/hr for ~56 hrs

2018 Shah et al.
- 0.75 mg/kg/hr (max 1.6 mg/kg/hr) for ~54 hrs

2018 Pizon et al.
- 0.15-0.3 mg/kg/hr for ~48 hrs

Wong A et al. *Ann Pharmacother*. 2015.
Shah P et al. *J Med Tox*. 2018.
Pizon AF et al. *Crit Care Med*. 2018.

Ketamine

- Role in therapy…..
  - **Salvage** therapy for **benzodiazepine refractory withdrawal**
    - Dosing
      - Literature supports:
        - **Bolus: 0.3-0.5 mg/kg**
        - **Infusion: 0.15-0.3 mg/kg/hr x 24 to 72 hrs**
- Monitoring…
  - Heart rate, blood pressure, sedation

Pharmacotherapy – Haloperidol

Dignity Health.

Haloperidol

- Role in therapy is not well defined
- Mechanism
  - Inhibits postsynaptic dopaminergic D2 receptors in the brain
    - In AWS, may reduce agitation, hallucinations
- **Does NOT have activity at GABA receptors**
  - Does not treat the underlying pathophysiology of AWS
    - **Will not prevent seizures associated with severe AWS**

Haloperidol - Literature

- Data for AWS is extremely limited
- 1972 Palestine ML *et al*. *Quart J Stud Alc.*
  - **Haloperidol vs hydroxyzine or haloperidol vs mesoridazine**
  - **Rapid control of agitation and hallucinations with haloperidol**
- 1976 Blum K *et al*. *Clin Tox.*
  - **Mouse model: haloperidol vs saline and chlordiazepoxide vs saline**
  - **Increased seizures in the haloperidol group**

Palestine ML et al. *Quart J Stuf Alc*. 1972.
Blum K et al. *Clin Tox.* 1976.

Haloperidol

- Role in therapy…..
  - **Salvage** therapy for ongoing **refractory agitation/hallucinations**
    - Dosing – individualized for each patient
- Monitoring…
  - Sedation, QTc, Extrapyramidal Symptoms

Pharmacotherapy – “Banana Bag”

Dignity Health™

Banana Bags

- Rationale for ordering “banana bag” is to supplement essential vitamins and nutrients
- Components of traditional “banana bag”
  - 1 L of NS
  - 100 mg of Thiamine
  - 1 mg of Folic Acid
  - 10 mL of Multivitamin

Banana Bags

- Concern for Wernicke's Encephalopathy
  - Thiamine 200-500 mg IV every 8 hrs for 3 to 5 days
- Other components of the "banana bag"
  - Oral supplementation likely sufficient
  - Fluids should be individualized on case by case basis

Flannery AH et al. *Crit Care Med*. 2016.

Pharmacotherapy – Recap

Dignity Health™

Alcohol Withdrawal Pharmacotherapy Recap

- **Benzodiazepines –** 1st line agent
- **Phenobarbital –** 1st/2nd line agent at this time
- **Dexmedetomidine –** Refractory agitation
- **Ketamine –** Not ready for prime time
- **Haloperidol –** Salvage therapy for agitation/hallucinations
- **Banana Bag** – Little clinical utility

Questions?

Beyond Benzodiazepines for Severe Alcohol Withdrawal

John Radosevich, PharmD, BCCCP, BCPS
Clinical Pharmacy Specialist – Medical/Surgical/Trauma ICU
St. Joseph's Hospital and Medical Center
Phoenix, Arizona

February 15th, 2019

Dignity Health