Beyond Benzodiazepines: Alternative Management of Alcohol Withdrawal Syndrome in the ICU Population

A presentation for HealthTrust Members
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Disclosures

- The presenter and her preceptor have no financial relationships with any commercial interests pertinent to this presentation.

- This program may contain the mention of drugs or brands presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular supplier, brand or drug.

Abbreviations Glossary

- ADR = adverse drug reaction
- AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
- AWS = alcohol withdrawal syndrome
- CBZ = carbamazepine

=kl;

CIWA-Ar = Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised

- BZDs = benzodiazepines
- DEX = dexmedetomidine
- DTs = delirium tremens
- DZP = diazepam
- ED = emergency department
- EtOH = alcohol / ethanol
- GABA = gamma-aminobutyric acid
- ICU = intensive care unit
- LOS = length of stay
- NMDA = N-methyl-D-aspartate
- PB = phenobarbital
- PK/PD = pharmacokinetics/pharmacodynamics
- RCT = randomized controlled trial
- SAS = sedation agitation scale
- VPA = valproic acid
- WAS = withdrawal assessment scale

Pharmacist & Nurse Objectives

- Identify limitations of benzodiazepine therapy for the management of alcohol withdrawal syndrome (AWS)
- Describe outcomes found in literature to support the use of alternative agents for AWS
- Classify therapeutic options for AWS by level of available evidence

Pharmacy Technician Objectives

- List the common signs and symptoms of alcohol withdrawal syndrome
- Identify agents that have been studied as alternatives to benzodiazepines

Epidemiology

- Alcohol use disorder affects approximately 17 million adults in the United States
- Up to 25% of patients who are hospitalized develop AWS
- Uncontrolled AWS is associated with severe morbidity and mortality
  - Delirium tremens (DTs) carry ~15–25% mortality risk
  - Wernicke's encephalopathy
  - Other complications include need for mechanical ventilation, gastrointestinal bleeding, etc.

Source: Dixit D, et al. *Pharmacotherapy* 2016 Jul;36(7):797-822. doi: 10.1002/phar.1770. Epub 2016 Jun 30.

Alcohol Withdrawal Timeline

Stage 1
6–24h after last drink

- Headache
- Insomnia
- Diaphoresis
- Tremor
- Tachycardia
- Nausea, vomiting

Stage 2
7–48h after last drink

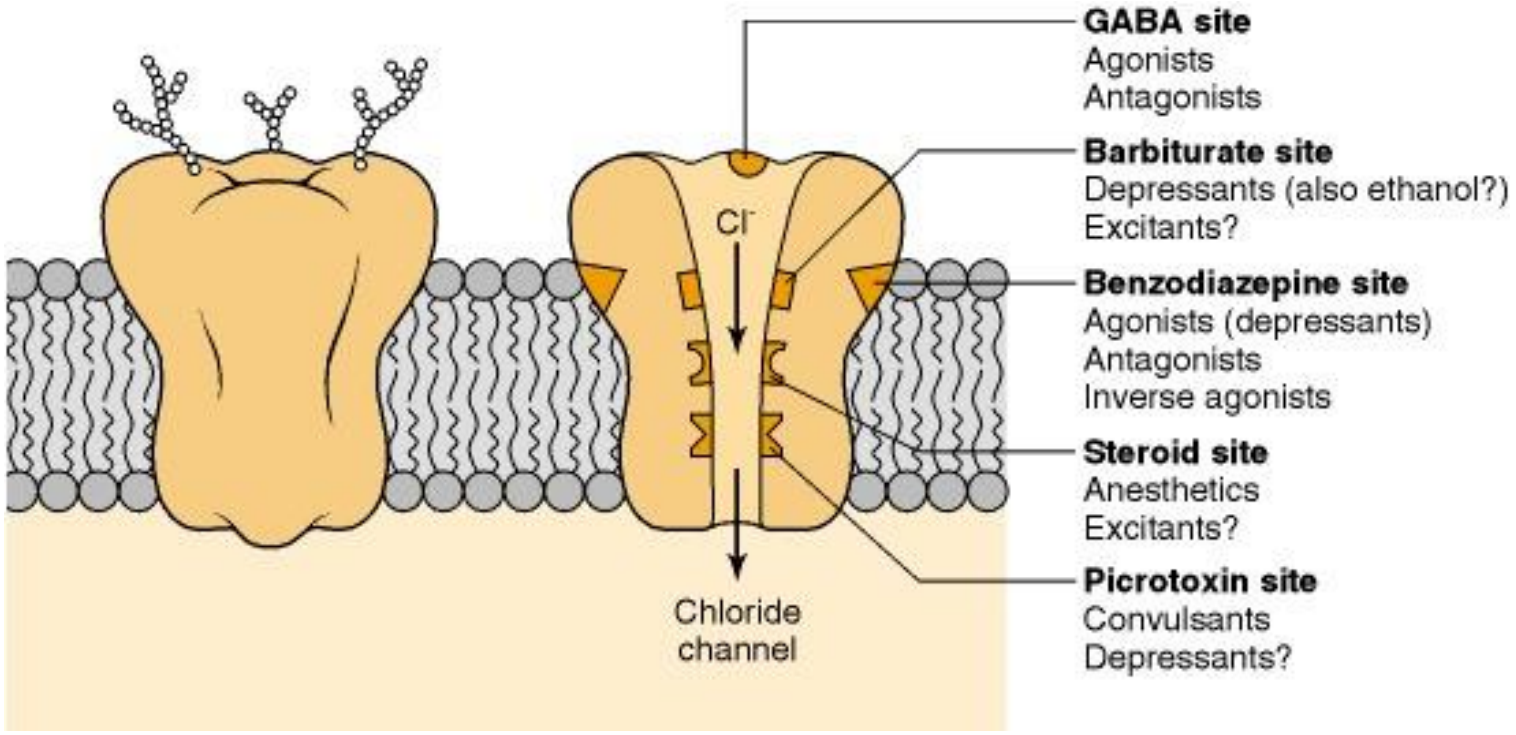
- Withdrawal seizures (10% of patients)
- Fever
- Increased blood pressure

Stage 3
49h to 1 week after last drink

- DTs
- Progressive hallucinations
- Progressive autonomic instability

Source: Dixit D, et al. *Pharmacotherapy* 2016 Jul;36(7):797-822. doi: 10.1002/phar.1770. Epub 2016 Jun 30.

The $GABA_A$ Receptor

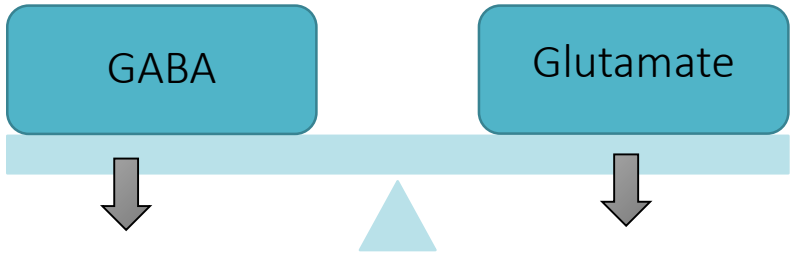


- Composed of α, β, γ subunits
- Allosteric binding sites on these subunits indirectly modulate receptor activity
- Opening of channel leads to influx of chloride which hyperpolarizes the postsynaptic membrane
- Ethanol binds to the $GABA_A$ receptor

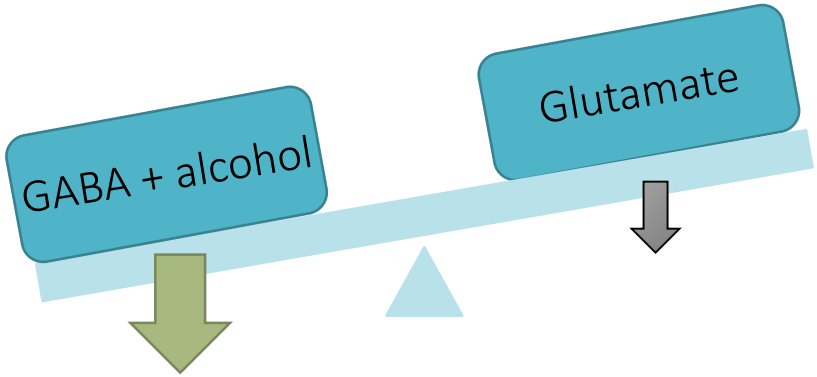
Source: Olsen RW. Basic Neurochemistry 6th Ed. Philadelphia: Lippincott-Raven; 1999.

Neurochemistry of Alcohol Withdrawal

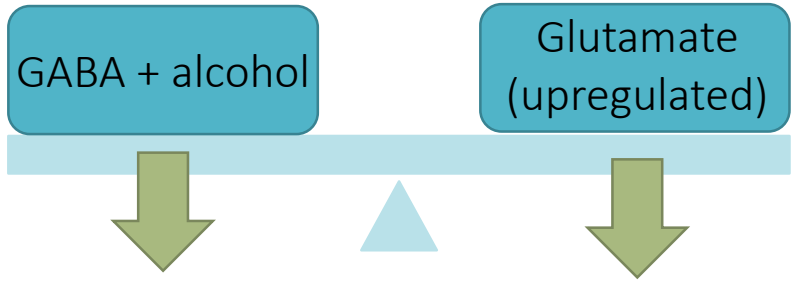
A. Homeostasis



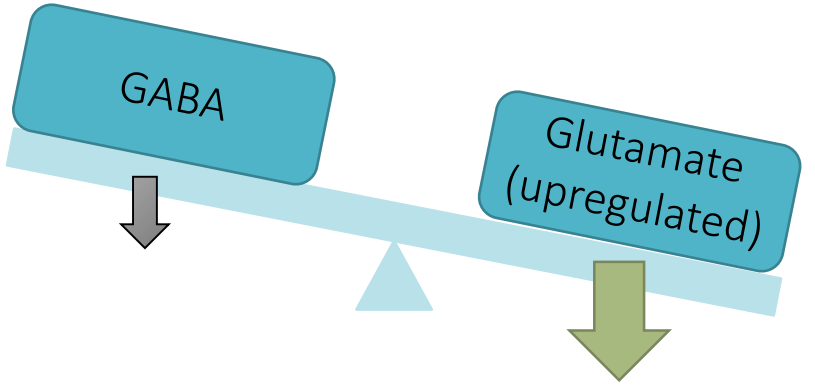
B. Acute intoxication



C. Chronic and Regular Use



D. Withdrawal after Chronic Use



Source: Kattimani S, Bharadwajlnd B. *Psychiatry J* 2013; 22(2): 100–108.

Benzodiazepines Used in AWS

	Duration	Dose Equivalent	Active metabolite	Formulation
Lorazepam	Intermediate acting	1 mg	None	IV, PO, IM
Diazepam	Long acting	5 mg	Yes	IV, PO, IM
Chlordiazepoxide	Long acting	10 mg	Yes	PO

Source: Benzodiazepine Comparison Table. In: Lexicomp.

Limitations of Benzodiazepines

- Tachyphylaxis
  - Chronic alcoholism downregulates GABA receptors an upregulates NMDA
  - Increased dose requirements over time

- In critically ill → worse patient outcomes
  - Longer ICU length of stay
  - Increased time on mechanical ventilation
  - Higher incidence and longer duration of delirium

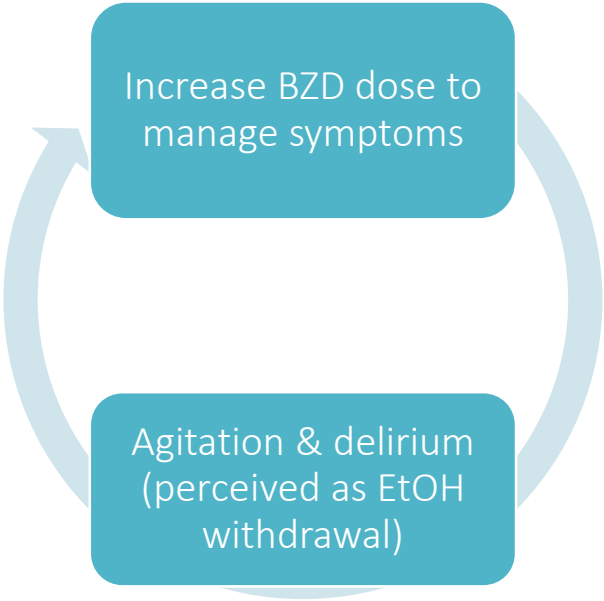
Source: Fraser GL, et al. *Crit Care Med* 2013;41(9 Suppl 1):S30-83.

Limitations of Benzodiazepines

Paradoxical excitation delirium: a vicious circle

Moore, et al., Safety and Efficacy of Flumazenil for Reversal of Iatrogenic Benzodiazepine-Associated Delirium Toxicity During Treatment of Alcohol Withdrawal

- N = 85
- Average time of flumazenil administration was 4.7 days
- 72.9 % of patients had significant objective improvement in cognition and behavior after receiving flumazenil



Source: Moore PW et al. *J Med Toxicol* 2014 Jun;10(2):126-32

Pharmacy Technician Question 1

Which of the following is NOT a sign of AWS?

A. Hallucinations
B. Rash
C. Sweating
D. Seizures

Pharmacy Technician Response 1

Which of the following is NOT a sign of AWS?

A. Hallucinations

B. Rash

C. Sweating

D. Seizures

Pharmacist & Nurse Question 1

Which of the following is (are) potential limitation(s) of using benzodiazepines at high doses and for prolonged periods of time in the intensive care unit?

A. Tachyphylaxis

B. Oversedation

C. Increased delirium incidence

D. All of the above

Pharmacist & Nurse Response 1

Which of the following is (are) potential limitation(s) of using benzodiazepines at high doses and for prolonged periods of time in the intensive care unit?

A. Tachyphylaxis

B. Oversedation

C. Increased delirium incidence

D. All of the above

A New Wave: Non-BZD Alternatives

- Phenobarbital
- Ketamine
- Dexmedetomidine
- Baclofen
- Propofol
- Gabapentin
- Valproic acid
- Carbamazepine

Source: : https://clarklittlephotography.com/products/memorial-day-panoramic?variant=16658253316

Phenobarbital

Mechanism:

- Acts on $GABA_A$ receptors to increase flow of chloride into channel
- Inhibits AMPA/kainite glutamate receptors
- Decreases post-synaptic excitability

Monitoring: Respiratory depression, hypotension, somnolence

Administration:

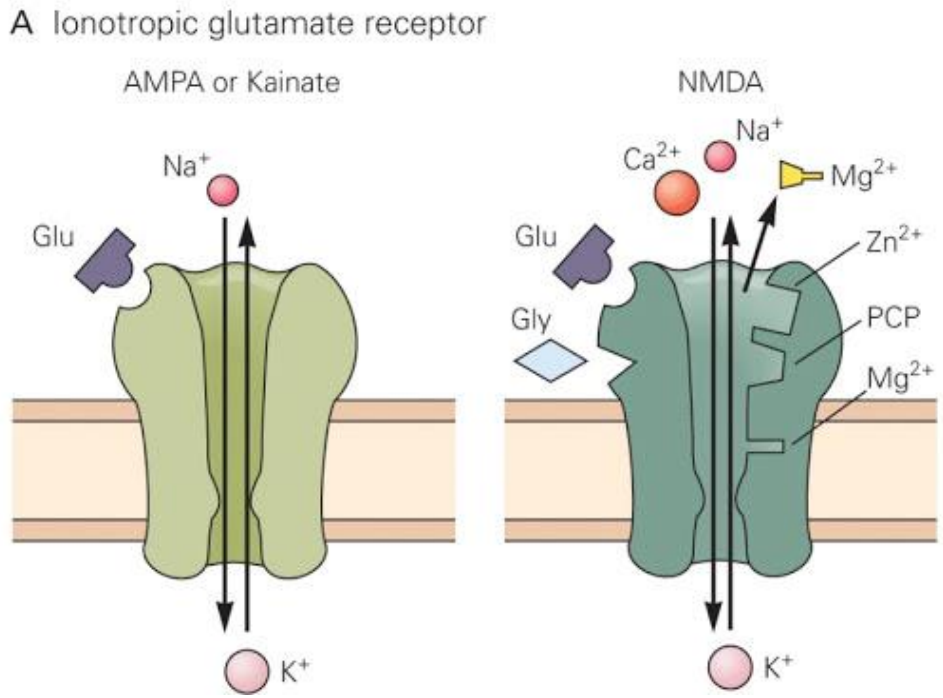
- IV, IM, PO
- Should not exceed 60 mg/min

Storage: Controlled substance

Drug Interactions: Strong CYP 3A4 inducer

PK/PD:

- Linear
- Onset- Oral: ≥60 minutes; IV: 5 minutes
- Long half-life; Duration- Oral: 10 to 12 hours; IV: >6 hours
- Hepatically metabolized



Source: Phenobarbital. In: Lexi-Drugs.

Phenobarbital

Rosenson, et al. 2013

- Prospective double-blind RCT of ED patients with AWS
- All patients were on symptom guided lorazepam protocol using CIWA-Ar
- Primary outcome: number of ICU admissions
- Randomized to receive a single dose of IV phenobarbital (N=51) vs. placebo (N=51)
  - 10 mg/kg in 100 mL normal saline infused over 30 min
  - Dosing weight was estimated by enrolling provider

- No baseline differences between groups
  - Study population primarily middle-aged men

- Background use of medications were documented and non statistically significant
  - fentanyl, hydromorphone, propofol, PO lorazepam, haloperidol

Source: Rosenson J, et al. *J Emerg Med* 2013;44:592-598.e2.

Phenobarbital

Rosenson, et al. 2013

Results

- **Early administration of a single dose of IV phenobarbital was associated with 17% difference in ICU admissions**
  - 8% vs. 25% [95% CI 4-32%] in the phenobarbital vs. placebo group
  - Median time to study drug administration, min (IQR): 144 (103-263) vs. 150 (100-264)
  - No difference in floor admissions, hospital LOS, or ICU LOS

- Reduced number of patients on continuous lorazepam infusion, n(%)
  - Median 42 (82%) vs. 49 (96%) in the phenobarbital vs. placebo group

- Rates of intubation did not differ between both groups, n(%)
  - Only one patient in each group

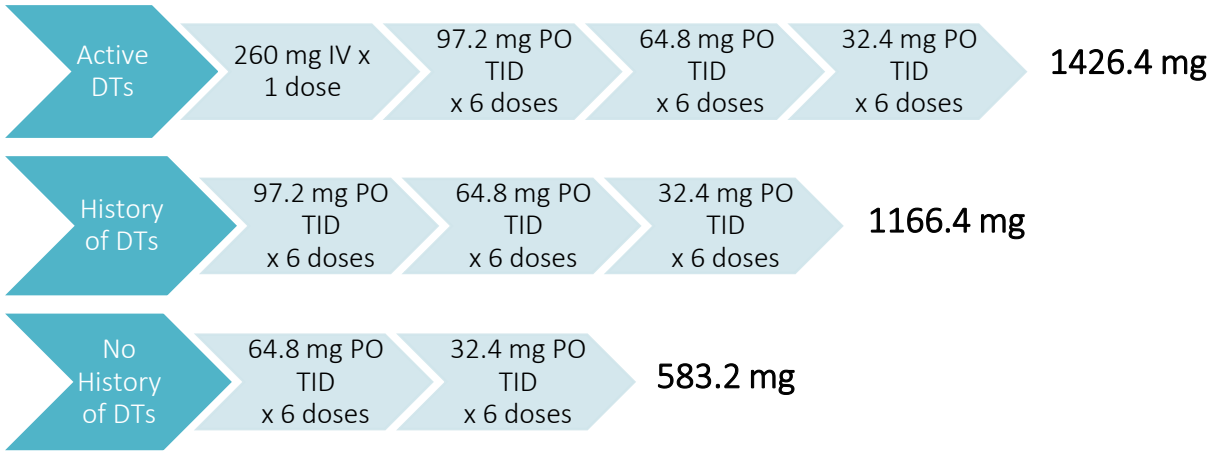
Source: Rosenson J, et al. *J Emerg Med* 2013;44:592-598.e2.

Phenobarbital

Tidwell, et al. 2018

- Retrospective cohort study (N =120)
- Compared patients with AWS who were managed with a phenobarbital protocol vs. patients managed with symptom triggered BZD therapy (CIWA-Ar)
- Primary outcome to evaluate LOS ICU

Phenobarbital Protocol, n= 60



Source: Tidwell WP. *Am J Crit Care* 2018;27(6):454-460.

CIWA-Ar Protocol, n= 60

CIWA-Ar Score*	Lorazepam Dose
5-9	1 mg IV q 4h
10-14	2 mg IV q 2h
15-19	3 mg IV q 1h
20-24	4 mg IV q 30 min
25-29	5 mg IV q 15 min
30-34	6 mg IV q 10 min
>35	6 mg IV x1 plus 4 mg/hr infusion titrating by 2 mg/hr q30min until score stabilizes or falls

* For stable or falling CIWA-Ar keep lorazepam dose same and decrease dosing interval to half (e.g. q 4h to q8h)

Phenobarbital

Tidwell, et al. 2018

- Baseline characteristics were similar between both groups
- Antipsychotic use (olanzapine, haloperidol, quetiapine) was not different between groups
- Results

Outcome	CIWA-Ar (n=60)	Phenobarbital (n=60)	P-value
ICU LOS, mean days (SD)	**4.4 (3.9)**	**2.4 (1.5)**	**<0.001**
Hospital LOS, mean days (SD)	6.9 (6.6)	4.3 (3.4)	0.004
Total lorazepam equivalents, mean mg (SD)	35.2 (48.5)	11.3 (18)	<0.001
Ventilator use, no. patients	14	1	<0.001
Dexmedetomidine use, no. patients	17	4	0.002

Source: Tidwell WP. *Am J Crit Care* 2018;27(6):454-460.

Phenobarbital

Oks, et al. 2018

- Retrospective observational study (N = 86), which evaluated intubated patients with AWS
- AWS defined as a CIWA score >15 in the ED
- Benzodiazepines were started in the ED
  - Average time to initiation of treatment: 1.0 ± 0.6 days
  - 74 of 86 patients received mean BZD equivalent dose 23 ± 25 mg
- Upon admission to the MICU phenobarbital was compared to placebo
  - Phenobarbital dose: 130mg IV every 15 minutes until RASS 0 to -1
  - Average time between hospital and ICU admission: 2.4 ± 1.2 days
  - Lorazepam-based CIWA protocol was continued in the phenobarbital group
- Patient characteristics

Mean Age	Mean IBW	•Mean initial CIWA-Ar score
• 49 years	• 70 kg	• 19

Source: Oks M, et al. *J Intensive Care Med* 2018 Jan; 1;885066618783947. Online ahead of print.

Phenobarbital

Oks, et al. 2018

- Lorazepam requirements were significantly less in the phenobarbital group
  - 4% of phenobarbital patients vs. 31% in the placebo group required continuous lorazepam infusion
- Seventeen patients (19.8%) required mechanical ventilation
  - 6 Obtundation with loss of airway clearance **before** phenobarbital administration
  - 6 GI bleed with hemodynamic instability ± airway needed for urgent endoscopy
  - 1 Seizure with loss of airway protection
  - 1 Aspiration pneumonia preceding MICU admission
  - 1 Cardiac arrest
  - 1 COPD with hypercarbic respiratory failure
  - 1 Progressive hepatic encephalopathy

Could be related to phenobarbital use, but likely a result of comorbidities instead

- All patients who were intubated were exposed to BZDs
- **Phenobarbital was not associated with increased adverse events compared to placebo**

Cumulative Phenobarbital Dose

Mechanically ventilated vs. not:

2075 ± 2184 mg vs. 1954 ± 1344 mg

P =0.96

Source: Oks M, et al. *J Intensive Care Med* 2018 Jan; 1;885066618783947. Online ahead of print.

Phenobarbital

Advantages

- Long half life and balanced GABA agonism + glutamate antagonism
- Well defined linear kinetics
- No active metabolites
- Available IV, PO, IM
- Years of experience in other countries

- Variety of dosing strategies
- Potential for drug interactions
- Risk for respiratory depression, although this may be perceived as more common than studies have shown

Disadvantages

Phenobarbital Considerations

- Titrate to CIWA or RASS?
- What is the ideal dose of phenobarbital? Fixed dose?
- Is therapeutic drug monitoring required?
- Is a taper required following stabilization of symptoms on a dose?
- What patients may NOT benefit from phenobarbital?

Ketamine

- **Mechanism:** NMDA receptor antagonist and mild agonism on opioid mu receptors
  - Shown in other literature to have opioid sparing properties

- **Administration:** Dose dependent effects
  - Sub-anesthetic “pain dose” typically ~ 0.1 to 0.5 mg/kg/hr
  - Anesthesia and dissociation typically induced when infusion ≥ 1-1.5 mg/kg/hr

- **Monitoring:** Respiratory depression, hallucinations, psychosis, hypertension, secretions
- **Storage:** Controlled substance

Source: Ketamine. In: Lexi-Drugs.

Ketamine

Wong, et al. 2015

- First study evaluating of ketamine for BZD sparing properties in AWS

- Ketamine was initiated in patients with either significant BZD requirements or DTs
  - Mean time to ketamine administration was 33.6 hours
  - Only 34.8% of patients had a primary diagnosis of AWS

- Mean ketamine initial infusion dose and median total infusion rate was relatively low
  - 0.21 mg/kg/hr and 0.20 mg/kg/hr

- 38.1% of patients received ketamine loading dose

- Mean duration of ketamine therapy 55.8 ± 30.5 hours

Source: Wong A, et al. *Ann Pharmacother* 2015;49:14-19.

Ketamine

Wong, et al. 2015

- Median change in sedation scores after ketamine initiation
  - WAS +1.0 (-4.5 to +2.0) ; SAS +1.0 (0 to +2.0)
  - CIWA not reported

- Median BZD requirements (diazepam equivalents)

Prior to initiation of ketamine	• 170 mg (100 to 500 mg)
Change in 12 hours pre→ post ketamine administration	• -40 mg (-106.7 to +21.7 mg)
Change in 24 hours pre→ post ketamine administration	• -13.3 mg (-86.7 to +50 mg)

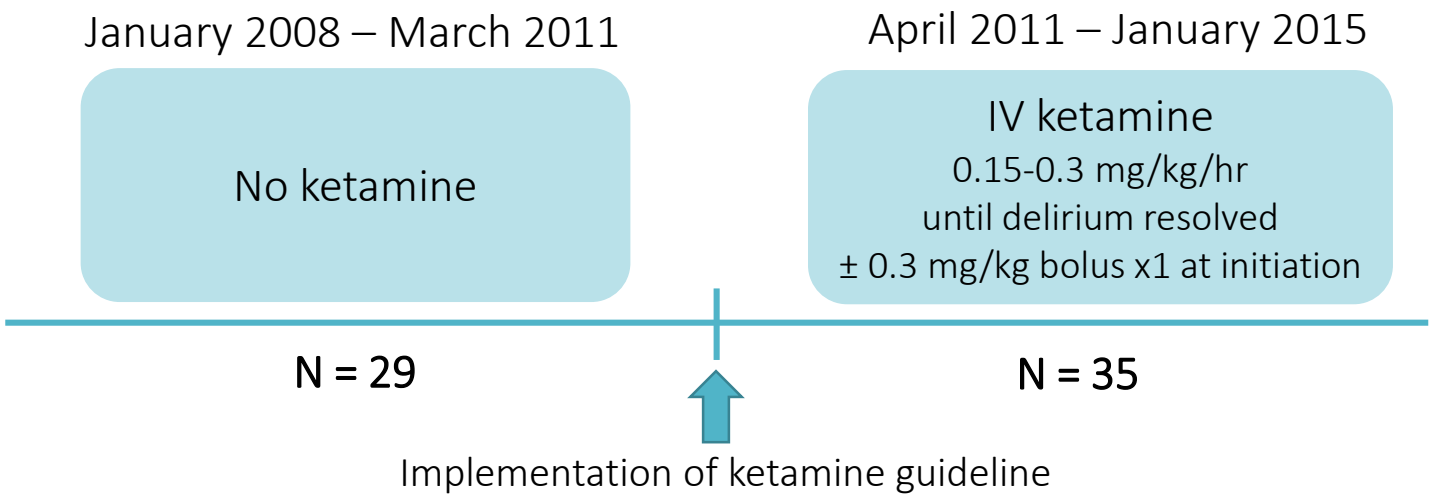
- Conclusion: Ketamine decreased amount of short-term BZDs used without changing level of sedation

Source: Wong A, et al. *Ann Pharmacother* 2015;49:14-19.

Ketamine

Pizon, et al. 2018

- Retrospective cohort study at the University of Pittsburgh
- Ketamine implemented for use as **adjunct** to GABA agonist therapy



Source: Pizon A. *Crit Care Med* 2018.

Ketamine

Pizon, et al. 2018

	No ketamine (n = 29)	Ketamine (n = 34)
Mean BZD dose, mg diazepam equivalents	2525.1	1508.5
Dexmedetomidine use, n	3	9
Mean dexmedetomidine time, days	2.33	1.77
Propofol use, n	20	9
Mean propofol time, days	4.57	2.4

Bolded outcomes were statistically significant

- Mean ICU LOS decreased by 2.83 days after ketamine guideline (11.2 vs. 5.7, p =0.043)
- Mean hospital LOS decreased by 4.1 days after ketamine guideline (16.6 vs. 12.5, p =0.03)
- 76% vs. 29% of patients were intubated in pre- and post- guideline implementation groups
    - BZD use among patients who were intubated was significantly less in the ketamine group
    - 3016.1 mg vs. 833.6 mg

Source: Pizon A, et al. *Crit Care Med* 2018;46(8):e768-e771.

Ketamine

Pizon, et al. 2018

Limitations:

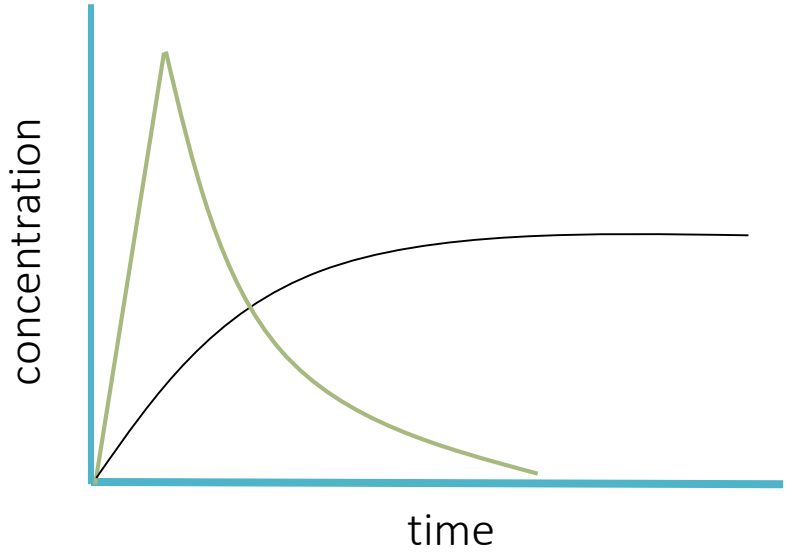
- No comparison of severity of illness between two groups
  - If ketamine patients less ill at baseline than outcomes could be significantly affected?
  - Potentially affected by advancements in critical care over 8 years

- Small sample size revealed trends that were not statistically significant groups
  - Dexmedetomidine use objectively increased from 3 to 9 patients – any impact on outcomes?

Source: Pizon A, et al. *Crit Care Med* 2018;46(8):e768-e771.

Ketamine Considerations

- Bolus dose or no bolus dose?
- What is the optimal timing of ketamine administration?
- Balancing efficacy with ADRs
  - Interpatient variability in thresholds for efficacy and neuropsychiatric effects



Dexmedetomidine

- **Mechanism:** α_2 agonist

- **Monitoring:** bradycardia, hypotension, hypertension, constipation
  - Potential for withdrawal after prolonged infusions (>24h) especially at high doses
  - Characterized by hypertension, tachycardia, agitation, nausea, vomiting

- **Administration:** titrate no more frequently than every 30 minutes to minimize hypotension

- **Storage:** NOT a controlled substance

Source: Dexmedetomidine. In: Lexi-Drugs.

Dexmedetomidine

Mueller, et al. 2014 and Bielka, et al. 2015

Comparison of two randomized controlled trials evaluating dexmedetomidine (DEX) effect on BZD requirements

Mueller	Bielka
24 ICU patients	72 ICU patients
Patients on lorazepam CIWA randomized to: 1. Low dose dexmedetomidine (0.4 mcg/kg/hr) 2. High dose dexmedetomidine (1.2 mcg/kg/hr) 3. Placebo	Patients receiving 10mg diazepam PRN symptoms randomized to: 1. Dexmedetomidine (0.2-1.4 mcg/kg/hr) 2. Placebo
24h pre → post lorazepam requirement lower in DEX group	24h diazepam consumption lower in DEX group
• Trial excluded 209 patients over 4 years	• Cumulative diazepam dose throughout ICU LOS was low ○ 60 vs. 90 mg over 50 – 70h median ICU LOS

How clinically relevant is reduction in BZD use as an outcome for dexmedetomidine?

Source: Mueller S, et al. *Crit Care Med* 2014;42(5):1131-1139.
Bielka K, et al. *Ann Intensive Care* 2015; 5(33):1-7.

Dexmedetomidine Considerations

- Can ONLY be used as adjunct – no effect on GABA / glutamate
- α_2 agonism decreases sympathetic output to help with symptom control
- Dexmedetomidine also associated with withdrawal symptoms
- Dose limiting ADR - bradycardia

Pharmacist & Nurse Question 2

Which of the following is true regarding dexmedetomidine when used for AWS?

A. Can be used as monotherapy or as an adjunct to benzodiazepines for AWS

B. Decreases short term benzodiazepine requirements in the ICU

C. Prevents seizures associated with ethanol withdrawal

D. Suppresses respiratory drive when used in combination with benzodiazepines

Pharmacist & Nurse Response 2

Which of the following is true regarding dexmedetomidine when used for AWS?

A. Can be used as monotherapy or as an adjunct to benzodiazepines for AWS

B. Decreases short term benzodiazepine requirements in the ICU

C. Prevents seizures associated with ethanol withdrawal

D. Suppresses respiratory drive when used in combination with benzodiazepines

Pharmacy Technician Question 2

Which of the following agents has not been discussed as an alternative to management of AWS:

A. Amantadine
B. Phenobarbital
C. Dexmedetomidine
D. Ketamine

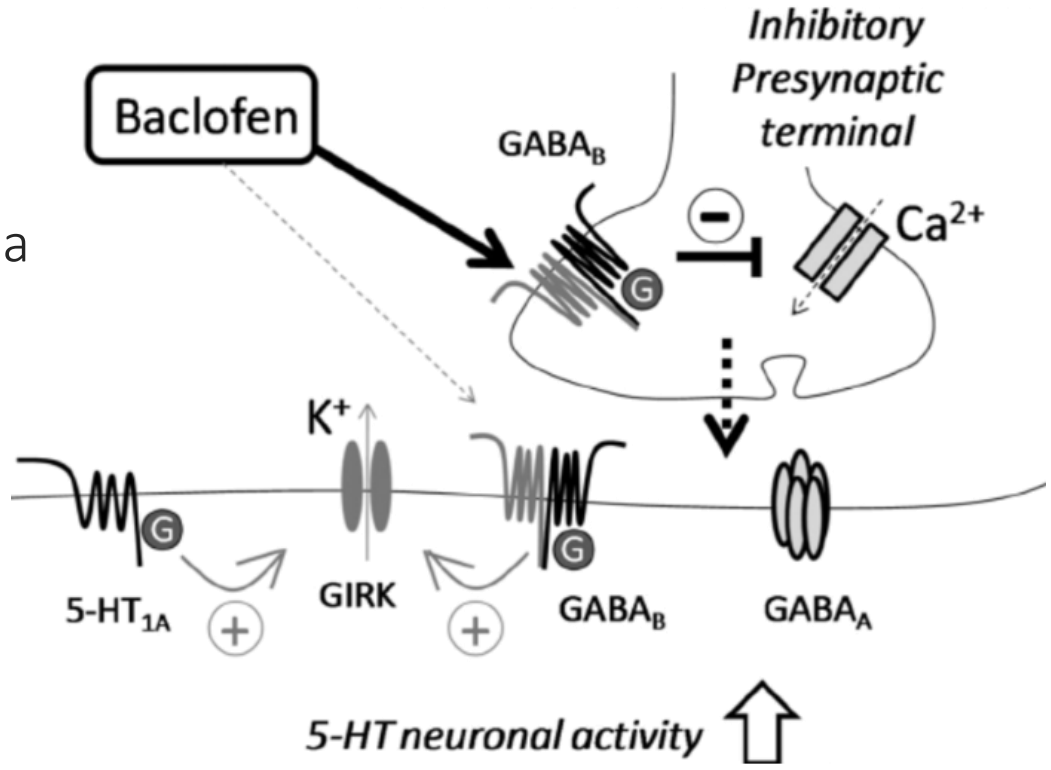
Pharmacy Technician Response 2

Which of the following agents has not been discussed as an alternative to management of AWS:

A. Amantadine
B. Phenobarbital
C. Dexmedetomidine
D. Ketamine

Baclofen

- **Mechanism**: $GABA_B$ agonist
- **Monitoring**: hypotonia, drowsiness, confusion, nausea
- **Administration**: oral only
  - Typical dosing: 5-10 mg TID
- **Storage**: NOT a controlled substance
- **PK/PD:** time to peak is 1 hour



Source: Baclofen. In: Lexi-Drugs.

Baclofen

Lee, et al.

- Abstract presented at CHEST annual meeting 2018
- Local retrospective observational study at Baylor University evaluating 23 patients receiving adjunctive baclofen for AWS
- 16 of 23 patients responded to baclofen use (69.57%)
  - Defined as decrease in benzodiazepine use
  - Numerical decrease in benzodiazepine use (-18.41 ± 19.67 mg BZD equivalents) but not statistically significant
  - 81.3% of patients who responded had CIWA protocol discontinued within 24h of treatment with baclofen

	24 hours before baclofen	24 hours after baclofen	
Mean BZD equivalents in all patients	20.61 ± 22.16	13.63 ± 19.98	
Mean peak CIWA score	21.95 ± 8.53	11.27 ± 9.00	*p = 0.006*

Source: Lee J, et al. *Chest* 2018; 154(4): Supplement 825A.

Baclofen

To be published- BACLOREA trial

- N=314 Double blind RCT study protocol published, pending results
- Enrolled mechanically ventilated patients with AWS in 12 ICUs in France
- **Baclofen vs. placebo** with dosing guided by creatinine clearance
- **Primary outcome**: restlessness-related side effects
  - Unplanned extubation
  - Removal of any catheters, lines, drains, restraints
  - Falling out of bed
  - Leaving ICU against medical advice
  - Aggression towards self or staff

- **Secondary outcomes**: duration of mechanical ventilation, ICU LOS, cumulative doses of sedatives and analgesics received within 28 days of ICU admission

Source: clinicaltrials.gov/ct2/show/NCT02723383

Pharmacist & Nurse Question 3

Which of the following non-benzodiazepine alternatives has randomized controlled data to support its use for AWS? Select all that apply.

A. Dexmedetomidine
B. Ketamine
C. Phenobarbital
D. Baclofen

Pharmacist & Nurse Response 3

Which of the following non-benzodiazepine alternatives has randomized controlled data to support its use for AWS? Select all that apply.

A. Dexmedetomidine
B. Ketamine
C. Phenobarbital
D. Baclofen

Other Agents: Propofol

- **Mechanism**: Global CNS depression via decreasing rate of GABA dissociation (→hyperpolarization); antagonist at NMDA receptors
- **Monitoring**: hypotension, triglycerides
- Preferred over midazolam infusion for ICU sedation including AWS
- Provides deeper level of sedation than dexmedetomidine
- Use is limited to intubated patients
- Quick on/off sedation, rapid titration

Source: Propofol. In: Lexi-Drugs.

Other Agents: Gabapentin

- **Mechanism**: GABA analog; but does not bind to GABA receptor or affect uptake/production of GABA
- One inpatient study of N=37 (non-ICU) found gabapentin 800mg PO helpful to reduce CIWA scores in less severe, uncomplicated AWS
- May reduce alcohol cravings
- Oral only
- Renally cleared

Source: Bonnet U. *Alcohol Alcohol* 2010;45(2):143-145.

Other Agents

Valproic Acid

- **Mechanism**: Blocks voltage dependent sodium channels
  - *Effects on GABA not completely understood*- may cause increased availability of GABA, enhance the action of endogenous GABA, or mimic its action at postsynaptic sites
- Two RCTs
  1. Divalproex sodium 500mg PO TID reduced BZD requirements
  2. Comparison of valproic acid, carbamazepine, and placebo in N=138
     - *Seizure rate: 2.2 % VPA vs. 4.7 % CBZ vs. 6.1 % placebo*
     - *DTs rate: 4.4 % VPA vs. 0 % CBZ vs. 2% placebo*
- Some evidence outside of AWS for decreased duration of ICU delirium

Carbamazepine

- Mechanism: Blocks voltage dependent sodium and calcium channels
  - *Effects on alcohol withdrawal and mood not well understood*
- All studies were underpowered to detect differences in seizures or DTs

Source: Hammond J. *CNS Drugs* 2015; 29(4):293-311.

Suggested Role in Therapy

Benzodiazepines	Drug of choice for AWS in most treatment settings
Phenobarbital	May be considered as an alternative to BZDs for monotherapy or as adjunct in refractory AWS with high BZD requirements. Avoid in hepatic dysfunction or cirrhosis and use caution when combined with other agents that suppress respiratory drive
Ketamine	Adjunct to reduce BZD requirements; caution in patients with underlying psychiatric disorders and uncontrolled hypertension
Dexmedetomidine	Adjunct to reduce BZD requirements; provides light sedation; avoid in bradycardia
Baclofen	May decrease BZD requirements; evidence is limited at this time
Propofol	Sedative of choice in intubated patients with AWS
Anticonvulsants (gabapentin, valproic acid, carbamazepine)	Limited evidence; may decrease probability of seizures, reduce cravings, do not appear to have abuse potential, effectively treat mood disorders

Conclusion

- Current mainstay of therapy for AWS is benzodiazepines, which have limitations especially in the ICU patient population.
- There are potential alternatives to benzodiazepines that may be used as monotherapy or as adjunctive therapy.
- Literature supports a multimodal approach to managing AWS has improved outcomes such as lowering BZD requirements and ICU length of stay.

References

1. Dixit D, Endicott J, Burry L, et al. Management of Acute Alcohol Withdrawal Syndrome in Critically Ill Patients. *Pharmacotherapy* 2016 Jul;36(7):797-822. doi: 10.1002/phar.1770. Epub 2016 Jun 30.
2. Olsen RW, DeLorey TM. GABA Receptor Physiology and Pharmacology. In: Siegel GJ, Agranoff BW, Albers RW, et al., editors. Basic Neurochemistry: Molecular, Cellular and Medical Aspects. 6th edition. Philadelphia: Lippincott-Raven; 1999.
3. Kattimani S and BharadwajInd B. Clinical management of alcohol withdrawal: A systematic review. *Psychiatry J* 2013; 22(2): 100–108.
4. Bird RD and Makela EH. Alcohol Withdrawal: What is the Benzodiazepine of Choice? *Ann Pharmacother* 1994;28(1):67-71.
5. Fraser GL, Devlin JG, Worby CP, et al. Benzodiazepine Versus Nonbenzodiazepine-Based Sedation for Mechanically Ventilated, Critically Ill Adults: A Systematic Review and Meta-Analysis of Randomized Trials. *Crit Care Med* 2013;41(9 Suppl 1):S30-8.
6. Moore PW, Donovan JW, Burkhart K, et al. Safety and Efficacy of Flumazenil for Reversal of Iatrogenic Benzodiazepine-Associated Delirium Toxicity During Treatment of Alcohol Withdrawal, a Retrospective Review at One Center. *J Med Toxicol* 2014 Jun;10(2):126-32.
7. Phenobarbital. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com. Accessed June 1, 2020.
8. Rosenson J et al. Phenobarbital for acute alcohol withdrawal: a prospective randomized double-blind placebo-controlled study. J Emerg Med 2013;44:592-598.e2.
9. Tidwell WP, Thomas TL, Pouliot JD, et al. Treatment of alcohol withdrawal syndrome: phenobarbital vs CIWA-AR protocol. *Am J Crit Care* 2018;27(6):454-460.
10. Oks M, Cleven CL, Healy L, et al. The Safety and Utility of Phenobarbital Use for the Treatment of Severe Alcohol Withdrawal Syndrome in the Medical Intensive Care Unit. J Intensive Care Med 2018 Jan; 1;885066618783947. Online ahead of print.
11. Ketamine. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com. Accessed June 1, 2020.

References

12. Wong A, Benedict N, Armahizer M, et al. Evaluation of adjunctive ketamine to benzodiazepines for management of alcohol withdrawal syndrome. *Ann Pharmacother* 2015;49:14-19.

13. Pizon A, Lynch M, Benedict N, et al. Adjunct Ketamine Use in the Management of Severe Ethanol Withdrawal. *Crit Care Med* 2018;46(8):e768-e771.

14. Dexmedetomidine. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com. Accessed June 1, 2020.

15. Mueller S, Preslaski C, Kiser T, et al. A randomized, double-blind, placebo-controlled dose range study of dexmedetomidine as adjunctive therapy for alcohol withdrawal. *Crit Care Med* 2014;42(5):1131-1139.

16. Bielka K, Kuchyn I, and Glumcher F. Addition of dexmedetomidine to benzodiazepines for patients with alcohol withdrawal syndrome in the intensive care unit: a randomized controlled study. *Ann Intensive Care* 2015; 5(33):1-7.

17. Baclofen. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com. Accessed June 1, 2020.

18. Lee J, Kramer C, Daoud Y, et al. Adjunctive baclofen therapy for alcohol withdrawal in critically ill patients. *Chest* 2018; 154(4): Supplement 825A.

19. Vourc'h M, Feuillet F, Mahe PJ, et al; BACLOREA trial group. Baclofen to prevent agitation in alcohol-addicted patients in the ICU: study protocol for a randomised controlled trial. *Trials* 2016 Aug 19;17(1):415. doi: 10.1186/s13063-016-1539-2. NCT02723383.

20. Propofol. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com. Accessed June 1, 2020.

21. Bonnet U, Hamvazi-Abedi Reza, Specka M, et al. An Open Trial of Gabapentin in Acute Alcohol Withdrawal Using an Oral Loading Protocol. *Alcohol Alcohol* 2010;45(2):143-145.

22. Hammond CJ, Niciu MJ, Drew S, et al. Anticonvulsants for the treatment of alcohol withdrawal syndrome and alcohol use disorders. *CNS Drugs* 2015; 29(4):293-311.

Thank You!

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