Here's the Buzz: Management of Moderate to Severe Alcohol Withdrawal Syndrome with Phenobarbital

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Faculty Disclosure

The author of this presentation has nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of the presentation.

Objectives

- Outline the pathophysiology and historical treatment of alcohol withdrawal syndrome
- Illustrate opportunities to use phenobarbital for management of moderate to severe alcohol withdrawal syndrome

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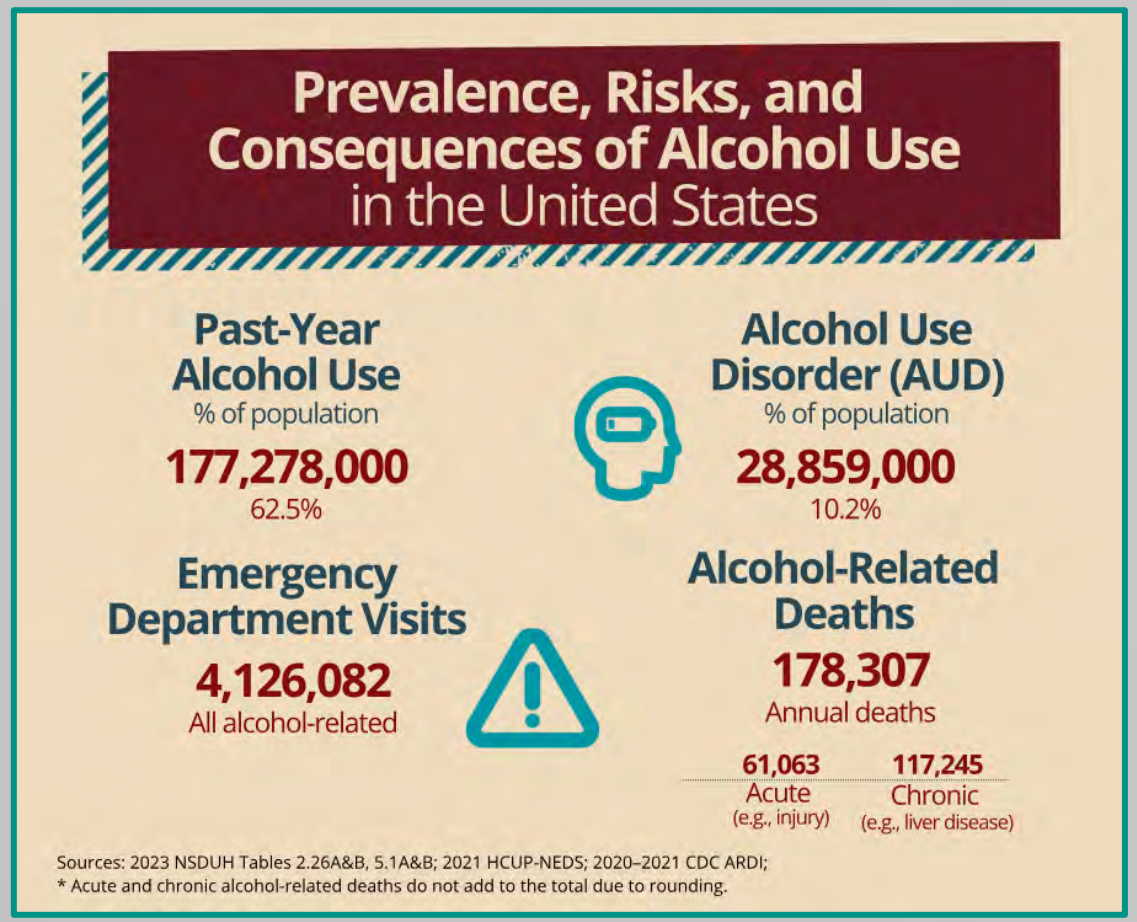
Epidemiology

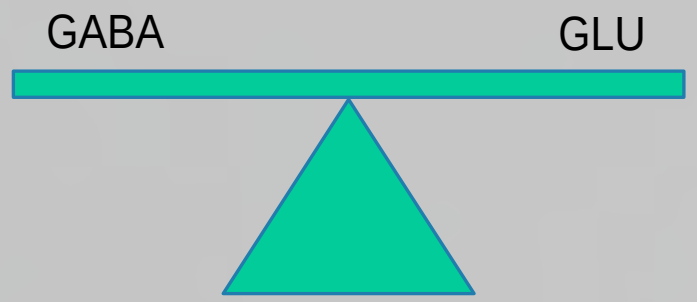


- Alcohol is among the most used drug around the world and the most used in the United States
- Alcohol Use Disorder is the most common type of substance use disorder in the United States
- Up to 25% of patients hospitalized with AUD develop acute AWS
- Mortality may be as high as 15% if untreated compared to 2% who are treated

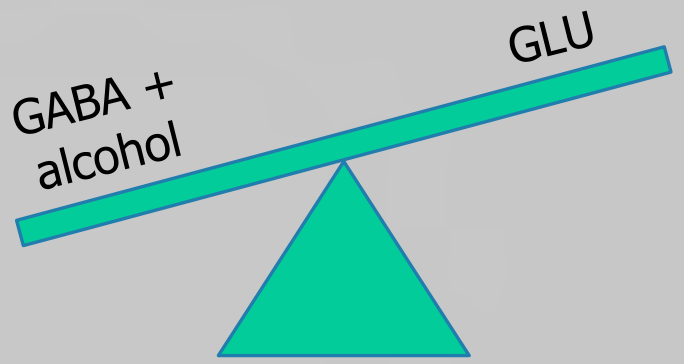
SAMHSA. 2023 NSDUH. Table 2.26A&B.
SAMHSA. 2021 NSDUH. Table 5.1A&B.

AWS: alcohol withdrawal syndrome

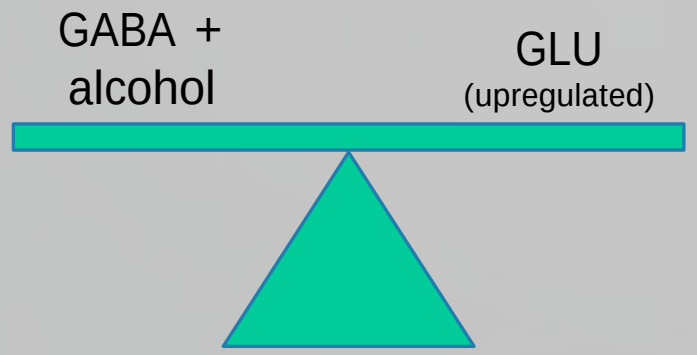
Physiologic Effects of Alcohol



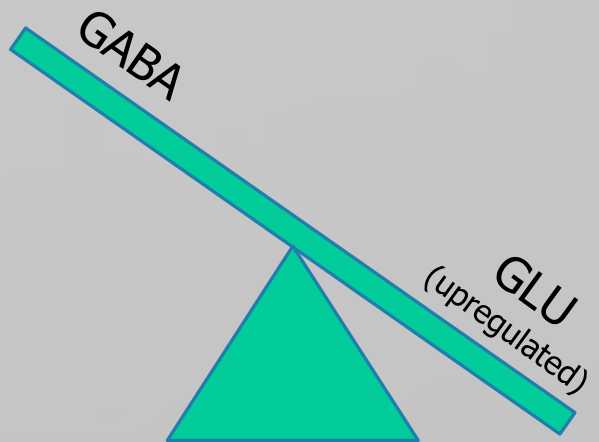
Homeostasis



Acute ingestion



Chronic ingestion

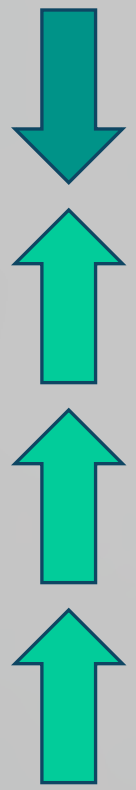


Acute withdrawal

Pharmacother. 2016;36(7):797-822.
Crit Care Clin. 2012;28:549-85.

GABA: gamma amino butyric acid
GLU: glutamate

Physiologic Changes in AWS



GABA receptors and GABA activity

NMDA receptors and glutamate activity

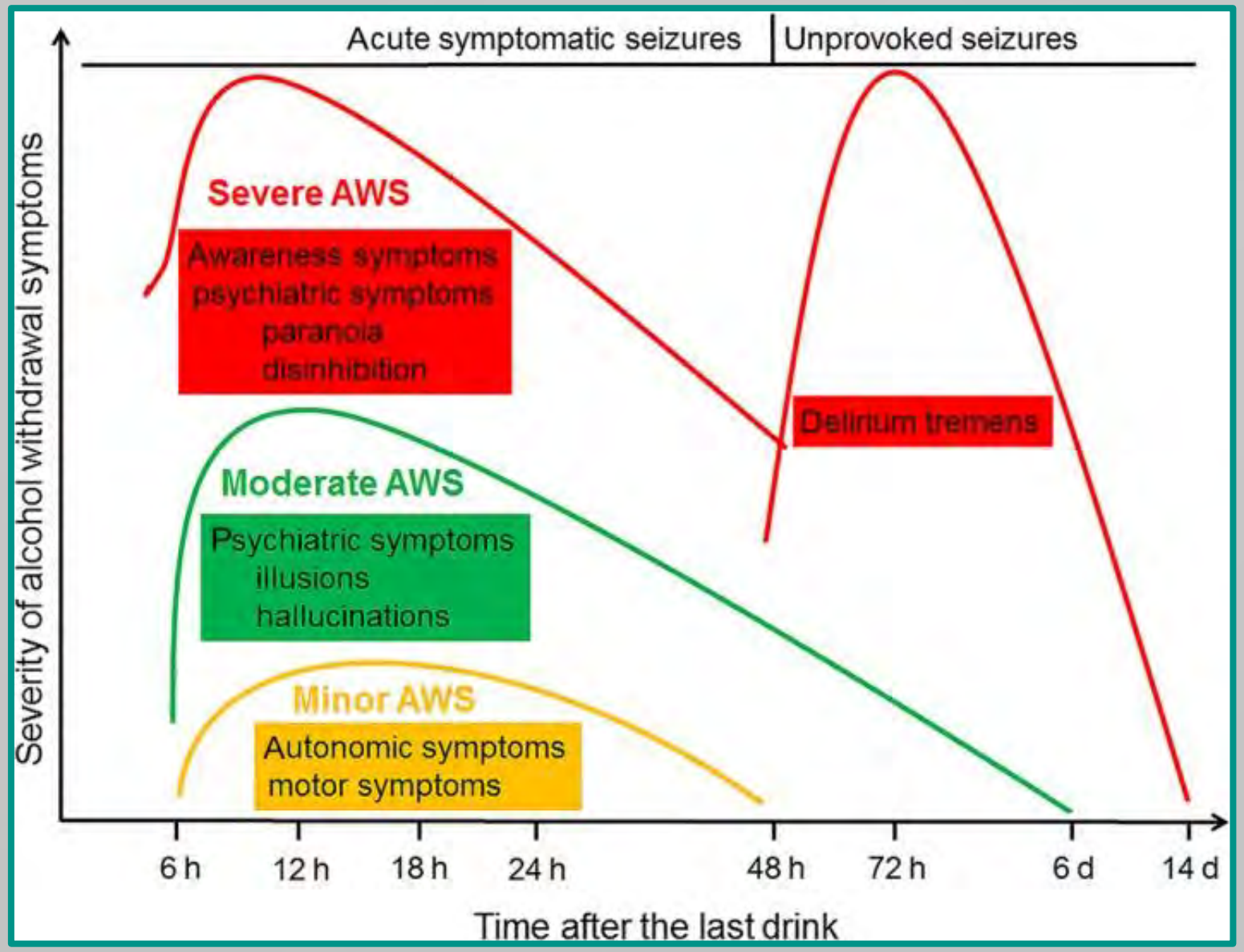
Dopaminergic system and dopamine release

Noradrenergic system and catecholamine release

Pharmacother. 2016;36(7):797-822.
Crit Care Clin. 2012;28:549-85.

AWS: alcohol withdrawal syndrome
GABA: gamma amino butyric acid
NMDA: N-methyl-D-aspartate

Time Course of AWS



Acta Neurol Scand. 2017;135:4-16.

AWS: alcohol withdrawal syndrome

The Birth of Benzodiazepines in AWS

- Population: 537 patients with AWS
- Intervention: chlordiazepoxide vs chlorpromazine vs hydroxyzine vs thiamine
- Comparator: placebo
- Outcome: delirium and seizure rates

	Chlordiazepoxide (n=103)	Chlorpromazine (n=98)	Hydroxyzine (n=103)	Thiamine (n=103)	Placebo (n=130)
Delirium	1%	7%	4%	4%	8%
Seizures	1%	12%	8%	7%	9%

Benzodiazepines are superior to non-GABAergic medications

Am J Psychiatry. 1969;125(12):1640-46.

AWS: alcohol withdrawal syndrome
GABA: gamma amino butyric acid

But What's the Buzz?

"Phenobarbital is an appropriate alternative for providers experienced with its use"

Recommendation IV.18: Patients experiencing severe, but not complicated, alcohol withdrawal (e.g., CIWA-Ar ≥ 19) may be treated in ambulatory Level 2-WM settings at the discretion of providers with extensive experience in management of alcohol withdrawal. Such patients should receive pharmacotherapy. Benzodiazepines are first-line treatment. Phenobarbital is an appropriate alternative for providers experienced with its use. For patients with a contraindication for benzodiazepine use, phenobarbital, carbamazepine, or gabapentin are appropriate. The use of adjunct medications is also appropriate.

Phenobarbital is an appropriate alternative in Level 2-WM setting for providers experienced with its use. For patients with a contraindication for benzodiazepine use, phenobarbital (in Level 2-WM settings by providers experienced with its use) or transfer to a more intensive level of care are appropriate options.

Recommendation V.17: Patients experiencing severe alcohol withdrawal (e.g., CIWA-Ar scores ≥19) should receive pharmacotherapy. Benzodiazepines are first-line treatment. For patients with a contraindication for benzodiazepine use, phenobarbital is appropriate for providers experienced with its use. If close monitoring is available, phenobarbital can be used as an adjunct to benzodiazepines. Other adjunct medications can be considered after a clinician ensures that an adequate dose of benzodiazepines has been administered.

J Addict Med. 2020 Sep/Oct;14(5):e280.

But What's the Buzz?

"Phenobarbital is an appropriate alternative for providers experienced with its use"

However, phenobarbital has a number of side effects including bradycardia, bradypnea, hypothermia, hypotension, pulmonary edema, acute renal failure and Steven-Johnson syndrome. It has a half-life of up to seven days, is primarily metabolized by the liver and induces many isoenzymes of the P450 system. This coupled, with a relatively narrow therapeutic window, caused it to fall out of favor in the 1960's as chlordiazepoxide and oxazepam were shown to be as effective, but harbor a much lower risk. Now we have solid

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- Illustrate opportunities to use phenobarbital for management of moderate to severe alcohol withdrawal syndrome

Ideal Properties of Phenobarbital

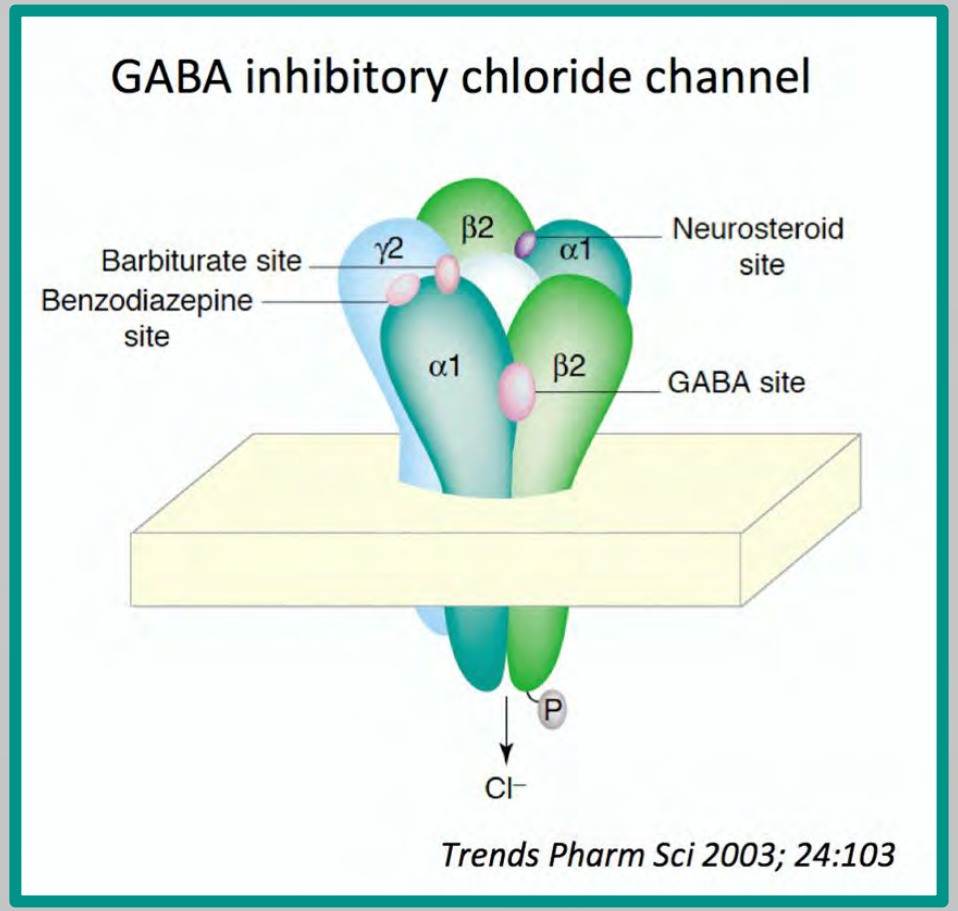
No GABA reliance

Degree of lipophilicity

Long duration

Limited misuse potential

Dual mechanism of action



Pharmacother. 2016;36(7):797-822.
Goldfrank's Toxicologic Emergencies, 11e Eds. McGraw Hill, 2019.

GABA: gamma amino butyric acid

Administration Considerations

- Population
- Dose
- Route of Administration
- Administration Time Frame
- Safety

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Select Populations

- **Moderate Disease**
  - CIWA-Ar 10-18
- **Severe or Complicated Disease**
  - CIWA-Ar ≥ 19
- **Benzodiazepine resistance**
  - Unique mechanism of action
- **Risk Factors for Severe Disease**
  - Multiple considerations

Pharmacother. 2016;36(7):797-822.
Ann Pharmacother. 2021;55(12):1515-24.

CIWA-Ar: Clinical Institute Withdrawal Assessment Alcohol Scale Revised

Risk Factors For Severe Disease

- History of alcohol withdrawal seizures or delirium
- Numerous prior withdrawal episodes
- Comorbid medical or surgical illness
- Age > 65 years
- Prolonged duration of heavy and regular alcohol consumption
- Seizures during current episode
- Physiologic dependence on GABAergic agents

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Dosing Strategies

Early Use

Bolus + Fixed/Escalated Dosing

260 mg IV followed by 65-130 mg IV every 15-30 minutes

→ Decreased benzodiazepine requirements

Novel Approach

Higher Dose, Front-loaded Dosing

10 mg/kg IV over 30 minutes

→ Decreased benzodiazepine requirements, occurrence of mechanical ventilation, and ICU admissions

Ann Emerg Med. 1987;16:847-50.
Ann Pharmacother. 2021;55(12):1515-24.

ICU: intensive care unit
IV: intravenous

Administration Considerations

- Population
- Dose
- **Route of Administration**
- Administration Time Frame
- Safety

Route of Administration

Oral or intramuscular

Intravenous

Quick onset

Predictable PK/PD

Single dose

Accessibility

Administration access

PD: pharmacodynamics
PK: pharmacokinetics

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Administration Time Frame

Early in disease course

- Reduce benzodiazepine use
- Reduce risk of respiratory depression
- Prevent progression of withdrawal
- Reduce health system burden and costs
- Reduce morbidity and mortality

Ann Pharmacother. 2021;55(12):1515-24.
J Emerg Med, 2013. 44(3): p. 592-598 e2

Administration Considerations

- Population
- Dose
- Route of Administration
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- Safety

Safety

Drug Interactions

- Strong CYP450 inducer
- Anticoagulants
- Immunosuppressants
- Midazolam

Adverse Effects

- Respiratory depression
- Over-sedation
- Skin reactions
- Hepatotoxicity

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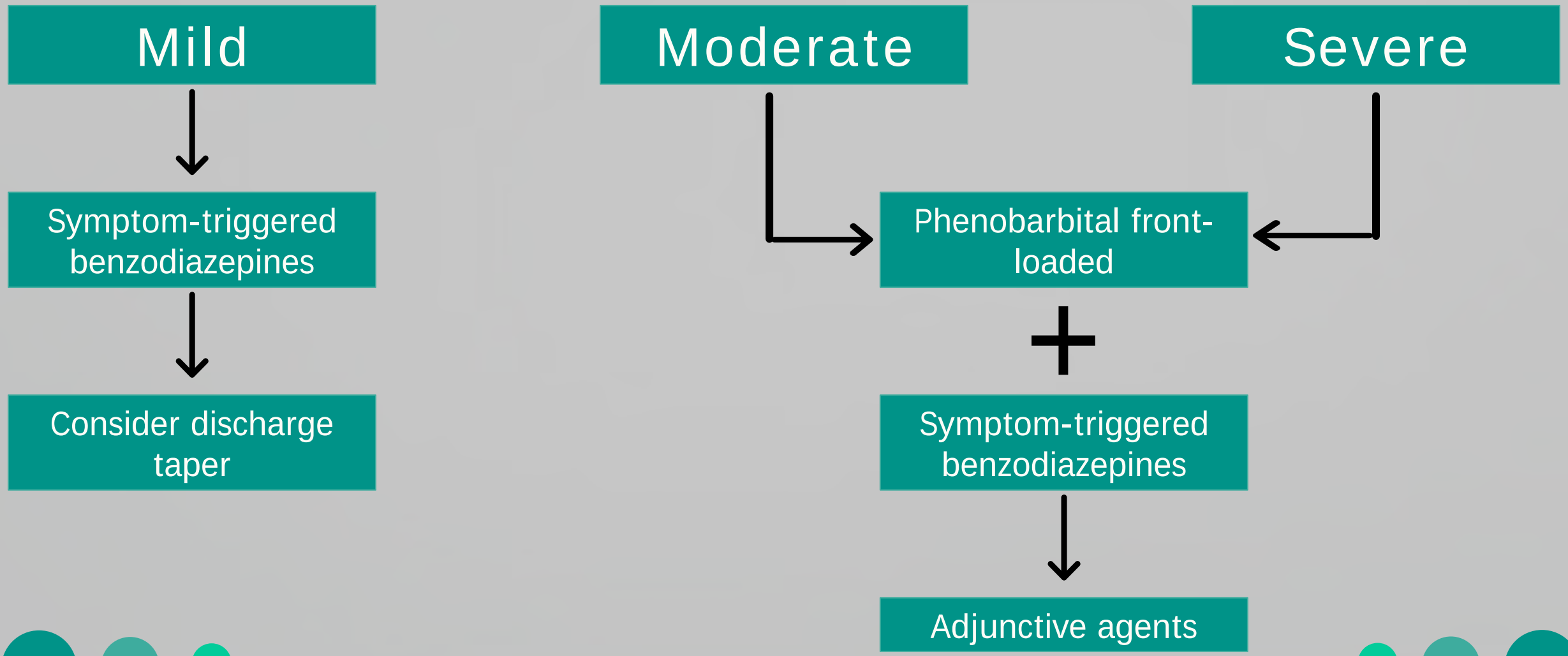
Proposed Algorithmic Approach



Conclusion

- Several pathophysiologic changes occur with AWS with benzodiazepines serving as the backbone of therapy
- Front-loaded, intravenous phenobarbital administration is safe and effective for moderate to severe alcohol withdrawal
- Pharmacists play a crucial role in appropriate use, dose, and administration techniques of phenobarbital

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