Updates in the Pharmacotherapy of Alcohol Withdrawal Management in the Outpatient and Inpatient Settings

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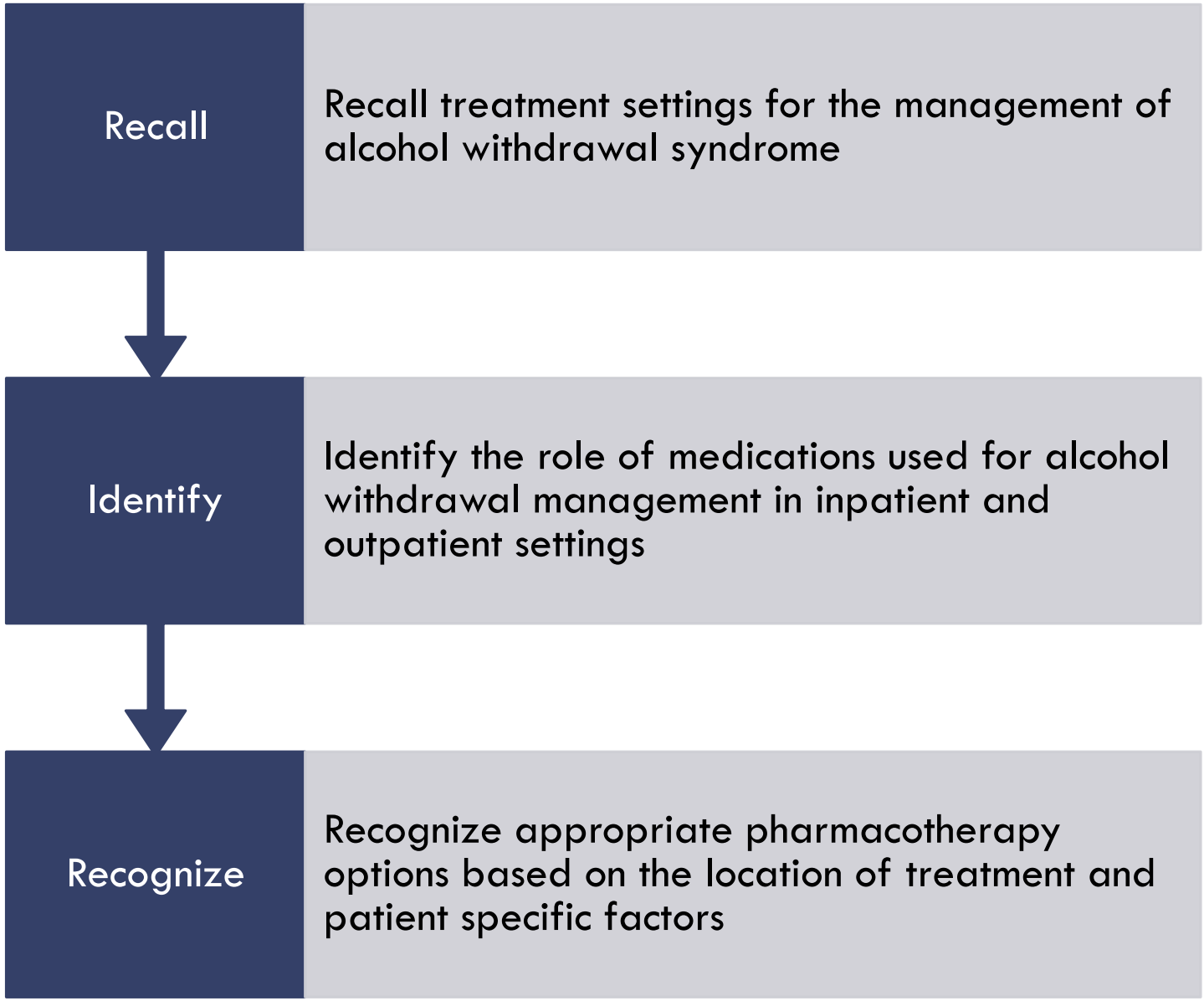
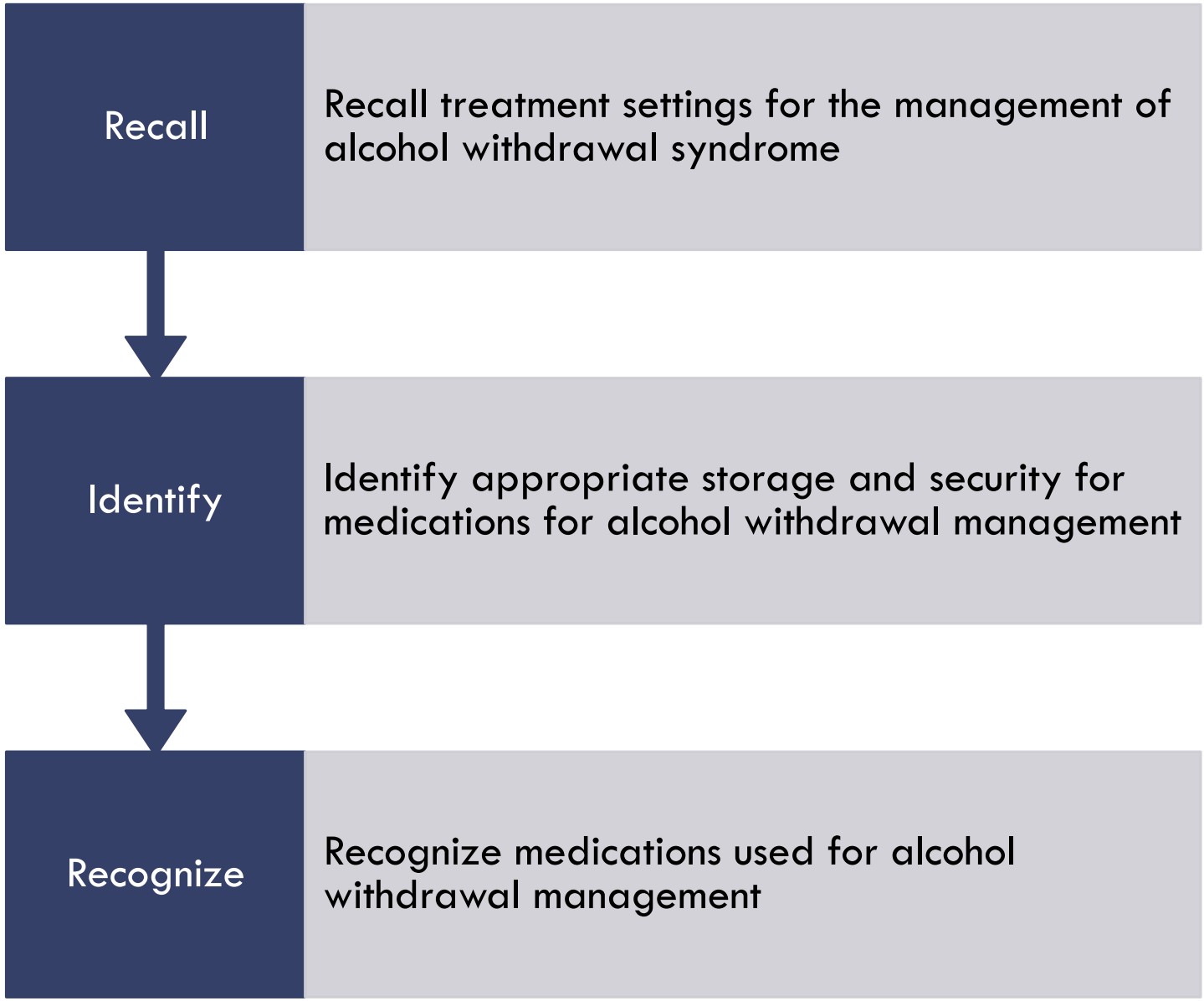
Objectives for Pharmacists and Nurses



Objectives for Pharmacy Technicians



Abbreviations

ASAM	American Society of Addiction Medicine	GABA	Gamma-aminobutyric acid
AUD	Alcohol Use Disorder	IM	Intramuscular
AWS	Alcohol Withdrawal Syndrome	IV	Intravenous
BID	Twice a day	NICE	National Institute for Health and Care Excellence
BZD	Benzodiazepine	NMDA	N-methyl-D-aspartate
CAR	Carbamazepine	PACS	Penn Alcohol Craving Scale
CI	Confidence interval	PAWSS	Prediction of Alcohol Withdrawal Severity Scale
CIWA-Ar	Clinical Institute Withdrawal Assessment Alcohol Scale Revised	PB	Phenobarbital
CNS	Central nervous system	PO	By mouth
DDI	Drug-drug interaction	QD	Daily
DT	Delirium tremens	QID	Four times a day
ER	Extended-release	SE	Side effect
ESS	Epworth Sleepiness Scale	TID	Three times a day
GAB	Gabapentin	WM	Withdrawal management

Purpose

- New guideline from ASAM (2020) that replaces the following guidelines:
  - Pharmacological Management of Alcohol Withdrawal (1997)
  - Management of Alcohol Withdrawal Delirium (2004)

- Addresses several practice concerns related to alcohol withdrawal treatment:
  - Use of BZDs as the mainstay of treatment as research on other agents have emerged
  - Treatment in outpatient settings which has become increasingly common
  - Uncertainty about the CIWA-Ar since it may not fit all patient populations and settings

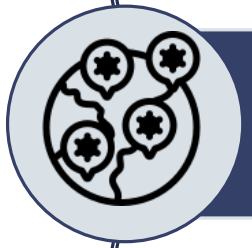
Wong J, et al. *J Addict Med*. 2020;14(3S Suppl 1):1-72.
Mayo-Smith MF, et al. *Arch Int Med*. 2004;164(13):1405-1412.

ASAM: AMERICAN SOCIETY OF ADDICTION MEDICINE, BZD: BENZODIAZEPINE, CIWA-AR: CLINICAL INSTITUTE WITHDRAWAL ASSESSMENT ALCOHOL SCALE REVISED

Background

AWS Overview

AWS occurs after a significant decrease or abrupt cessation of heavy or prolonged drinking in patients with AUDs

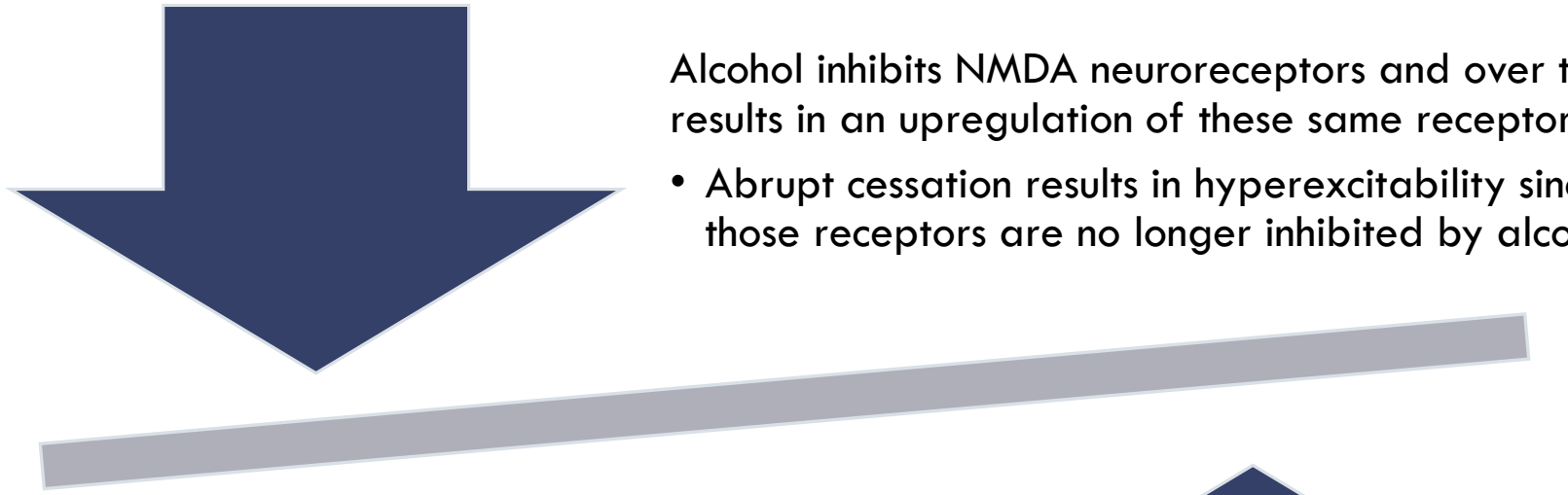


An estimated 76.3 million people worldwide have an AUD with AWS occurring in 8% of hospitalized inpatients

Ethanol is the primary alcohol ingested by chronic users

Bayard M, et al. *Am Fam Physician*. 2004;69(6):1443-1450.
Jesse S, et al. *Acta Neurological Scandinavica*. 2017;135(1): 4-16.

Pathophysiology



Alcohol inhibits NMDA neuroreceptors and over time results in an upregulation of these same receptors

- Abrupt cessation results in hyperexcitability since those receptors are no longer inhibited by alcohol

Alcohol enhances the effect of GABA on GABA-A neuroreceptors, resulting in decreased brain excitability

- Chronic exposure results in a compensatory decrease of GABA-A neuroreceptors response to GABA which leads to an increased tolerance of alcohol

Bayard M, et al. *Am Fam Physician.* 2004;69(6):1443-1450.
Jesse S, et al. *Acta Neurological Scandinavica.* 2017;135(1): 4-16.
Carlson RW, et al. *Critical Care Clinics.* 2012;28(4):549-585.

NMDA: N-METHYL-D-ASPARTATE, GABA: GAMMA-AMINOBUTYRIC ACID

Diagnosis

Diagnostic and Statistical Manual, 5th Edition (DSM-5)

- Cessation or reduction of alcohol that has been heavy and prolonged
- Two (or more) of the following, developing within several hours to a few days after cessation of alcohol use:
  - Autonomic hyperactivity
  - Increased hand tremor
  - Insomnia
  - Nausea or vomiting
  - Transient visual, tactile, or auditory hallucinations or illusions
  - Psychomotor agitation
  - Anxiety
  - Generalized tonic-clonic seizures
- Clinically significant distress or impairment in social, occupation, or other areas of functioning
- Symptoms not due to a general medical condition or mental disorder

Bayard M, et al. *Am Fam Physician*. 2004;69(6):1443-1450.
Jesse S, et al. *Acta Neurological Scandinavica*. 2017;135(1): 4-16.

Clinical Presentation

Signs	Symptoms
• Elevated blood pressure • Tachycardia • Sweating • Elevated body temperature • Tremulousness of body/hand tremor • Dilated pupils • Seizure • DT	• Anxiety • Insomnia • Hallucinations • Illusions • Irritability • Nausea/vomiting • Difficulty concentrating • Paranoia

Bayard M, et al. *Am Fam Physician*. 2004;69(6):1443-1450.
Jesse S, et al. *Acta Neurological Scandinavica*. 2017;135(1): 4-16.

DT: DELIRIUM TREMENS

Stages of AWS

Stage 1
- Mild symptoms
- 6-12 hours from last drink

Stage 2
- Moderate symptoms
- 12-48 hours from last drink

Stage 3
- Severe symptoms
- 48+ hours from last drink

Jesse S, et al. *Acta Neurological Scandinavica* vol. 135,1 (2017): 4-16.

Risk Factors for Severe, Complicated, or Complications of Withdrawal

History of alcohol withdrawal delirium or alcohol withdrawal seizure	Numerous prior withdrawal episodes in the patient's lifetime	Comorbid medical or surgical illness (especially traumatic brain injury)	Increased age (>65)
Long duration of heavy or regular alcohol consumption	Seizure(s) during current withdrawal episode	Marked autonomic hyperactivity on presentation	Physiological dependence on GABAergic agents such as BZDs or barbiturates

Assessment Tools

- Predict AWS
  - ➢ Prediction of Alcohol Withdrawal Severity Scale (PAWSS)
    - First validated tool to assess risk for the development of complicated AWS
- Detect severity of AWS
  - ➢ Clinical Institute Withdrawal Assessment Alcohol Scale Revised (CIWA-Ar)
    - Most widely used tool based on observations of the rater and patient participation
    - 10-item tool performed bedside to determine severity as symptoms are actively experienced
  - ➢ Alcohol Withdrawal Scale
    - Require less reliance on patient response
    - Consists of six vegetative and five mental symptom items used to place the patient in one of five categories to predict the course of withdrawal

Bayard M, et al. *Am Fam Physician*. 2004;69(6):1443-1450.
Jesse S, et al. *Acta Neurological Scandinavica*. 2017;135(1): 4-16
Kattimani S, et al. *Ind Psychiatry J*. 2013;22(2): 100–108.
Maldonado JR, et al. *Alcohol and alcoholism (Oxford)*. 2015;50(5):509-518.

Management

Guideline Protocol

Identification – AWS Suspected?	• Screen for unhealthy alcohol use • Indicators for risk of AWS
Diagnosis	• History and physical • DSM-5 criteria
Initial Assessment	• Risk of severe, complicated, or complications of withdrawal? • Withdrawal severity → Use assessment tool
Level of Care Determination	• Inpatient setting • Ambulatory setting
Management	• Inpatient management • Ambulatory management

Identification and Diagnosis of AWS

Identification

- Use a validated scale to help identify patients with or at risk for AWS
- Assess the quantity, frequency, and time of day when alcohol was last consumed

Diagnosis

- CIWA-Ar should not be used as a diagnostic tool
- Assess for medications and/or illnesses that can mask signs and symptoms of alcohol withdrawal

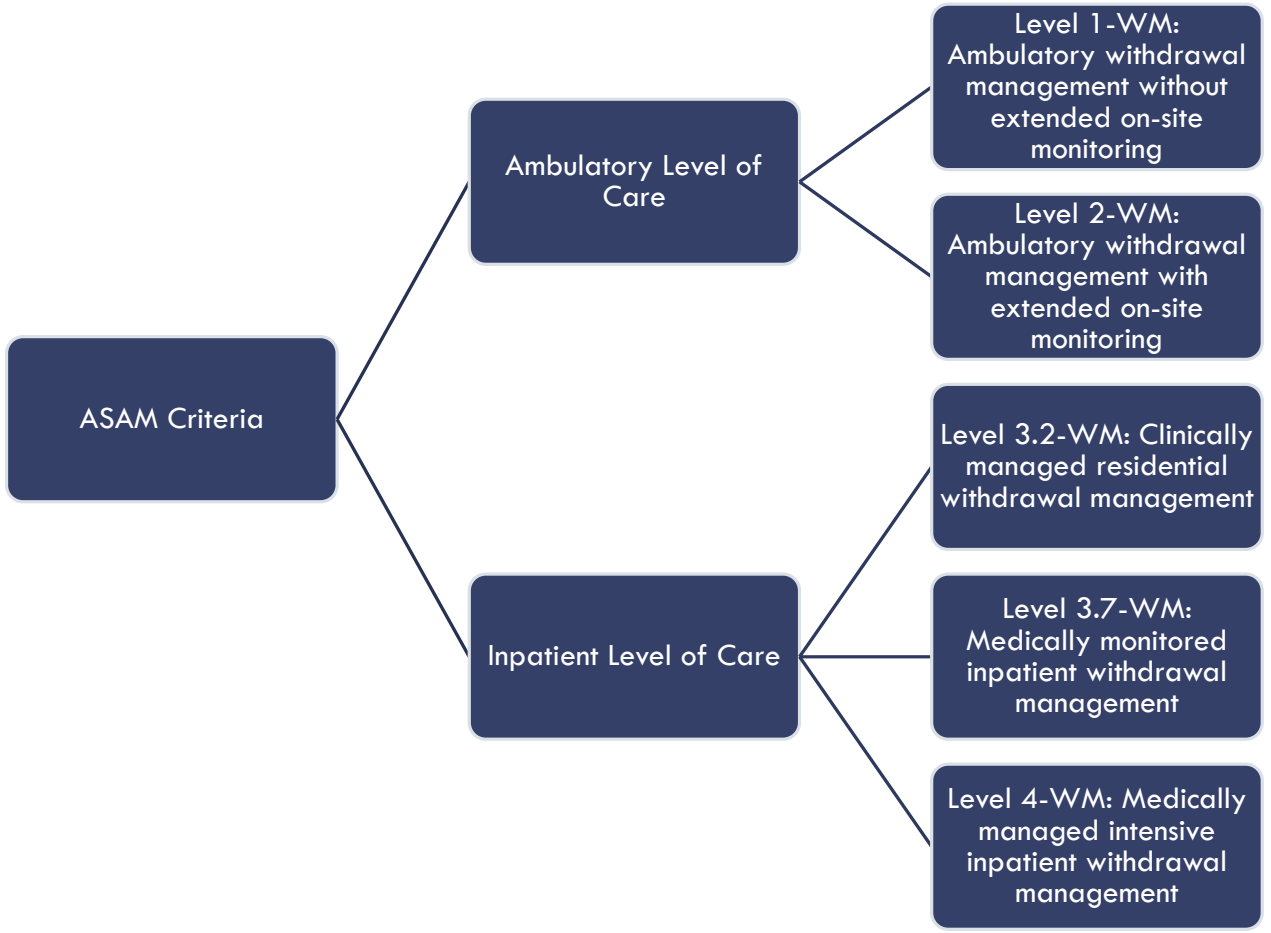
Initial Assessment of AWS

- General Approach
  - Determine if the patient is at risk of developing severe and/or complicated alcohol withdrawal, or complications from alcohol withdrawal by utilizing a validated risk assessment scale
  - Inquire about time since cessation or reduction in alcohol use

Severity Category	CIWA-Ar Range	Symptom Description
Mild	CIWA-Ar <10	Mild or moderate anxiety, sweating and insomnia, but no tremor
Moderate	CIWA-Ar 10-18	Moderate anxiety, sweating, insomnia, and mild tremor
Severe	CIWA-Ar ≥19	Severe anxiety and moderate to severe tremor but no confusion, hallucinations, or seizure
Complicated	CIWA-Ar ≥19	Seizure, new onset hallucinations, or delirium

Wong J, et al. *J Addict Med*. 2020;14(3S Suppl 1):1-72.

Levels of Care



Levels of Care in the Ambulatory Setting

Level 1-WM: Without extended on-site monitoring	Level 2-WM: With extended on-site monitoring
• Physician's office • Home health care agency • Addiction treatment facility	• Day hospital setting • General health care facility • Mental health facility • Addiction treatment facility

Levels of Care in the Inpatient Setting

Level 3.2-WM: Clinically managed residential withdrawal management	Level 3.7-WM: Medically monitored inpatient withdrawal management	Level 4-WM: Medically managed intensive inpatient withdrawal management
• Residential service providing 24-hour structure and support by trained, non-medical staff • Medical care not provided 24/7 • Staff may supervise patients to self-administer medications	• Residential service providing 24-hour structure and support by medical and nursing staff • Located in a specialty addiction treatment or mental health setting with addiction treatment services	• Medical or psychiatric hospital service with an addiction specialist physician

Indicators for Inpatient Management

- Severity of withdrawal
- Coexisting medical or psychiatric problems
- Pregnancy
- Need for non-oral route of medication administration
- Need for intensive or specialized counseling services
- Lack of transportation for ambulatory attendance
- Lack of safe housing

Assessment Question #1

For Pharmacy Technicians

Which of the following are treatment settings for the management of alcohol withdrawal syndrome?

A) Physician's office

B) Addiction treatment facility

C) Home health care agency

D) All of the above

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Determining Appropriateness of the Level of Care in Ambulatory Settings

	Level 1-WM			Level 2-WM		
Factor	Appropriate	Neutral/Uncertain	Inappropriate	Appropriate	Neutral/Uncertain	Inappropriate
Withdrawal severity	Mild (CIWA-Ar <10)	Moderate (CIWA-Ar 10-18)	Severe or complicated (CIWA-Ar >19)	Mild or moderate (CIWA-Ar <18)	Severe but not complicated (CIWA-Ar >19)	Complicated (CIWA-Ar ≥19)
Concurrent withdrawal of physiological dependence		Withdrawing from other substance(s). Physiological dependence on opioids or opioid use disorder.	Physiological dependence on benzodiazepines or benzodiazepine use disorder.	Physiological dependence on opioids or opioid use disorder.	Withdrawing from other substance(s). Physiological dependence on opioids or opioid use disorder.	
Recent alcohol consumption		Consumes >8 standard drinks per day.			Consumes >8 standard drinks per day.	
Alcohol withdrawal history		Previous severe withdrawal episode. Complicated withdrawal >1 year ago.	Recent complicated withdrawal episode.	Severe withdrawal >1 year ago.	Previous complicated withdrawal episode. Recent severe withdrawal episode.	
Treatment history		Previous failure to benefit from ambulatory WM.			Previous failure to benefit from ambulatory WM.	

Wong J, et al. *J Addict Med*. 2020;14(3S Suppl 1):1-72.

WM: WITHDRAWAL MANAGEMENT, CIWA-AR: CLINICAL INSTITUTE WITHDRAWAL ASSESSMENT ALCOHOL SCALE REVISED

Assessment Question #2

For Pharmacists and Nurses

Which of the following is **false** about the management of alcohol withdrawal in different treatment settings?

A) An appropriate setting to treat a patient with mild alcohol withdrawal is inpatient

B) An appropriate setting to treat a patient with moderate alcohol withdrawal is outpatient

C) An appropriate setting to treat a patient with severe alcohol withdrawal is inpatient

D) An appropriate setting to treat a patient with complicated alcohol withdrawal is the outpatient setting

Assessment Question #2

For Pharmacists and Nurses

Which of the following is **false** about the management of alcohol withdrawal in different treatment settings?

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Supportive Care

Thiamine can be offered in the ambulatory setting and should be given in the inpatient setting to prevent Wernicke encephalopathy

- IV or IM administration is preferred in the inpatient setting, but oral thiamine can be offered
- Recommendation from National Institute for Health and Excellence (NICE) which states parenteral administration of thiamine should be given to any hospitalized patient who is a harmful or dependent drinker

Folate supplementation may be considered as alcohol use is associated with hyperhomocysteinemia

Wong J, et al. *J Addict Med.* 2020;14(3S Suppl 1):1-72.
BC Guidelines. Province of British Columbia; 2013.

Thiamine Insufficiency

- Wernicke encephalopathy is a severe complication resulting from insufficient thiamine
  - State of reversible acute confusion which can progress to Korsakoff syndrome which is an irreversible syndrome that includes dementia and gait abnormalities
  - Large alcohol consumption leads to an increased risk of Wernicke encephalopathy due to inadequate nutrition as well as biological interactions between cellular functioning and alcohol
  - Thiamine is required for carbohydrate metabolism and plays a key role in normal body functioning
    - The body does not synthesize thiamine so daily ingestion through food or supplements is required to maintain adequate metabolic functioning

Thiamine

- Mechanism of action
  - Essential coenzyme in carbohydrate metabolism by combining with adenosine triphosphate to form thiamine pyrophosphate
- Dose
  - Ambulatory: 100 mg PO QD for 3-5 days
  - Inpatient:
    - 100-200 mg IV/IM/PO QD for 3-5 days for prevention
    - 200-500 mg IV/IM TID for 2-7 days followed by 250 mg for 3-5 days, then 100 mg QD for treatment
- Formulations
  - 50 mg, 100 mg, and 250 mg tablets
  - 100 mg/mL injection
- DDIs
  - Administration of dextrose may precipitate acute symptoms of thiamine deficiency
- Pharmacokinetics
  - Absorption:
    - PO: Adequate
    - IV/IM: Rapid and complete
  - Metabolism: Hepatic
  - Elimination: Urine
- Side effects
  - Flushing
  - Hemorrhage
  - Cyanosis
  - Pulmonary edema
- Storage
  - Protect from light
  - Store at 15°C to 30°C (59°F to 86°F)

Thiamine [monograph]. In: Lexicomp Online [online database]. Hudson, OH: Lexicomp (accessed 2022 Mar 12).

PO: BY MOUTH, QD: DAILY, IV: INTRAVENOUS, IM: INTRAMUSCULAR, TID: THREE TIMES A DAY, DDI: DRUG-DRUG INTERACTION

Folic Acid

- Mechanism of action
  - Necessary for the formation of coenzymes, purine and pyrimidine synthesis
  - Stimulates white blood cell count and platelet production
- Dose
  - 400 mcg to 1 mg IV/PO QD until no longer at risk for prevention or treatment
- Formulations
  - 400 mcg, 800 mcg, 1 mg tablets
  - 5 mg/mL injection
- DDIs
  - May decrease serum concentrations of phenobarbital
- Pharmacokinetics
  - Absorption: Small intestine
  - Metabolism: Hepatic
  - Elimination: Urine
- Side effects
  - Flushing
  - Malaise
  - Bronchospasm
  - Pruritis
- Storage
  - Protect from light
  - Store at 20°C to 25°C (68°F to 77°F)

Folic acid [monograph]. In: Lexicomp Online [online database]. Hudson, OH: Lexicomp (accessed 2022 Mar 27).

IV: INTRAVENOUS, PO: BY MOUTH, QD: DAILY, DDI: DRUG-DRUG INTERACTION

Supportive Care

- Magnesium should be administered with hypomagnesemia, cardiac arrhythmias, electrolytes disturbances, or a previous history of alcohol withdrawal seizures

Study	Findings
Search for randomized or quasi-randomized trials through Cochrane Drugs and Alcohol Group Register or Controlled Trails, PubMed, EMBASE, CINAHL, and Web of Science	• Insufficient evidence to determine whether magnesium is beneficial or harmful for the treatment or prevention of AWS

- Supplementation of phosphorus should be administered if levels are <1 mg/dL

Study	Findings
PubMed search from January 1960 to October 2015	• Lack of data supporting phosphate replenishment in asymptomatic patients and with moderate hypophosphatemia (1-2 mg/dL) • Self-correction with proper nutrition is preferred

Wong J, et al. *J Addict Med.* 2020;14(3S Suppl 1):1-72.
Inouye SK, et al. *N Engl J Med.* 1999;340(9):669 – 676.
Sarai M, et al. Cochrane library. 2013;2013(6):CD008358-CD008358.
Schmidt KJ, et al. *Annals of Pharmacotherapy.* 2016;50(5):389-401.

Key Differences in Supportive Care Management

Ambulatory Setting

- Patients should be advised to drink non-caffeinated fluids and that a daily multivitamin may be beneficial since IV fluids are not provided
- Patients can be offered oral thiamine 100 mg PO for 3-5 days

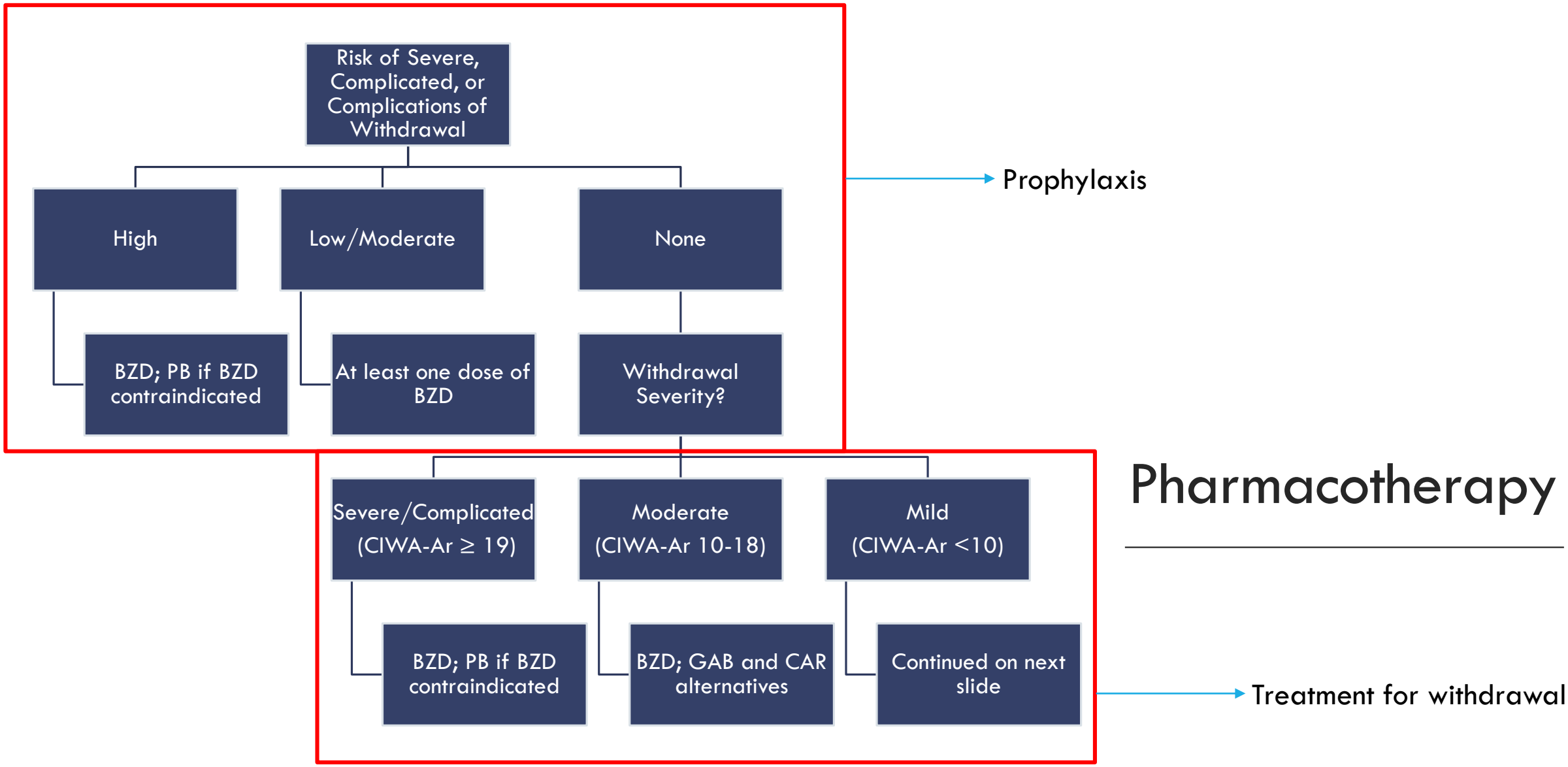
Inpatient Setting

- Thiamine should be provided as either IV or IM route of administration for prophylaxis or treatment
- Folate supplementation may be considered in critically ill patients
- Magnesium and phosphate replenishment should be provided dependent on patient presentation and serum levels

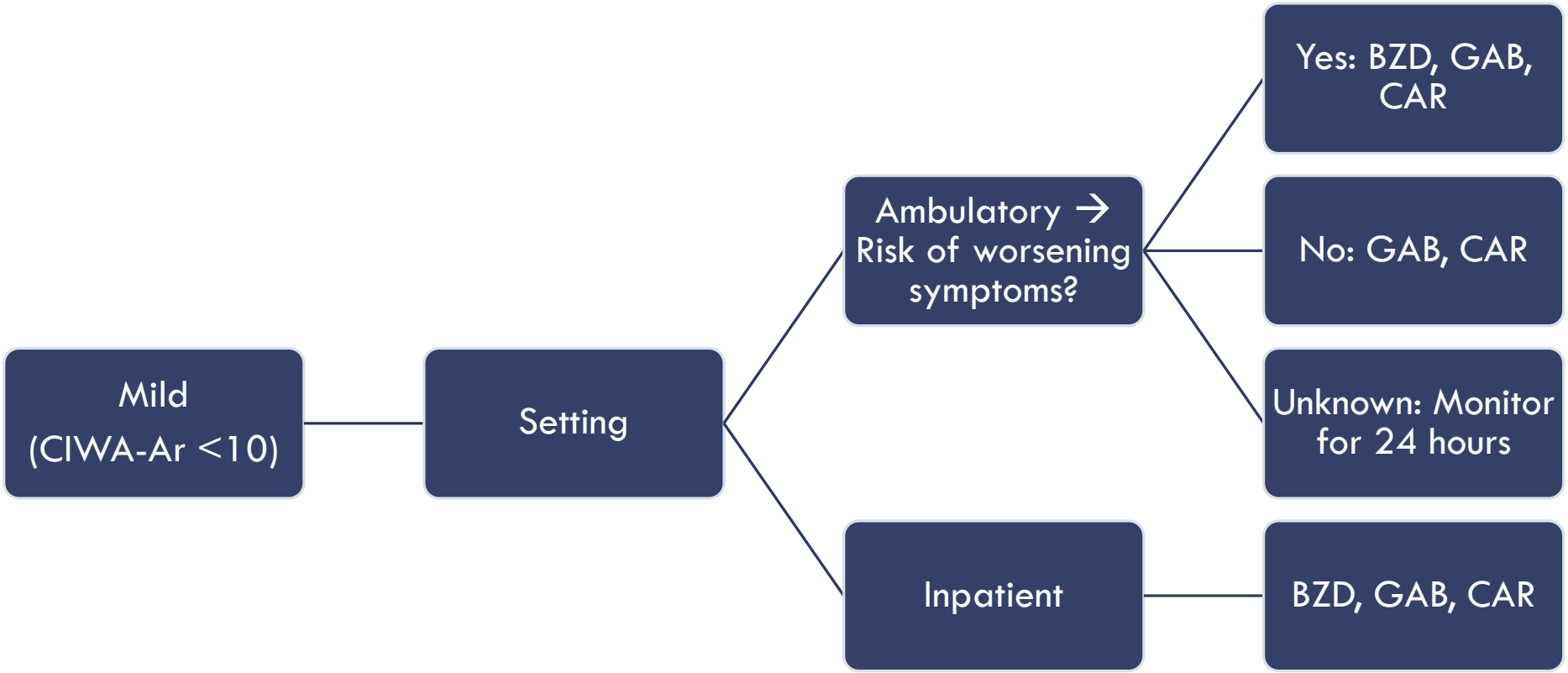
Wong J, et al. *J Addict Med*. 2020;14(3S Suppl 1):1-72.

IV: INTRAVENOUS, PO: BY MOUTH, IM: INTRAMUSCULAR

Pharmacotherapy



Pharmacotherapy



Wong J, et al. *J Addict Med*. 2020;14(3S Suppl 1):1-72.

CIWA-AR: CLINICAL INSTITUTE WITHDRAWAL ASSESSMENT ALCOHOL SCALE REVISED, BZD: BENZODIAZEPINE, GAB: GABAPENTIN, CAR: CARBAMAZEPINE

Prophylaxis

Providing a single dose of preventative medication in **either treatment setting** is appropriate for lower levels of risk in cases such as:

- History of severe or complicated withdrawal
- Acute medical, psychiatric, or surgical illness
- Severe coronary artery disease
- Displaying signs or symptoms of withdrawal concurrent with a positive blood alcohol content

Patients at risk of developing new or worsening signs or symptoms of withdrawal while away from the **ambulatory setting** should be provided with pharmacotherapy

- Risks include a history of withdrawal episodes of at least moderate severity and being within the window for the development of symptoms in the time course of withdrawal

Prophylaxis

- Patients at risk of developing severe, complicated, or complications of alcohol withdrawal **may be treated in ambulatory settings** and **preventative pharmacotherapy in the inpatient setting should be provided**
  - ➢BZDs are first-line regardless of the risk level

Study	Study Design	Outcome

Pharmacological Management of Alcohol Withdrawal (1997)	Meta-analysis of articles published before July 1, 1995	• BZDs reduce:
		  • **Withdrawal severity**
		  • **Incidence of delirium** (-4.9 cases per 100 patients; 95% CI, -9.0 to -0.7, p=0.04)
		  • **Seizures** (-7.7 seizures per 100 patients; 95% CI, -12.0 to -3.5, p=0.003)

Wong J, et al. *J Addict Med*. 2020;14(3S Suppl 1):1-72.
Mayo-Smith MF. *JAMA*. 1997;278(2):144-151.

BZD: BENZODIAZEPINE, CI: CONFIDENCE INTERVAL

Treatment Dosing Regimens

Symptom-triggered dosing

- Medication administered only when experiencing withdrawal symptoms according to a severity scale
- Further refined by giving a different dose depending on the score

Fixed-dosing

- Pre-determined dose administered at fixed intervals according to a schedule
- Doses usually decreased in a gradual taper over several days

Front-loading

- Moderate-to-high doses of a long-acting agent are given frequently to achieve rapid control of withdrawal
- Medication level is tapered through metabolism
- Driven by either a symptom assessment scale (e.g., 20 mg of diazepam every hour until CIWA-Ar <10) or a fixed-dosing schedule (e.g., 20 mg of diazepam every hour for 1-2 hours or until patient is sedated)

Wong J, et al. *J Addict Med.* 2020;14(3S Suppl 1):1-72.

CIWA-AR: CLINICAL INSTITUTE WITHDRAWAL ASSESSMENT ALCOHOL SCALE REVISED

Front-loading Regimen

- Front-loading regimen is recommended for high risk of severe withdrawal

Study	Study Design	Outcome
Impact of an Alcohol Withdrawal Treatment Pathway on Hospital Length of Stay: A Retrospective Observational Study Comparing Pre and Post Pathway Implementation	Retrospective observational study that involved 582 subjects that incorporated 4 treatment pathways using front-loading regimens for prophylaxis, mild-to-moderate withdrawal, moderate-to-severe withdrawal, and severe withdrawal/alcohol withdrawal delirium	• There was a 1 day [95% CI, 1-2 days] **reduction in median hospital length of stay** (5 versus 4 days) • Changes found in the **proportion of subjects admitted to the ICU** (24% vs 29.3%), **length of stay in the ICU** (7.1±8 days vs 5.6±6.9 days), and **proportion of patients discharged with a diagnosis of delirium tremens** (17.8% vs 15.3%)

Wong J, et al. *J Addict Med*. 2020;14(3S Suppl 1):1-72.
Muzyk AJ, et al. *J Psychiatr Pract*. 2017;23(3):233-241.

CI: CONFIDENCE INTERVAL, ICU: INTENSIVE CARE UNIT

Benzodiazepine Treatment Dosing Regimens

Symptom-triggered:

- Preferred in short-term observational settings with continuous monitoring (e.g., **Level 2-WM**) and can be used in the **inpatient setting**
- Appropriate in settings without extended on-site monitoring (**Level 1-WM**) if signs and symptoms can be reliably monitored

Front-loading:

- Recommended for severe alcohol withdrawal (e.g., CIWA-Ar ≥19) which will most often be in the **inpatient setting**
- Diazepam and chlordiazepoxide are preferred agents for front loading

Withdrawal Severity

Mild alcohol withdrawal at risk of developing severe, complicated, or complications of alcohol withdrawal may be provided pharmacotherapy or supportive care alone

- CAR or GAB are appropriate in **either treatment setting**
- For patients at risk of developing new or worsening withdrawal while **away from the ambulatory setting**, BZDs, CAR, or GAB are appropriate

Moderate alcohol withdrawal should receive pharmacotherapy in either treatment setting

- BZDs are first-line with CAR or GAB as alternatives

Severe alcohol withdrawal may be treated in a Level 2-WM setting and can be treated in the inpatient setting

- BZDs are first-line with PB, CAR, or GAB as alternatives

Benzodiazepines

- Medications:
  - Lorazepam
  - Diazepam
  - Chlordiazepoxide
- Schedule: C-IV
- Mechanism of action:
  - Binds to BZD receptors on the postsynaptic GABA neuron
  - Enhances inhibitory effect of GABA by increasing permeability to chloride ions
- Storage
  - Protect from light
  - Store at 15°C to 30°C (59°F to 86°F)
  - Controlled substances that must be locked with limited access
- DDIs:
  - Caution with other CNS depressing agents
  - CYP2C19 and CYP3A4 inducers may decrease serum concentrations
  - CYP2C19 and CYP3A4 inhibitors may increase serum concentrations
- SE:
  - Beers Criteria
  - CNS depression
  - Respiratory depression
  - Hepatic impairment
  - Physiologic dependence and tolerance
  - Delirium

Lorazepam [monograph]. In: Lexicomp Online [online database]. Hudson, OH: Lexicomp (accessed 2022 Mar 28).
Diazepam [monograph]. In: Lexicomp Online [online database]. Hudson, OH: Lexicomp (accessed 2022 Mar 28).
Chlordiazepoxide [monograph]. In: Lexicomp Online [online database]. Hudson, OH: Lexicomp (accessed 2022 Mar 28).

BZD: BENZODIAZEPINE, GABA: GAMMA-AMINOBUTYRIC ACID, DDI: DRUG-DRUG INTERACTION, CNS: CENTRAL NERVOUS SYSTEM

Lorazepam

- Dose (Examples of treatment regimens)
  - Fixed-dosing: Days 1-2: 2 mg every 8 hours; day 3: 1 mg every 8 hours; day 4: 1 mg every 12 hours; day 5: 1 mg at bedtime
  - Symptom-triggered: Days 1-2: 2-4 mg every 6 hours as needed; day 3: 1-4 mg every 8 hours as needed; days 4-5: 1-4 mg every 12 hours as needed dependent on CIWA-Ar score
- Formulations
  - 0.5 mg, 1 mg, and 2 mg tablets
  - 2 mg/mL oral concentrate
  - 2 mg/mL and 4 mg/mL injection
- Pharmacokinetics
  - Metabolism: Hepatically but rapidly conjugated to lorazepam glucuronides (inactive)
  - Half-life
    - PO: ~12 hours
    - IM: ~13 to 18 hours
  - Time to peak
    - PO: ~2 hours
    - IM: ≤3 hours
  - Excretion: Urine

Wong J, et al. *J Addict Med*. 2020;14(3S Suppl 1):1-72.
Lorazepam [monograph]. In: Lexicomp Online [online database]. Hudson, OH: Lexicomp (accessed 2022 Mar 28).
Muncie HL, et al. *Am Fam Physician*. 2013;88(9):589-595.

CIWA-AR: CLINICAL INSTITUTE WITHDRAWAL ASSESSMENT ALCOHOL SCALE REVISED, PO: BY MOUTH, IM: INTRAMUSCULAR

Diazepam

- Dose (Examples of treatment regimens)
  - Fixed-dosing: Day 1: 10 mg every 6 hours; day 2: 10 mg every 8 hours; day 3: 10 mg every 12 hours; days 4-5: 10 mg at bedtime
  - Front-loading: 20 mg every 1 to 2 hours until symptoms improve
  - Symptom-triggered: Day 1: 10-20 mg every 4 hours as needed; days 2-3: 10-20 mg every 6 hours as needed; days 4-5: 10-20 mg every 12 hours as needed depending on CIWA-Ar score
- Formulations
  - 2 mg, 5 mg, and 10 mg tablets
  - 5 mg/mL oral solution and injection
- Pharmacokinetics
  - Metabolism:
    - Hepatic
    - N-demethylated by CYP3A4 and 2C19 to N-desmethyldiazepam (active)
  - Half-life:
    - PO: Parent → 44 to 48 hours, Desmethyldiazepam → 100 hours
    - IV: Parent → 33 to 45 hours, Desmethyldiazepam → 87 hours
  - Time to peak:
    - PO: 15 minutes to 2.5 hours
    - IV: ~1 minute
  - Excretion: Urine

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Diazepam [monograph]. In: Lexicomp Online [online database]. Hudson, OH: Lexicomp (accessed 2022 Mar 28).
Muncie HL, et al. *Am Fam Physician*. 2013;88(9):589-595.

CIWA-AR: CLINICAL INSTITUTE WITHDRAWAL ASSESSMENT ALCOHOL SCALE REVISED, PO: BY MOUTH, IV: INTRAVENOUS

Chlordiazepoxide

- Dose (Examples of treatment regimens)
  - Fixed-dosing: Day 1: 50 mg every 6 to 12 hours; Day 2: 25 mg every 6 hours; Day 3: 25 mg twice a day; Day 4: 25 mg at bedtime
  - Front-loading: 50 to 100 mg every 1 to 2 hours for 3 doses may precede the fixed regimen
  - Symptom-triggered regimen: Day 1: 50 mg every 6 to 12 hours as needed; days 2 to 5: 25 mg every 6 hours as needed dependent on CIWA-Ar score
- Formulations
  - 5 mg, 10 mg, and 25 mg capsules
- Pharmacokinetics
  - Metabolism: Hepatically to desmethyldiazepam (active), desmethylchlordiazepoxide, and demoxepam
  - Half-life:
    - Parent: 24 to 48 hours
    - Demoxepam: 14 to 95 hours
  - Time to peak: 0.5 to 2 hours
  - Excretion: Urine

Wong J, et al. *J Addict Med*. 2020;14(3S Suppl 1):1-72.
Chlordiazepoxide [monograph]. In: Lexicomp Online [online database]. Hudson, OH: Lexicomp (accessed 2022 Mar 28).
Muncie HL, et al. *Am Fam Physician*. 2013;88(9):589-595.

Key Considerations with Benzodiazepines

- Longer-acting BZDs are preferred due to the clinical benefits of their longer duration of action
- A BZD prescription to treat alcohol withdrawal should be discontinued following treatment
- Clinicians can manage BZD misuse or diversion risk in the **ambulatory setting** by dispensing or prescribing the minimum amount necessary given level of stability and timing of next in-person clinic visit
- BZDs should not be prescribed to patients with a history of even mild adverse events with BZD use because rapid intervention is not typically available in the **ambulatory setting**

Assessment Question #3

For Pharmacy Technicians

Which of the following is a BZD used in alcohol withdrawal management?

A) Chlordiazepoxide

B) Gabapentin

C) Carbamazepine

D) Phenobarbital

Assessment Question #3

For Pharmacy Technicians

Which of the following is a BZD used in alcohol withdrawal management?

A) Chlordiazepoxide

B) Gabapentin

C) Carbamazepine

D) Phenobarbital

Assessment Question #4

For Pharmacists and Nurses

True or False: Monotherapy with BZDs, CAR, or GAB can be given to patients in the ambulatory treatment setting if there is a concern for developing signs and symptoms of withdrawal.

A) True

B) False

Assessment Question #4

For Pharmacists and Nurses

True or False: Monotherapy with BZDs, CAR, or GAB can be given to patients in the ambulatory treatment setting if there is a concern for developing signs and symptoms of withdrawal.

A) True

B) False

Carbamazepine

- Class: Anticonvulsant
- Mechanism of action
  - Decrease synaptic transmission of sodium ions across cell membrane and potentiate GABAergic neurotransmission
- Dose (Example regimen)
  - Day 1: 200 mg QID; day 2: 200 mg TID; day 3: 200 mg BID; and days 4-5: 200 mg QD
- Formulations
  - 100 mg, 200 mg, and 300 mg ER capsules
  - 100 mg, 200 mg, 400 mg ER tablets and 200 mg tablets
  - 100 mg/5 mL oral suspension
- DDIs
  - Strong CYP3A4 inducer which may decrease the serum concentrations of concomitant medications
- Pharmacokinetics
  - Metabolism: Hepatic
  - Half-life: Variable → 12 to 17 hours
  - Time to peak: Unpredictable → 4 to 26 hours
  - Excretion: Urine
- Side effects
  - Hepatotoxicity
  - Neuropsychiatric effects
  - Cardiac effects
  - Dermatologic reactions
  - Toxic concentrations: >15 mcg/mL
- Storage
  - Protect from light and moisture
  - Hazardous agent → use gloves when handling
  - Store at controlled room temperature 25°C (77°F)

Wong J, et al. *J Addict Med*. 2020;14(3S Suppl 1):1-72.
Carbamazepine [monograph]. In: Lexicomp Online [online database]. Hudson, OH: Lexicomp (accessed 2022 Mar 28).

GABA: GAMMA-AMINOBUTYRIC ACID, QID: FOUR TIMES A DAY, TID: THREE TIMES A DAY, BID: TWO TIMES A DAY, QD: DAILY, ER: EXTENDED RELEASE, DDI: DRUG-DRUG INTERACTION

Carbamazepine as an Alternative

Study	Study Design	Findings
Anticonvulsants for Alcohol Withdrawal	Literature search that included 56 randomized controlled trials with a total of 4,076 participants that examined the effectiveness, safety, and overall risk-benefit of anticonvulsants in comparison with a placebo or other pharmacological treatment	• Results **favored CAR versus BZDs for withdrawal symptoms**
The Effects of CAR and Lorazepam on Single versus Multiple Previous Alcohol Withdrawal in an Outpatient Randomized Trial	Randomized double-blind trial comparing 136 responses to carbamazepine and lorazepam across 2 levels of detoxification histories using CIWA-Ar	• **CAR group drank less in the post-treatment period and in those with past detoxifications** • **Lorazepam group had a significant rebound of symptoms post-treatment and the risk of having a first drink was 3 times greater than for the carbamazepine group**
Double-blind Controlled Trial Comparing CAR to Oxazepam Treatment of Alcohol Withdrawal	Double-blind controlled trial that compared CAR 800 mg to oxazepam 120 mg per day	• Both equally efficacious in treating withdrawal symptoms • **Oxazepam group had an increase in psychological distress from days 3-7 whereas CAR group had a decline**

Minozzi S, et al. *Cochrane library*. 2010;2010(3):CD005064-CD005064.
Malcolm R, et al. *J Gen Intern Med*. 2002;17(5):349–55.
Malcolm R, et al. *Am J Psychiatry*. 1989;146(5):617–21.

CAR: CARBAMAZEPINE, BZD: BENZODIAZEPINE, CIWA-AR: CLINICAL INSTITUTE WITHDRAWAL ASSESSMENT ALCOHOL SCALE REVISED

Gabapentin

- Class: Anticonvulsant
- Schedule: C-V in some states
- Mechanism of action
  - Works by showing a high affinity for binding sites throughout the brain of voltage-gated calcium channels which inhibits the release of excitatory neurotransmitters
- Dose (Example regimen)
  - Days 1-3: 300 to 400 mg TID; day 4: 300 to 400 mg BID; then discontinue
  - Days 1-4: 100 mg up to TID for breakthrough symptoms
- Formulations
  - 100 mg, 300 mg, and 400 mg capsules
  - 600 mg and 800 mg tablets
  - 250 mg/5 mL oral solution
- DDIs
  - Caution with other CNS depressing agents
- Pharmacokinetics
  - Metabolism: None
  - Half-life: 5 to 7 hours → increased with renal dysfunction
  - Time to peak: 2 to 8 hours
  - Excretion: Urine
- Side effects
  - CNS and respiratory depression
  - Neuropsychiatric effects
  - Immediate and delayed hypersensitivity reactions
- Storage
  - Capsules and tablets: Store at controlled room temperature 25°C (77°F)
  - Oral solution: Refrigerated at 2°C to 8°C (36°F to 46°F)

Gabapentin [monograph]. In: Lexicomp Online [online database]. Hudson, OH: Lexicomp (accessed 2022 Mar 28).

TID: THREE TIMES A DAY, BID: TWO TIMES A DAY, DDI: DRUG-DRUG INTERACTION, CNS: CENTRAL NERVOUS SYSTEM

Gabapentin as an Alternative

- GAB is a favorable choice for treating alcohol withdrawal in **either treatment setting** when the plan is to use it for ongoing treatment of AUD

Study	Study Design	Findings
The Role of GAB in the Management of Alcohol Withdrawal and Dependence	Literature search from 1966 to March 2015 included 10 publications and 612 patients using GAB in alcohol withdrawal and dependence	• Demonstrated **benefits for complete abstinence, rates of no heavy drinking, cravings, and had positive sleep and mood/anxiety outcomes**
GAB versus Chlordiazepoxide for Outpatient Alcohol Detoxification Treatment	Randomized, double-blind study conducted in 26 U.S. veterans with alcohol withdrawal	• ESS and PACS scores did not differ significantly between treatment groups in the early treatment period (days 1-4) but were **lower at the end of the treatment period (days 5-7) in GAB-treated patients**
A Double-blind Trial of GAB versus Lorazepam in the Treatment of Alcohol Withdrawal	• 100 patients with CIWA-Ar ≥10 were randomized to treatment with 2 doses of GAB for 4 days • Severity measured on days 1 to 4 of treatment and on days 5, 7, and 12 post-treatment	• CIWA-Ar scores decreased; **high-dose GAB was statistically superior and clinically similar to lorazepam** • **GAB-treated patients had less probability of drinking in the post-treatment period**

Wong J, et al. *J Addict Med*. 2020;14(3S Suppl 1):1-72.
Leung JG, et al. *Annals of Pharmacotherapy*. 2015;49(8):897-906.
Stock CJ, et al. *Ann Pharmacother*. 2013;47(7–8):961–9.
Myrick H, et al. *Alcohol Clin Exp Res*. 2009;33(9):1582–8.

GAB: GABAPENTIN, AUD: ALCOHOL USE DISORDER, CIWA-AR: CLINICAL INSTITUTE WITHDRAWAL ASSESSMENT ALCOHOL SCALE REVISED, ESS: EPWORTH SLEEPINESS SCALE, PACS: PENN ALCOHOL CRAVING SCALE

Phenobarbital

- Class: Barbiturate
- Schedule: C-IV
- Mechanism of action
  - Exerts its effects on the GABA-A receptor by increasing the duration of channel opening when bound to GABA which increases hyperpolarization, indirectly increasing the sedative effects of GABA
  - Direct blockade on excitatory glutamate signaling
- Dose (Example regimen)
  - Initial: 130 mg or 260 mg IV once, followed by 130 mg IV every 15 to 30 minutes as needed
  - Maintenance: 130 mg to 260 mg IV per day in 2 or 3 divided doses for 3 to 5 days
  - 60 to 260 mg IM single dose
- Formulations
  - 15 mg, 16.2 mg, 30 mg, 32.4 mg, 60 mg, 64.8 mg, 97.2 mg, and 100 mg tablets
  - 20 mg/5 mL oral solution
  - 65 mg/mL and 130 mg/mL injection
- DDIs
  - Strong CYP3A4 inducer which may decrease the serum concentrations of concomitant medications
  - Caution with other CNS depressing agents

Wong J, et al. *J Addict Med*. 2020;14(3S Suppl 1):1-72.
Phenobarbital [monograph]. In: Lexicomp Online [online database]. Hudson, OH: Lexicomp (accessed 2022 Mar 28).

GABA: GAMMA-AMINOBUTYRIC ACID, IV: INTRAVENOUS, IM: INTRAMUSCULAR, DDI: DRUG-DRUG INTERACTION, CNS: CENTRAL NERVOUS SYSTEM

Phenobarbital

- Pharmacokinetics
  - Onset of action:
    - PO: ≥60 mins
    - IV: 5 mins
  - Duration: 6-12 hours
  - Metabolism: Hepatic
  - Half-life: 53 to 118 hours (~79 hours)
  - Time to peak: 2 to 4 hours
  - Excretion: Urine

- Side effects
  - CNS and respiratory depression
  - Paradoxical stimulatory response
  - Hypersensitivity reactions
  - Tolerance
  - Physical and physiological dependence
  - Blood dyscrasias
  - Toxic concentrations: 50 mcg/mL

- Storage
  - Protect from light
  - Store between 20°C and 25°C (68°F and 77°F)
  - Controlled substance that must be locked with limited access

Wong J, et al. *J Addict Med*. 2020;14(3S Suppl 1):1-72.
Phenobarbital [monograph]. In: Lexicomp Online [online database]. Hudson, OH: Lexicomp (accessed 2022 Mar 28).

PO: BY MOUTH, IV: INTRAVENOUS, CNS: CENTRAL NERVOUS SYSTEM

Phenobarbital as an Alternative

- Monotherapy is an appropriate alternative for patients who are experiencing severe alcohol withdrawal or who are at risk of developing severe, complicated or complications of alcohol withdrawal in a **Level 2-WM ambulatory setting and in the inpatient setting**

Study	Study Design	Findings
Patient Outcomes Associated with PB Use With or Without BZDs for AWS: A Systematic Review	• Literature search from 1950 to 2017 included 4 controlled trials and 5 observational studies (n=270) for AWS of any severity	• PB groups had **similar ICU admission rates, decreased mechanical ventilation, decreased benzodiazepine requirements by 50% to 90%, similar ICU and hospital lengths of stay**, and **similar AWS symptom resolution** versus comparator groups
Use of PB in Alcohol Withdrawal Management – A Retrospective Comparison Study of PB and BZDs for Acute Alcohol Withdrawal Management in General Medical Patients	• Retrospective chart review of 562 patients admitted over a 2-year period to a general hospital and treated for AWS • Development of AWS-related complications, including seizures and DT, was the primary outcome	• PB patients had **overall similar primary and secondary treatment outcomes** • Subset of patients (n = 16) initially treated with BZDs displayed treatment nonresponse, and higher rates of delirium and ICU admission rates, but were **well-managed following transition to the PB protocol**
A Prospective, Randomized, Trial of PB versus BZDs for Acute Alcohol Withdrawal	• Compared PB versus lorazepam in the treatment of alcohol withdrawal in the emergency department and at 48 hours • 44 patients were assessed using CIWA-Ar and given either IV PB (mean 509 mg) or lorazepam (mean 4.2 mg)	• **Both reduced CIWA-Ar scores from baseline to discharge** (15 to 5.4 and 16.8 to 4.2, p<0.001)

Wong J, et al. *J Addict Med*. 2020;14(3S Suppl 1):1-72.
Hammond DA, et al. *Hospital pharmacy (Philadelphia)*. 2017;52(9):607-616.
Nisavic M, et al. *Psychosomatics (Washington, DC)*. 2019;60(5):458-467.
Hendey GW, et al. *Am J Emerg Med*. 2011;29: 382-385.

WM: WITHDRAWAL MANAGEMENT, PB: PHENOBARBITAL, BZD: BENZODIAZEPINE, AWS: ALCOHOL WITHDRAWAL SYNDROME, DT: DELIRIUM TREMENS, ICU: INTENSIVE CARE UNIT, CIWA-AR: CLINICAL INSTITUTE WITHDRAWAL ASSESSMENT ALCOHOL SCALE REVISED

Assessment Question #5

For Pharmacy Technicians

Controlled substances used for alcohol withdrawal are appropriately stored in which of the following:

A) Locked drawer of the automated dispensing cabinet

B) Unlocked drawer

C) Bedside with the patient

D) Locked drawer of a medication room

E) A and D

Assessment Question #5

For Pharmacy Technicians

Controlled substances used for alcohol withdrawal are appropriately stored in which of the following:

A) Locked drawer of the automated dispensing cabinet

B) Unlocked drawer

C) Bedside with the patient

D) Locked drawer of a medication room

E) A and D

Key Differences with Ambulatory Settings

Patients at risk of developing new or worsening signs or symptoms of withdrawal while away from the ambulatory setting should be provided with pharmacotherapy

Severe alcohol withdrawal may be treated in a Level 2-WM ambulatory setting only

PB may be considered in a Level 2-WM ambulatory setting only

BZDs should not be prescribed to patients with a history of even mild adverse events because rapid intervention is not typically available

BZD misuse or diversion risk in the ambulatory setting can be managed by dispensing or prescribing the minimum amount necessary

Treatment Considerations

- If a patient is taking medication as prescribed and symptoms are not controlled as expected:
  - ➢ Consider increasing the dose
    - Amount of medication required to control symptoms is variable and determined by clinical judgement
    - More severe withdrawal may require larger doses
  - ➢ Consider switching to an alternative medication
  - ➢ Reassess for appropriate level of care
    - Failure to respond may reflect more severe withdrawal and significant risk of complications
  - ➢ If using BZDs, consider alternatives or adding an adjunct medication
    - Failure to respond to BZDs may reflect resistance due to kindling
    - Previous withdrawal episodes is associated with decreased responsiveness to BZDs

Summary

- Ambulatory settings are appropriate for the management of mild to moderate AWS
- BZDs are first-line agents for the treatment of AWS due to clear evidence that they prevent the development of seizures and delirium
- GAB and CAR are anticonvulsants that have the potential to be monotherapy agents for mild-to-moderate AWS in patients who are at low risk for progressing to severe AWS symptoms or complications
- PB has a mechanism of action that targets both the inhibitory and excitatory pathways of AWS and may be used as monotherapy for patients at risk for developing severe or complicated withdrawal

AWS: ALCOHOL WITHDRAWAL SYNDROME, BZD: BENZODIAZEPINE, GAB: GABAPENTIN, CAR: CARBAMAZEPINE, PB: PHENOBARBITAL

Assessment Question #6

For Pharmacists and Nurses

Which of the following is true about the role of medications used in alcohol withdrawal?

A) GAB may provide an effective bridge therapy from alcohol withdrawal treatment to long-term outpatient alcohol use disorder treatment

B) Front-loading regimen with BZDs is often accomplished with lorazepam

C) PB is first line in the outpatient setting

D) CAR is often used for severe alcohol withdrawal

Assessment Question #6

For Pharmacists and Nurses

Which of the following is true about the role of medications used in alcohol withdrawal?

A) GAB may provide an effective bridge therapy from alcohol withdrawal treatment to long-term outpatient alcohol use disorder treatment

B) Front-loading regimen with BZDs is often accomplished with lorazepam

C) PB is first line in the outpatient setting

D) CAR is often used for severe alcohol withdrawal

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Thank you!

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