IN-PATIENT MANAGEMENT OF ACUTE ALCOHOL WITHDRAWAL

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OBJECTIVES

Understand	Understand the pathophysiology of ethanol in regards to the various mechanisms for which it is involved in
Understand	Understand the complications associated with alcohol withdrawal
Identify	Identify when a patient may benefit from phenobarbital and which dosing would be most appropriate
Explain	Explain why various supplements are used to manage alcohol withdrawal and list the appropriate doses
Summarize	Summarize treatment options available for alcohol withdrawal

INTRODUCTION

8 million alcohol-dependent individuals in the U.S

- 500,000 severe enough requiring treatment
- 2 – 7% of patients admitted for medical care may develop moderate to severe alcohol withdrawal
  - 33% will progress to severe alcohol withdrawal and delirium trememens

PATHOPHYSIOLOGY

Transketolase

GABA-A

NMDA-r

Hyperexcitability

Liver

↑NADH

Acetaldehyde → Acetyl-CoA

↑Lactate

Reactive Oxygen Specifies

Oxidative stress

↓B6
↑ mAST

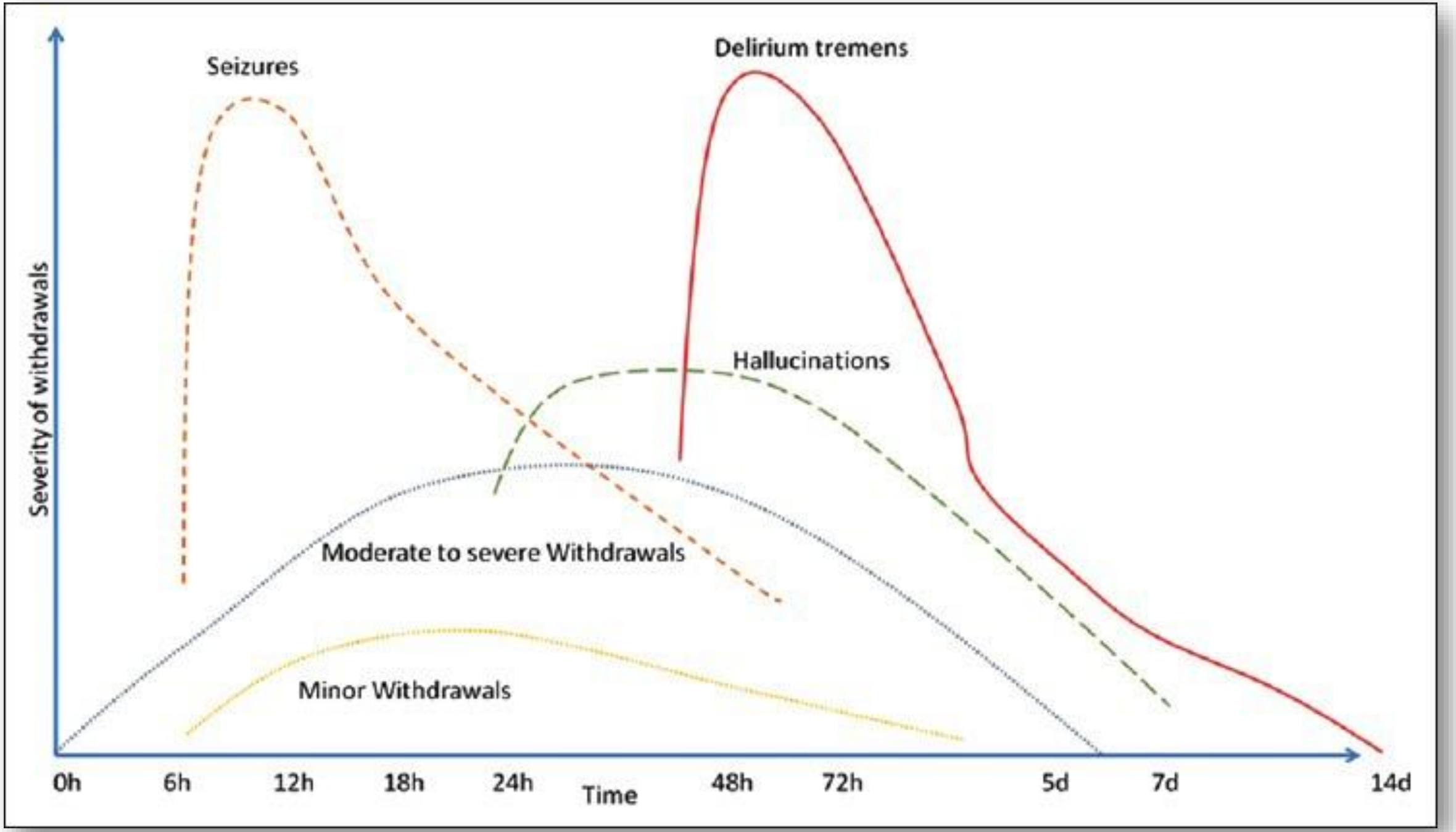
Glipin et. al, Neurobiology of Alcohol Dependence

COMPLICATIONS OF ALCOHOL WITHDRAWAL

Cardiomyopathy	Arryhtmias	Stroke	Inflammatory changes in the liver
Steatosis	Fibrosis	Cirrhosis	Pancreatitis
Cancers (Mouth, esophagus, lier, throat, breast)	Vitamin Deficiencies	Wernicke-Korsakoff (Vision changes, impairemed memory, ataxia)	NEED REFERENCE FOR THIS SLIDE

COMPLICATIONS OF ALCOHOL WITHDRAWAL

Manifestations	Onset	Findings
Mild Symptoms	<24 hours CIWA <10	Nausea, Vomiting, Insomnia, anxiety, and diaphoresis
Alcoholic Hallucinosis	12 – 24 hours CIWA 10 - 18	Moderate anxiety, sweating, insomnia, mild tremor
Seizures	12 – 48 hours CIWA ≥19	Severe anxiety, moderate to severe tremor, hallucinations (but not confused), or seizures
Delirium Tremens (DT's)	48 – 96 hours CIWA ≥19	Hallucinations, fever, confusion, tachycardia, hypertension, hyperthermia, agitation, and diaphoresis, hyperventilate,


Seizures
Delirium tremens
Hallucinations
Moderate to severe Withdrawals
Minor Withdrawals
Severity of withdrawals
0h
6h
12h
18h
24h
Time
48h
72h
5d
7d
14d

RISK FACTORS FOR SEVERE OR COMPLICATED WITHDRAWAL

History of:

- Alcohol withdrawal delirium
- Alcohol withdrawal seizure
- Numerous prior withdrawal episodes
- Age ≥65
- Long duration of heavy and regular alcohol consumption
- Autonomic hyperactivity on presentation
- Dependence on benzodiazepines or barbiturates

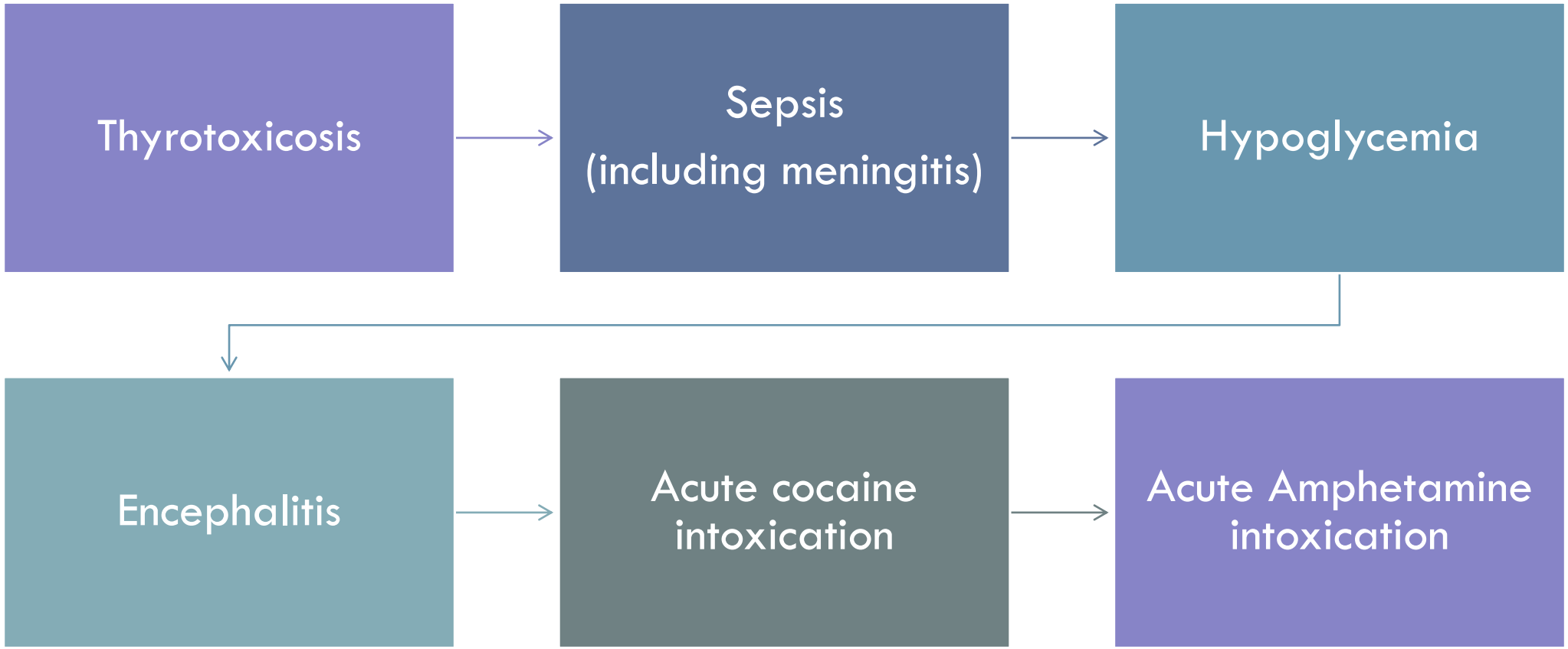
RISK ASSESSMENT TOOLS

Prediction of Alcohol Withdrawal Severity Scale (PAWSS)	Points if Yes
Recently intoxicated or drunk within the last 30 days	1
History of alcohol withdrawal	1
History of alcohol withdrawal seizures	1
History of Delirium Tremens	1
History of Alcohol Rehabilitation Treatment	1
History of blackouts	1
Combined alcohol with other downers in the last 90 days	1
Combined alcohol with any other substance of abuse in the last 90 days	1
Positive BAL	1
Evidence of autonomic activity	1

SIGNS/SYMPTOMS

Signs	Symptoms
Tachycardic	Nausea
Hypertensive	Vomiting
Hyperthermia	Anxious
Diaphoretic	Agitated
Tremulousness	Insomnia
Electrolyte Abnormalities	Irritable

DIFFERENTIAL DIAGNOSIS



DIAGNOSIS

- Diagnostic and Statistical Manual 5
- Evidence of Liver Disease
  - De Ritis Ratio
    - AST/ALT is >2 x ULN
      - Decreased ALT activity is a result of B6 depletion in the liver
    - Hepatitis Panel
- Electrolyte Disturbance
- Clinical Institute Withdrawal Assessment (CIWA)
- Ethanol Level or Blood Alcohol Content (BAC)

0.08% = Legally intoxicated → 0.16 – 0.3% = Alcohol Poisoning (blackouts, amnesia) → >0.3% = Reduced breathing, death

Box 2: DSM-5 Criteria for Alcohol Withdrawal

A. Cessation of (or reduction in) alcohol use that has been heavy and prolonged.
B. Two (or more) of the following, developing within several hours to a few days after the cessation of (or reduction in) alcohol use described in Criterion A:
   1. Autonomic hyperactivity (e.g., sweating or pulse rate greater than 100 bpm)
   2. Increased hand tremor
   3. Insomnia
   4. Nausea or vomiting
   5. Transient visual, tactile, or auditory hallucinations or illusions
   6. Psychomotor agitation
   7. Anxiety
   8. Generalized tonic-clonic seizures
C. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupation, or other important areas of functioning.
D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

Box 3: DSM-5 Criteria for Alcohol Withdrawal Delirium (generic criteria for delirium in the presence of heavy and prolonged alcohol use)

A. A disturbance in attention (i.e., reduced ability to focus, sustain, and shift attention) and awareness (reduced orientation to the environment).
B. Disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.
C. An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).
D. The disturbances in Criteria A and C are not better explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.
E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.

Specify:

Substance withdrawal delirium

a. This diagnosis should be made instead of substance withdrawal when the symptoms in Criteria A and C predominate in the clinical picture and when they are sufficiently severe to warrant clinical attention.

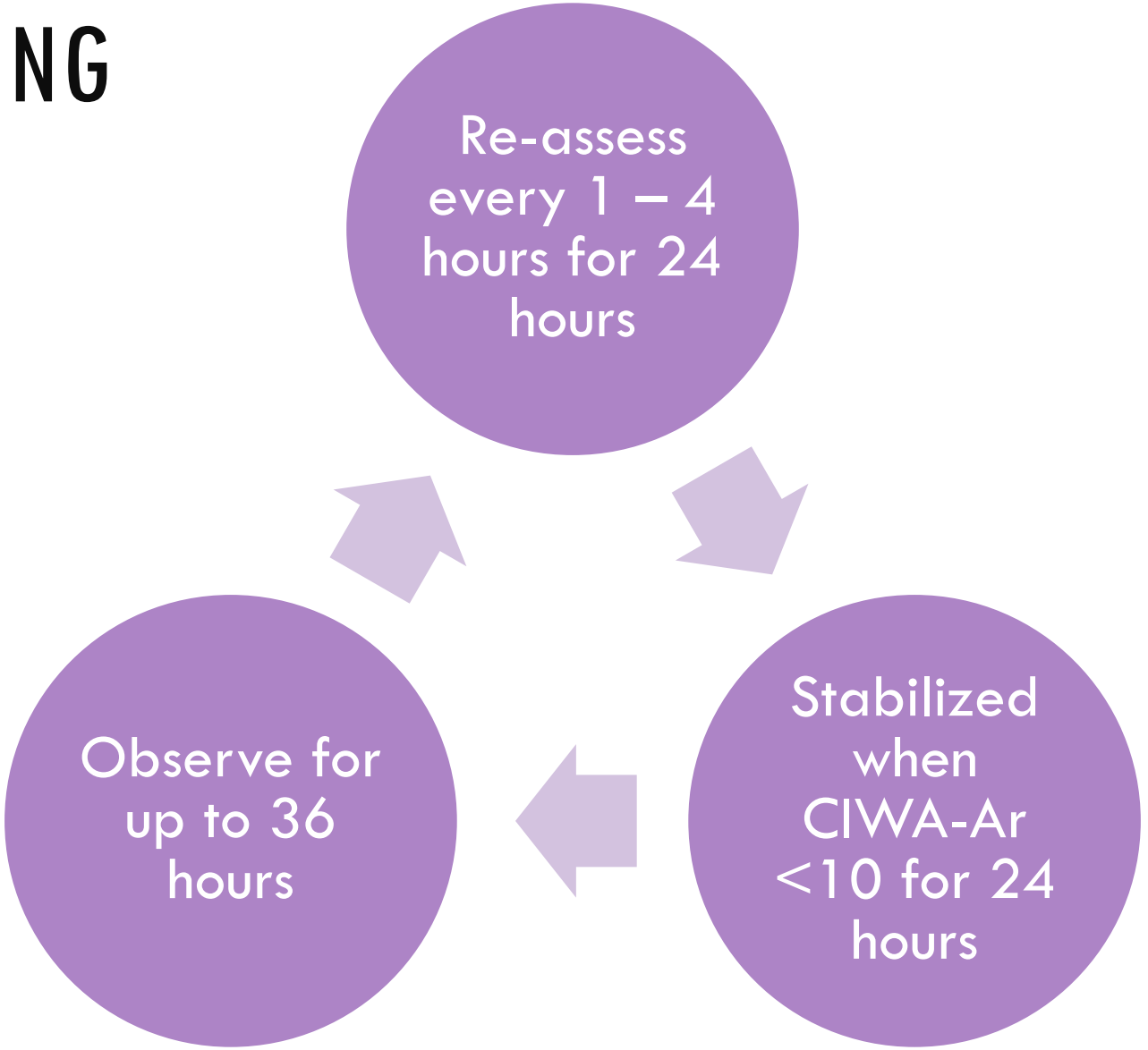
CIWA

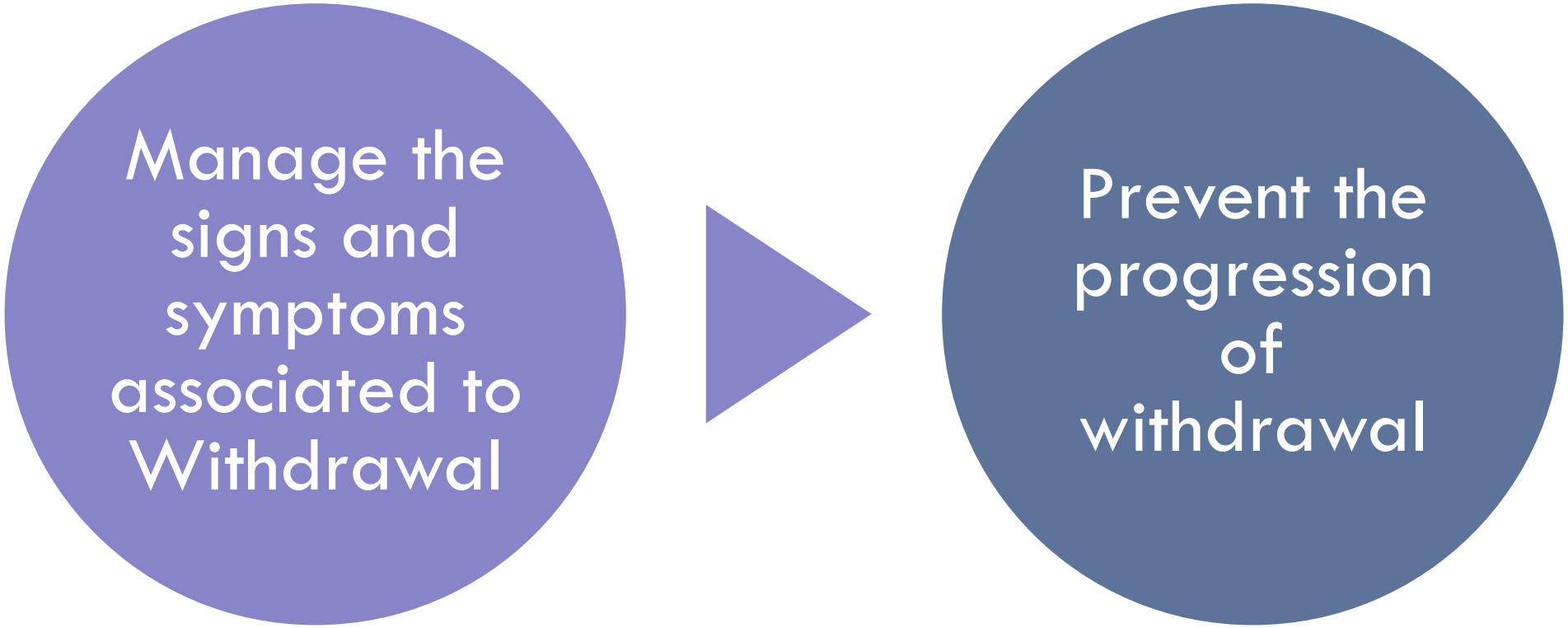
Assesses the severity of Alcohol Withdrawal

- Categorizes the severity of 10 signs and symptoms of withdrawal
  - Nausea/Vomiting, Tremor, Sweats, Anxiety, Agitation, Tactile Disturbances, Auditory Disturbances, Visual Disturbances, Headache, Clouding
- Maximum Score = 67

CIWA Score	Findings
<8	Very Mild
9 – 14	Mild
15 – 20	Moderate
>20	Severe

MONITORING


Re-assess every 1 – 4 hours for 24 hours
Stabilized when CIWA-Ar <10 for 24 hours
Observe for up to 36 hours



MANAGEMENT GOALS

MANAGEMENT

Supportive Care

Pharmacologic Agents

Combination therapy

Nutritional Supplementation

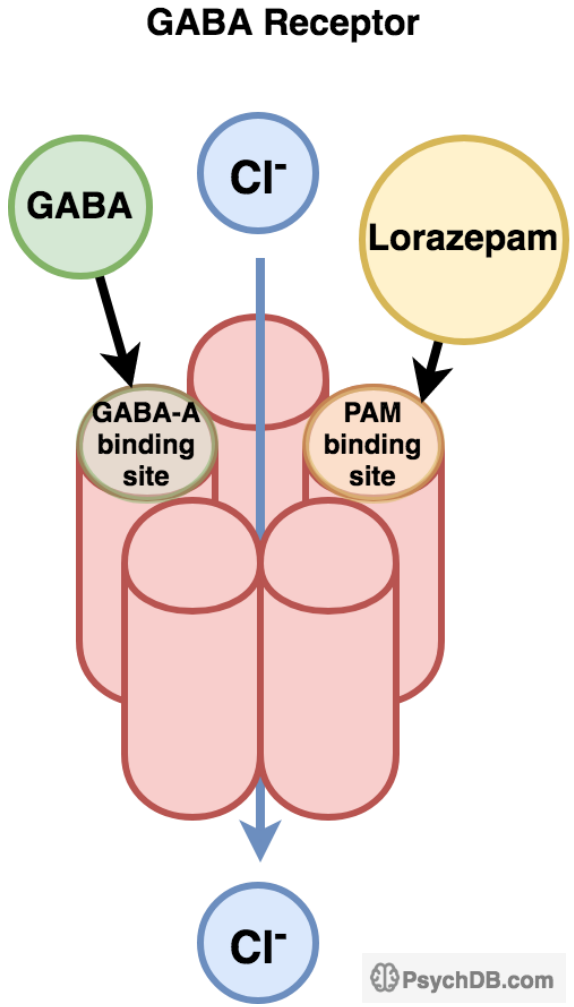
- Multivitamins
- Folic Acid
- Thiamine

Frequent Clinical Re-assessment

Image Credit: https://www.health.harvard.edu/staying-healthy/the-best-foods-for-vitamins-and-minerals

FIRST LINE MANAGEMENT: BENZODIAZEPINES

- Control psychomotor agitation and prevents progression to worsening withdrawal
- Symptom-triggered treatment is preferred in-patient*
- Why do we use Lorazepam In-Patient?
  - Short Duration
  - Lacks active metabolites and may prevent prolonged effects of over sedation



BENZODIAZEPINE HALF LIFE CHART

Pharmaceutical Mnemonics

Short acting BDZs have half-life values less than 5 hours (remember of ATOM)

Alprazolam
Triazolam
Oxazepam
Midazolam

Intermediate acting BDZs have half-life values from 5-24 hours (remember of Thin Layer Chromatography TLC)

Temazepam
Lorazepam
Clonazepam

Long acting BDZ have half-life values usually exceeding 24 hours (remember of the alphabet …CDeF…)

Clorazepate, **C**lordiazepoxide
Diazepam
Flurazepam

BDZ ones not metabolized by the liver and safe to use in liver failure (Remember of OTL which stands for Out The Liver)

Oxazepam
Temazepam
Lorazepam

BENZODIAZEPINE HALF LIFE

Benzo	Dose Equivalent	Half Life	Potency
Alprazolam	0.5	12 – 15 hours	High
Oxazepam	15	6 – 11 hours	Low
Midazolam	1.5	1 – 12 hours	High
Temazepam	5	10 hours	Low
Lorazepam	1	12 hours	High
Clonazepam	0.25	18 – 50 hours	High
Chlordiazepoxide (Librium)	10	24 – 48 hours	Low
Diazepam	5	20 – 70 hours	Low

CLAM – High Potency

MANAGEMENT: PHENOBARBITAL

Historically used for refractory Delirium Tremens

Quick IV onset (5 min), long half life (3 days)

Mechanistically:

- Increase the duration of GABA chloride channel opening
- Antagonizes excitatory NMDA and AMPA receptors

Adverse Reaction:

- Dose dependent Respiratory Depression
- Phenobarbital level

MANAGEMENT: PHENOBARBITAL

D. Pharmacotherapy

(1) Prophylaxis

Recommendation IV.13: Patients at risk of developing severe or complicated alcohol withdrawal or complications of alcohol withdrawal may be treated in ambulatory settings at the discretion of providers with extensive experience in management of alcohol withdrawal. Such patients should be provided with preventative pharmacotherapy. Benzodiazepines are first-line treatment because of their well-documented effectiveness in reducing the signs and symptoms of withdrawal including the incidence of seizure and delirium. Phenobarbital is an appropriate alternative in a 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.

MANAGEMENT: PHENOBARBITAL

Treatment of Alcohol Withdrawal Syndrome: Phenobarbital vs. CIWA Protocol (American Journal of Critical Care, 2018)

- **Objective:** Compare CIWA vs. phenobarbital protocol
- **Methods:**

MANAGEMENT: PHENOBARBITAL

Treatment of Alcohol Withdrawal Syndrome: Phenobarbital vs. CIWA Protocol (American Journal of Critical Care, 2018)

Primary Objective	Secondary Objective
ICU Length of Stay	Hospital Length of Stay Incidence of Invasive Mechanical Ventilation Use of adjunctive Pharmacotherapy

Table 2
Baseline patient demographics

Demographics	CIWA-Ar arm (n = 60)	Phenobarbital arm (n = 60)	*P*
Age, mean (SD), y	52 (15.5)	45 (11.4)	.003
Race, No. (%) of patients			>.99
White	57 (95)	57 (95)	
Black or African American	2 (3)	1 (2)	
Other	1 (2)	2 (3)	
Male sex, No. (%) of patients	43 (72)	44 (73)	.84
Left against medical advice, No. (%) of patients	1 (2)	3 (5)	
Comorbid conditions			
Psychiatric disorder	29	29	>.99
Polysubstance abuse	10	10	>.99
Seizure disorder	5	8	.41
Reactive airway disorder	8	6	.59
Liver disease	14	16	.68
Previous delirium tremens or withdrawal seizures	27	32	.92
Clinical presentation on admission			
Abnormal liver laboratory values	30	38	.17
Active alcohol withdrawal/delirium tremens	20	28	.46

Abbreviation: CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol, revised.

MANAGEMENT: PHENOBARBITAL

Treatment of Alcohol Withdrawal Syndrome: Phenobarbital vs. CIWA Protocol (American Journal of Critical Care, 2018)

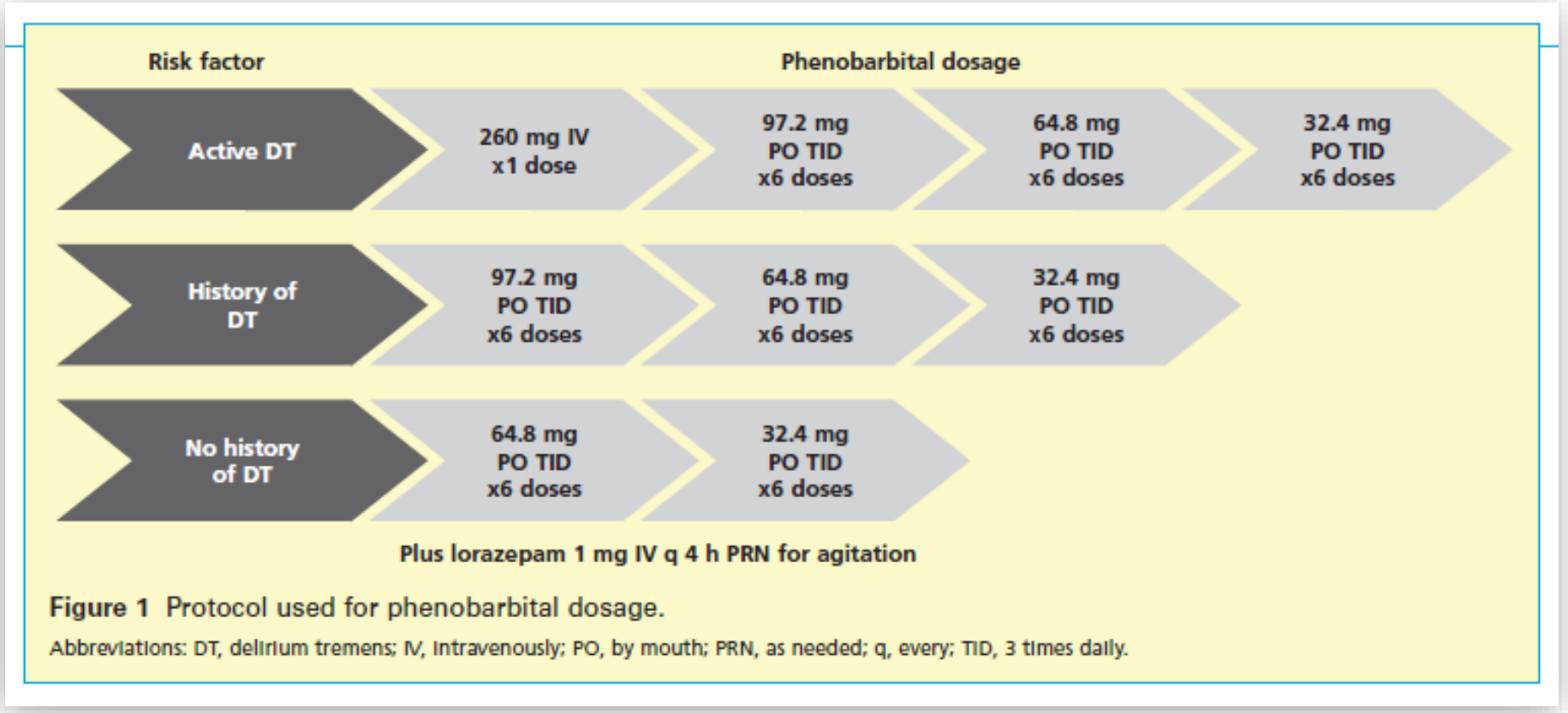
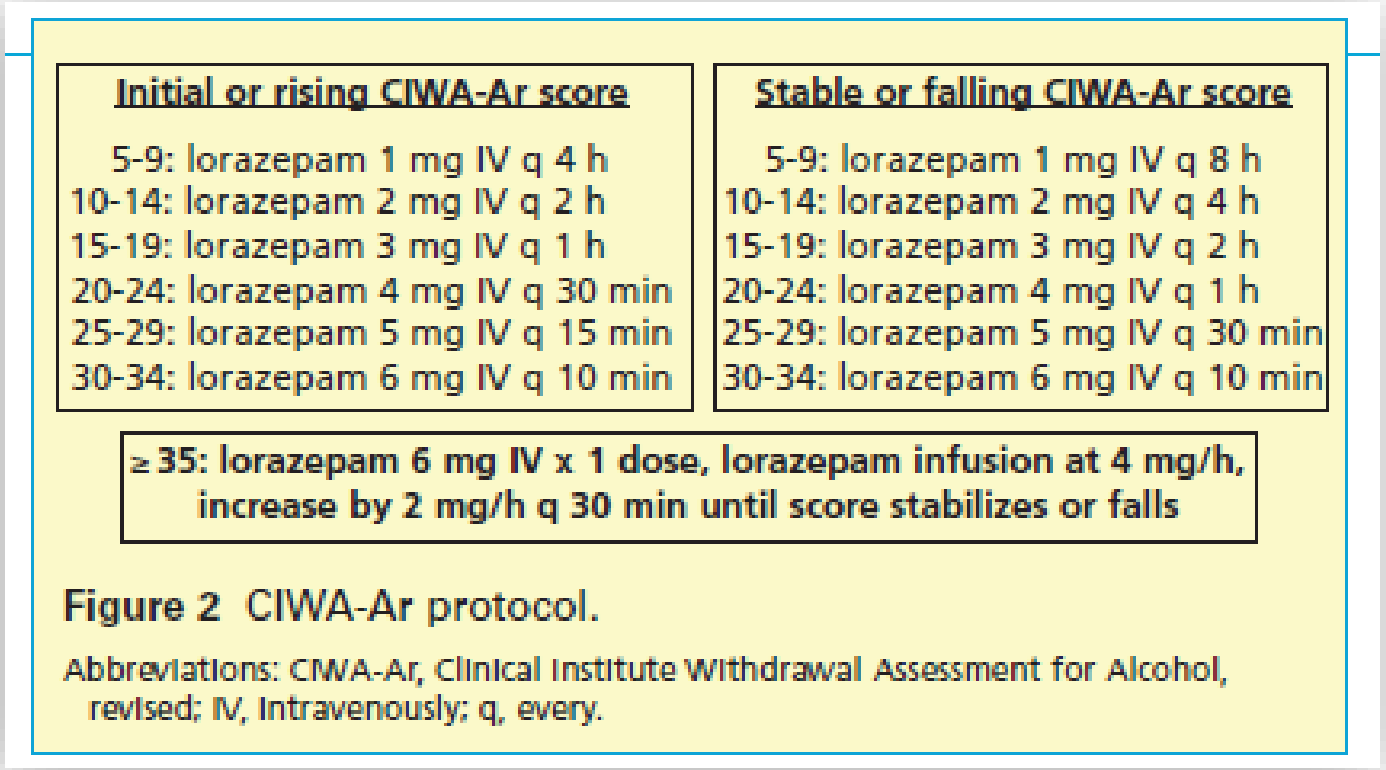


Figure 1 Protocol used for phenobarbital dosage.

Abbreviations: DT, delirium tremens; IV, intravenously; PO, by mouth; PRN, as needed; q, every; TID, 3 times daily.

MANAGEMENT: PHENOBARBITAL

Treatment of Alcohol Withdrawal Syndrome: Phenobarbital vs. CIWA Protocol (American Journal of Critical Care, 2018)



Initial or rising CIWA-Ar score	Stable or falling CIWA-Ar score
5-9: lorazepam 1 mg IV q 4 h	5-9: lorazepam 1 mg IV q 8 h
10-14: lorazepam 2 mg IV q 2 h	10-14: lorazepam 2 mg IV q 4 h
15-19: lorazepam 3 mg IV q 1 h	15-19: lorazepam 3 mg IV q 2 h
20-24: lorazepam 4 mg IV q 30 min	20-24: lorazepam 4 mg IV q 1 h
25-29: lorazepam 5 mg IV q 15 min	25-29: lorazepam 5 mg IV q 30 min
30-34: lorazepam 6 mg IV q 10 min	30-34: lorazepam 6 mg IV q 10 min

≥ 35: lorazepam 6 mg IV x 1 dose, lorazepam infusion at 4 mg/h, increase by 2 mg/h q 30 min until score stabilizes or falls

Figure 2 CIWA-Ar protocol.

Abbreviations: CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol, revised; IV, Intravenously; q, every.

MANAGEMENT: PHENOBARBITAL

Table 3
Outcomes and clinical characteristics

Outcome or clinical characteristic	CIWA-Ar arm (n=60)	Phenobarbital arm (n=60)	*P*
ICU stay (midnights), mean (SD)	4.4 (3.9)	2.4 (1.5)	<.001
Hospital stay (midnights), mean (SD)	6.9 (6.6)	4.3 (3.4)	.004
Total lorazepam equivalents, mean (SD), mg	35.2 (48.5)	11.3 (18)	<.001
Ventilator use, No. of patients	14	1	<.001
Dexmedetomidine use, No. of patients	17	4	.002
Olanzapine use, No. of patients	7	5	.54
Haloperidol use, No. of patients	10	4	.08
Quetiapine use, No. of patients	5	2	.24

Abbreviations: CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol, revised; ICU, Intensive care unit.

MANAGEMENT: PHENOBARBITAL

Treatment of Alcohol Withdrawal Syndrome: Phenobarbital vs. CIWA Protocol (American Journal of Critical Care, 2018)

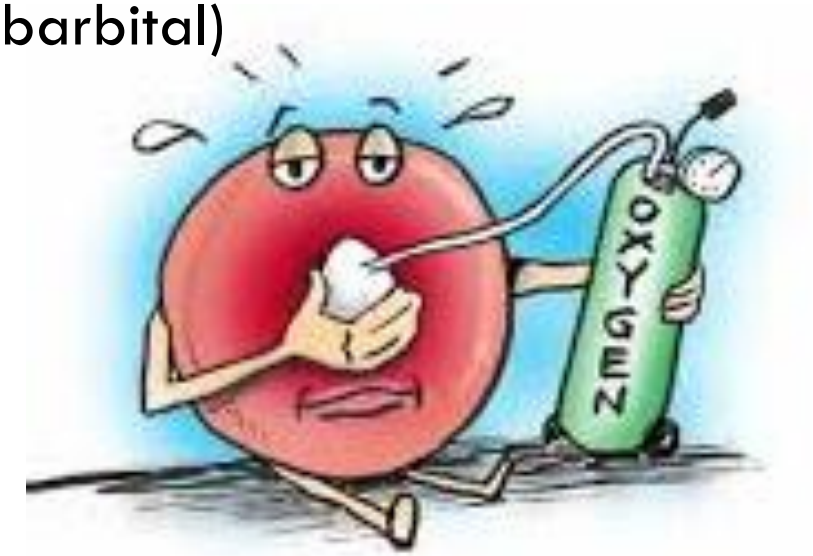
- **Conclusion:**
  - "Phenobarbital for the treatment of alcohol withdrawal is an effective alternative to the standard-of-care protocol of symptom-triggered benzodiazepine therapy."
- **Study Strengths:**
  - Similar study population
- **Limitations:**
  - Efficacy of phenobarbital may have been diminished by lower dosing
  - Severity of alcohol withdrawal was not reported
  - Relatively small population

	Aim	Method	Result	Conclusion
Schmidt KJ, Doshi MR, Holzhausen JM, et al.[3]	To summarize the literature pertaining to the pharmacotherapy of severe alcohol withdrawal	PubMed (January 1960 to October 2015) search yielded 739 articles of which 27 were included.	Benzodiazepines remain the treatment of choice, with diazepam having the most favorable pharmacokinetic profile. Propofol is a viable alternative for patients refractory to benzodiazepines	The roles of phenobarbital, dexmedetomidine, and ketamine remain unclear.
Rosenson J, Clements C, Simon B, et al. [5]	To investigate whether a single dose of phenobarbital combined with a standardized lorazepam-based alcohol withdrawal protocol decreases ICU admission	51 patients received a single dose of phenobarbital (10 mg/kg in 100 mL normal saline) and 51 placebo (100 mL normal saline) in this prospective, randomized, double-blind, placebo-controlled study	Phenobarbital reduced ICU admissions (8% vs. 25%, 95% confidence interval 4-32). There were no differences in adverse events.	A single dose of intravenous phenobarbital combined with a symptom-guided lorazepam-based alcohol withdrawal protocol decreases ICU admission and increases adverse outcomes.
Hendey GW, Dery RA, Barnes RL, et al. [13]	To compare phenobarbital (PB) versus lorazepam (LZ) in the treatment of alcohol withdrawal	Of 44 patients, 25 received PB, and 19 LZ in the ED and at 48 hours.	Both PB and LZ reduced CIWA scores from baseline to discharge (15.0-5.4 and 16.8-4.2, $P < .0001$).	PB and LZ were similarly effective in the treatment of mild/moderate alcohol withdrawal
Tidwell WP, Thomas TL, Pouliot JD et al. [14]	To compare the benzodiazepine and phenobarbital protocols	Retrospective cohort study conducted from January 2016 through June 2017 at a 42-bed ICU	Patients who received phenobarbital had significantly shorter stays in the ICU than those who received therapy based on the CIWA-Ar scale (mean [SD], 2.4 [1.5] vs 4.4 [3.9] days; $P < .001$).	A phenobarbital protocol for AWS is an effective alternative to the standard-of-care protocol of symptom-triggered benzodiazepine therapy
Oks M, Kleven K, et al.	To evaluate symptom triggered phenobarbital for the treatment of AWS as an alternative to benzodiazepines	Retrospective observational study conducted from 2011 – 2015 in patients with AWS admitted to MICU	Analyzed 86 AWS patients with a mean CIWA of 19 and mean phenobarbital dose of 1977.5 mg (130 mg q30 min PRN)	Sole use of phenobarbital may be a safe alternative to benzodiazepines
Nisavic M, Nejad SH, et al. (2019)	To compare the effectiveness of phenobarbital vs. benzodiazepines	Retrospective chart review of 562 patients admitted over a 2 year period	143 patients received phenobarbital vs 419 who received benzodiazepines.	Patients initiated on phenobarbital had similar primary and secondary treatment outcomes compared to those with a benzodiazepine

MANAGEMENT

What about adjunctive phenobarbital to benzodiazepines for synergy?

- Both may act synergistically on GABA-A receptors
  - One increases the frequency of chloride channel opening (benzodiazepines)
  - The other increases the duration of the opening (phenobarbital)
- Increased risk for over-sedation
  - Patient's may become more sensitive to this mechanism
  - Increased risk for respiratory depression



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MANAGEMENT: PHENOBARBITAL

In regard to Clinical Practice:

- Phenobarbital produces similar results as compared to benzodiazepines
- Studies comparing phenobarbital vs. benzodiazepine's:
  - Similar or lower rates of intubation with phenobarbital
  - Possible lower rates of delirium
- Mechanistically, phenobarbital may be superior to benzodiazepine's
  - Benzodiazepines: Stimulate GABA-A
  - Barbiturates: Enhance GABA activity and suppress glutaminergic activity via NMDA blockade
    - Synergistic mechanism is comparable to the physiology of alcohol withdrawal

MANAGEMENT:

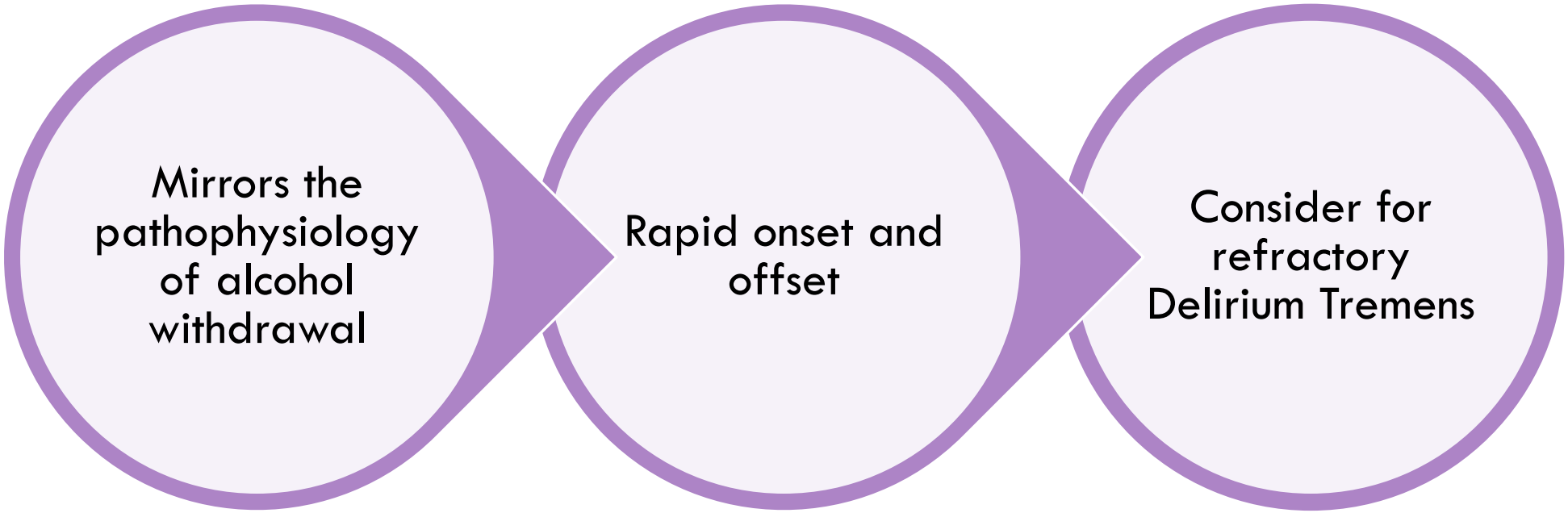
Classification	ICU and <65 yo	ICU and ≥65 yo	Non-ICU
Severe AUD	Phenobarbital 260 mg IV q6h x4 doses followed by 130 mg q6h. Alternatively can consider 260 mg IV x1 followed by 130 mg IV q6h. *If the patient is in DT's, may consider 10 mg/kg (max 1000 mg) x1, followed by 130 mg IV q6h to begin the following day	Phenobarbital 130 mg IV q6h	Phenobarbital 129.6 mg PO q6h
Mild/moderate AUD (~6 pack of beer a day equivalent)	Phenobarbital 130 mg IV q6h	Phenobarbital 65 mg IV q6h	Phenobarbital 64.8 mg PO q6h

**Check Phenobarbital level at 72 hours.* *If the level is therapeutic (15 – 40 mcg/mL), adjust dose to 97.2 mg PO BID until discharge OR until hospital day 7, then discontinue. Consider re-checking a level if the patient's mental status changes.*

***Alternative dosing options may be considered pending clinical status and may include alternate weaning options*

Protocol Credit: Allison Lauver, PharmD, BCPS, BCCCP and Dr. Tiffany Marchand, MD

MANAGEMENT: PROPOFOL



Agent	Dose	Onset	Metabolism	Duration
Propofol	5 – 50 mcg/kg/min	30 seconds	Hepatic	10 minutes

ADJUNCTIVE AGENTS

Clonidine

Dexmedetomidine

Folic Acid

Thiamine

Multivitamin

Banana Bags

AUTONOMIC HYPERACTIVITY

Alpha-2 Adrenergic Agonists

- Used as adjuncts to decrease the kindling effects of sympathetic-mediated symptoms
- Neither address the underlying pathophysiology of alcohol withdrawal and should never be used as monotherapy

α – 2 Adrenergic Agonist	Dose	Onset
Clonidine	0.1 – 0.3 mg every 6 to 8 hours	30 – 60 minutes
Dexmedetomidine	0.2 – 1.4 mcg/kg/hr	5 – 10 minutes

MANAGEMENT: SUPPLEMENTS

Chronic alcohol use leads to inadequate dietary intake/absorption of essential vitamins & minerals:

- **Folic Acid**
  - Synthesizes genetic material of the cell and plays a role in maturation of blood cells. Deficiencies are linked to anemia or hyperhomocysteinemia.
- **Thiamine**
  - Cofactor for cerebral energy metabolism (i.e. transketolase, alpha-ketoglutarate dehydrogenase, pyruvate dehydrogenase). Deficiency leads to neuronal injury via metabolic inhibition in area's of high metabolic demand with high thiamine turnover leading to BBB breakdown and increased ROS
    - As a result, Wernicke's Encephalopathy can manifest from neuronal loss
      - *MRI:* Mamillary body atrophy, diencephalic and periventricular lesions, bilateral symmetrical hyperintensity in the frontal-parietal cortices
      - *Symptoms:* Encephalopathy, oculomotor dysfunction, gait ataxia

MANAGEMENT: SUPPLEMENTS

Folic Acid (IV or PO)

1 mg daily

Prevents Hyperhomocysteinemia

Thiamine IV

100 mg daily x5 days

Prevents Weirnicke Encephalopathy

Wernicke's Thiamine Dose (IV): 500 mg every 8 hours x2 days followed by 250 mg daily x5 days, then 100 mg daily thereafter

MANAGEMENT: SUPPLEMENTS

What about banana bags?

- 1 liter of fluid
- 10 mL vial of multivitamins
- 100 mg thiamine
- 1 mg of folic acid
- 1 – 2 g of magnesium

- **Use has not been well studied**
  - Flannery et al, Critical Care Medicine (2016):
    - Evaluated the use of standard banana bags in critically ill patients with alcohol use disorder
    - Banana bag failed to optimize the delivery and dose of thiamine to the central nervous system
      - Especially with Wernicke's Encephalopathy

SUMMARY

- Alcohol (Ethanol) is a GABA agonist and Glutamate Antagonist at the NMDA receptor
- Abrupt alcohol cessation can lead to uncomfortable symptoms that may manifest over hours to days to delirium tremens.
- Various pharmacologic therapies can be incorporated into inpatient management of alcohol withdrawal
- All patients with a history of excess alcohol use should be initiated on folic acid and thiamine

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