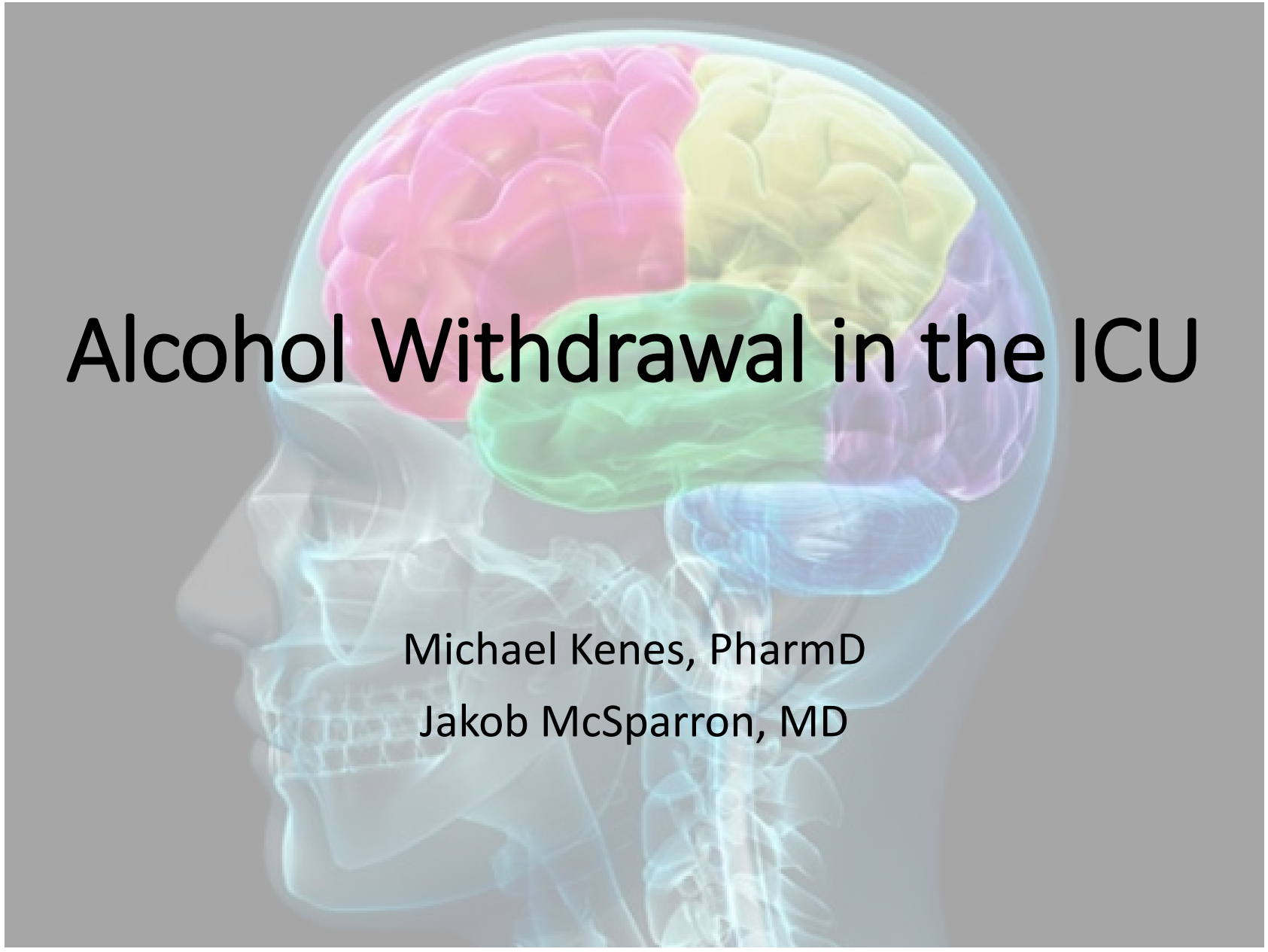


Alcohol Withdrawal in the ICU

Michael Kenes, PharmD
Jakob McSparron, MD

PULMONARY & CRITICAL CARE MEDICINE
DEPARTMENT OF INTERNAL MEDICINE
UNIVERSITY OF MICHIGAN HEALTH SYSTEM

Objectives

- Explain the mechanism of alcohol withdrawal
- Describe strategies to manage severe alcohol withdrawal
- Define key differences between benzodiazepine and phenobarbital
- List adjunctive treatment options for patients with alcohol withdrawal

AMERICAN THORACIC SOCIETY DOCUMENTS

Research Needs for Inpatient Management of Severe Alcohol Withdrawal Syndrome

An Official American Thoracic Society Research Statement

Tessa L. Steel, Majid Afshar, Scott Edwards, Sarah E. Jolley, Christine Timko, Brendan J. Clark, Ivor S. Douglas, Amy L. Dzierba, Hayley B. Gershengorn, Nicholas W. Gilpin, Dwayne W. Godwin, Catherine L. Hough, José R. Maldonado, Anuj B. Mehta, Lewis S. Nelson, Mayur B. Patel, Darius A. Rastegar, Joanna L. Stollings, Boris Tabakoff, Judith A. Tate, Adrian Wong, and Ellen L. Burnham; on behalf of the American Thoracic Society Assembly on Critical Care, Assembly on Behavioral Science and Health Services Research, and Assembly on Nursing

This official research statement of the American Thoracic Society was approved May 2021

- Syndrome lacking clear definitions and assessments of severity
  – difficult to differentiate from other etiologies
- Evidence not directly translatable across severity of syndrome
- Objective baseline/risk factor assessment does not predict severity of withdrawal
- Multiple challenges in conducting robust clinical trials

Group poses three questions:

1. Optimal 1st line therapy?
2. Ideal dosing strategy?
3. Protocolized/bundled-care vs. “usual care”?

A familiar case…

- 47 year old man with history of alcohol use disorder, prior admissions for withdrawal, presents with severe nausea, emesis, headache, tremors

- His last drink was approximately 14 hours prior to presentation

History

- Medical / Surgical history:
  - Alcohol use disorder (prior seizures, prior ICU admission)
  - Hypertension
  - Previous GI bleed due to gastric ulcer

- Medications:
  - Not taking prescribed antihypertensive medication

Exam

- Afebrile
- HR 110 bpm
- BP 170/88 mmHg
- RR 24
- SpO2 97%

Labs unrevealing

AST/ALT slightly elevated

EtOH/UDS negative

- Cachectic, ill appearing
- Tremulous and diaphoretic
- OP clear with dry mucous membranes
- Tachycardic, regular
- Lung clear bilaterally
- Abdomen nondistended, +BS, nontender
- Hyperreflexic

Clinical Course

- Patient increasingly agitated and restless, refusing care, notes seeing things on the wall that are not there.

- Next step?

Clinical Course

- Patient receives 6mg IV lorazepam for EtOH withdrawal with minimal improvement in symptoms. He has witnessed seizure activity and receives additional 4mg IV lorazepam with cessation of seizure activity.

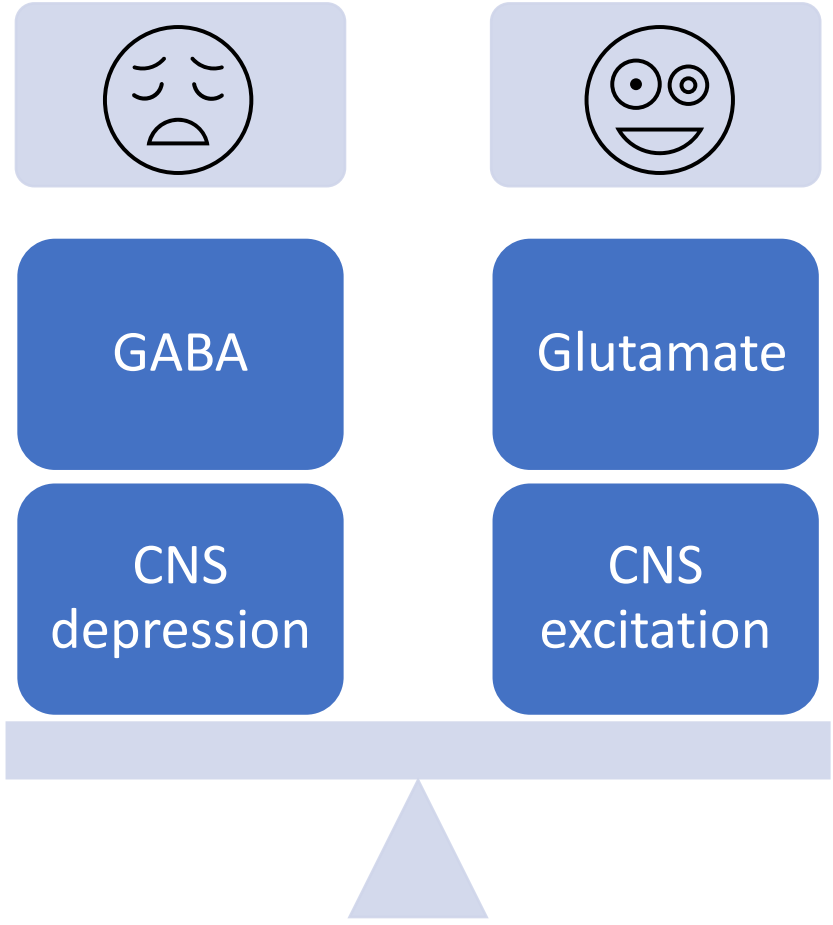
- He continues to demonstrate adrenergic symptoms, intermittently combative.

- Next step?

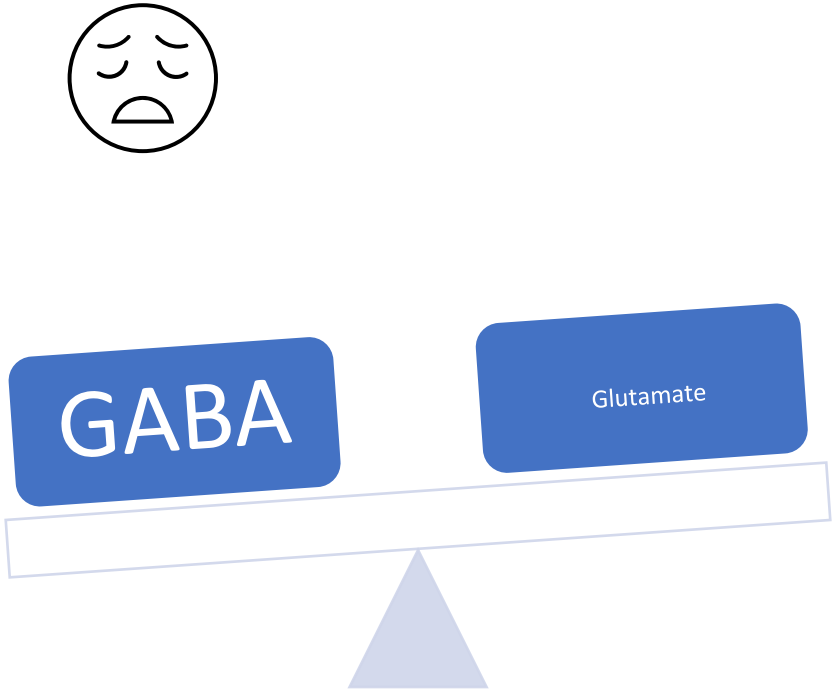
Clinical Course

- Patient receives increasing doses of lorazepam over next 30 minutes with subsequent prolonged generalized seizure. He is intubated and sedated with propofol. His course is notable for VAP, delirium. He is extubated on hospital day 7 and discharged home on day 12.

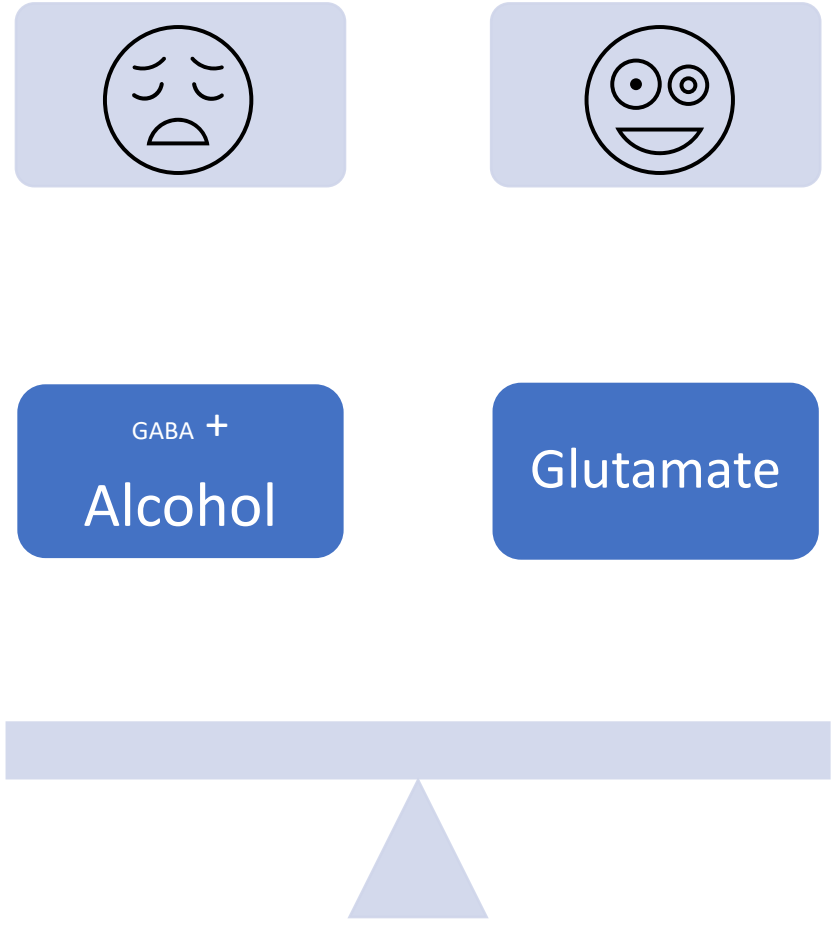
Homeostasis – even balance



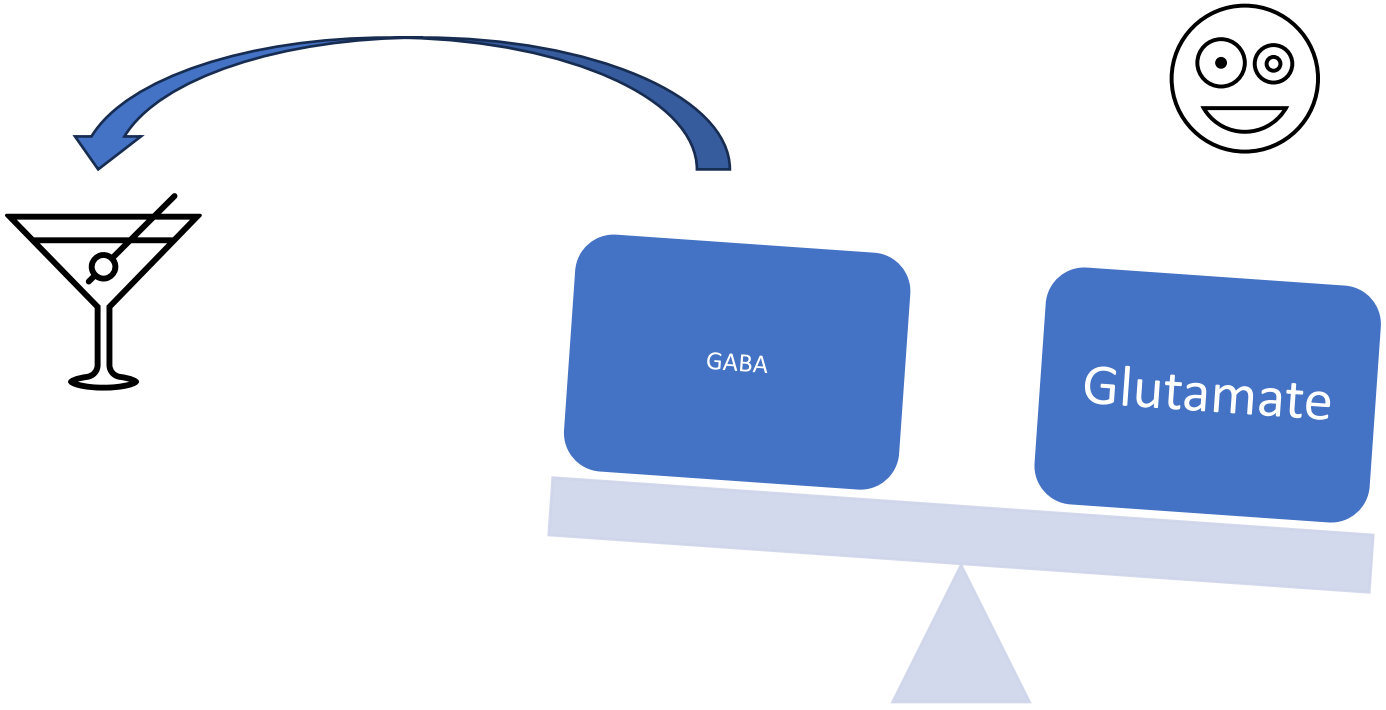
Occasional Alcohol → Intoxication / CNS Depression



Homeostasis: Chronic Alcohol Use



Alcohol Withdrawal → CNS Hyperexcitation



Mechanism of Withdrawal – complex and heterogenous

- **Acute alcohol consumption**
  - Activates *inhibitory* gamma-aminobutyric acid (GABA) receptors at high concentrations
  - Inhibits *excitatory* *N*-methyl-D-aspartate (NMDA) receptors

- **Chronic alcohol consumption**
  - Downregulation of inhibitory "GABA-ergic" system
  - Upregulation of excitatory NMDA receptors
  - ---> Upregulation of excitatory glutamine receptors

Hall W. Lancet. 1997.

Mechanism of Withdrawal – complex and heterogenous

- Withdrawal sx mainly caused by unoccupied, up-regulated NMDA receptors

- Multiple, repeated intoxication/withdrawal episodes contribute a "kindling effect"

- Other mechanisms often present
  - Increased dopamine (-> hallucinations)
  - Increased adrenergic (-> sympathetic hyperactivity)
  - Increased HPA activation (-> increased cortisol)

Hall W. Lancet. 1997.

Severity and Spectrum of Alcohol Withdrawal Syndrome (AWS)

- Alcohol consumption is common (55% of adults)
- Lifetime prevalence of AUD 29%
- Complex and dynamic

Jesse S. Acta Neurologica Scandinavica. 2016.

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Autonomic	Motor	Awareness	Psychiatric
Tachycardia Tachypnea Dilated Pupils Elevated BP Elevated temp Diaphoresis Nausea Vomiting Diarrhea	Hand tremor Tremulousness Seizures Ataxia Gait Disturbances Hyperreflexia Dysarthria	Insomnia Agitation Irritability Delirium Disorientation	Illusions Delusions Hallucinations Paranoia Anxiety Affective Instability Combativeness Disinhibition

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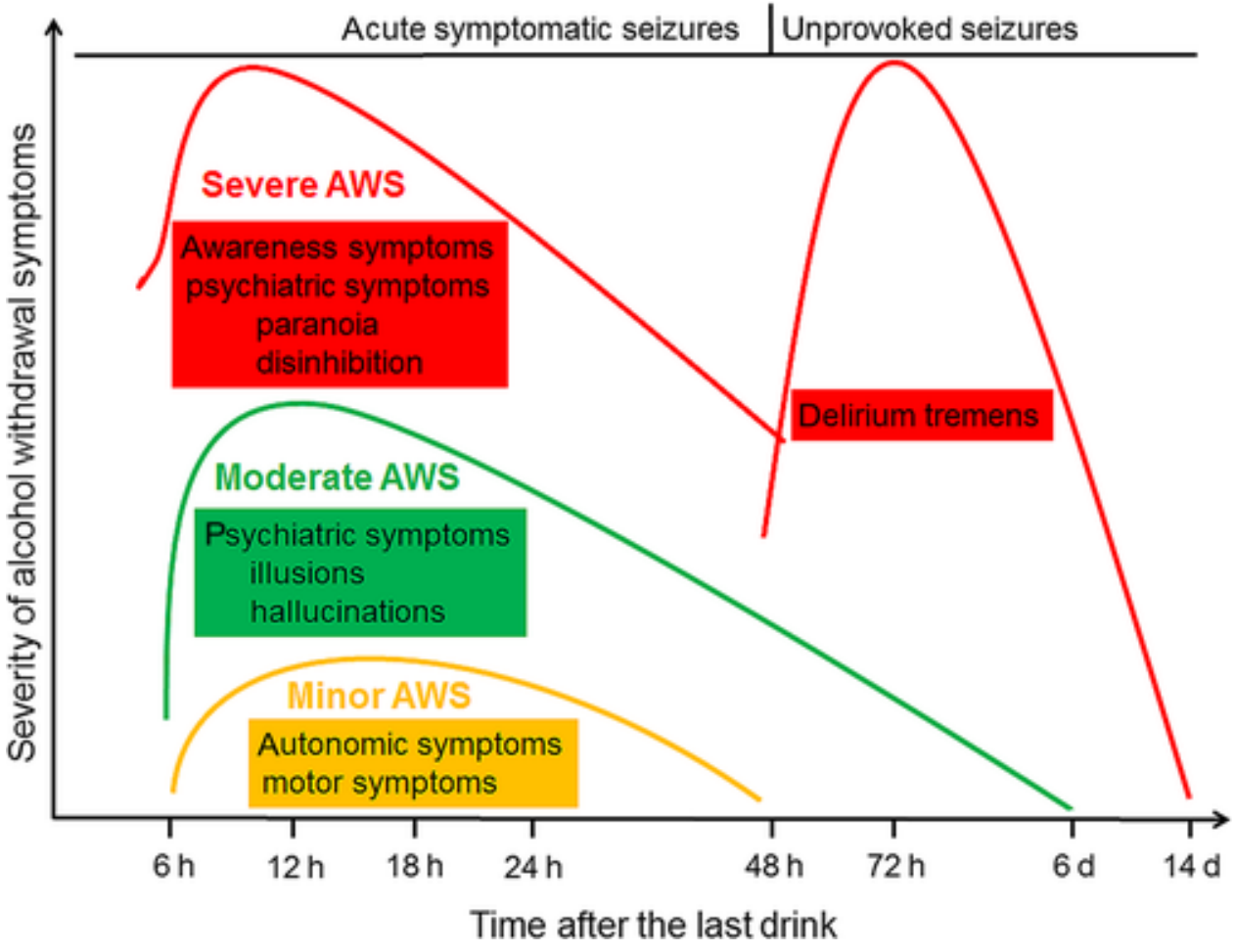


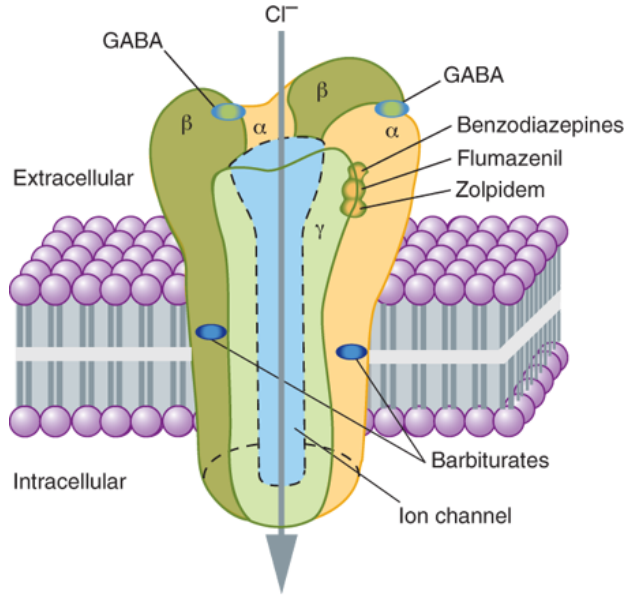
Jesse S. Acta Neurologica Scandinavica. 2016.

Benzodiazepines

- Binds to inhibitory GABA receptor -> Increase influx of chloride ions in channel
  - Increases frequency of channel opening
  - But remember... Alcohol use disorder down-regulates GABA receptors

- Historically regarded as 1st line therapy
  - Control psychomotor agitation
  - Effective at reducing risk of withdrawal seizures and DTs
  - 2011 Cochrane review of 7,333 patients
    - BZDs reduced seizures compared to placebo (RR 0.16) and antipsychotics (RR 0.24)
    - No statistical difference between BZD agents (trend toward benefit with chlordiazepoxide?)

- Selection generally guided by pharmacokinetics
- IV administration preferred (oral when able); variable absorption with IM



Source: Bertram G. Katzung, Todd W. Vanderah:
Basic & Clinical Pharmacology, Fifteenth Edition
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Hammond D. Hospital Pharmacy. 2017.

Pharmacokinetics of Select Benzodiazepines

Medication	Time to Peak Plasma Level (Hours)	Elimination Half-Life, Parent (Hours)	Metabolic Pathway	Clinically Significant Metabolites	Protein Binding (%)
Chlordiazepoxide	1-4	5-30	*N*-Dealkylation	Desmethyl-chlordiazepoxide	96
			Oxidation	Demoxepam	
				DMDZ	
Diazepam	0.5-2	20-80	Oxidation	DMDZ	98
				Oxazepam	
Lorazepam	2-4	10-20	Conjugation	—	85

DMDZ = desmethyldiazepam; half-life 50-100 hours

Chapter 86. DiPiro's Pharmacotherapy, 12e, 2023.

Strategies for Use of Benzodiazepine

- **Symptom-triggered**
  - Patients need to be symptomatic, coupled with regular (re-) assessment
  - Most common scale = Addiction Research Foundation Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)
    - Not validated in ICU (intubated)
  - ICU → Richmond Agitation-Sedation Scale (RASS)?

- Medication only given when exhibiting symptoms
  - Generally, prefer short-acting (i.e., lorazepam, diazepam)
  - Longer acting not contraindicated (i.e., chlordiazepoxide)

- Historically demonstrated to lead to shorter treatment duration, reduced risk of oversedation compared to fixed-dosing

Alcohol Withdrawal Assessment Scoring Guidelines (CIWA - Ar)

Nausea/Vomiting - Rate on scale 0 - 7

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

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

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

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

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

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

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

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

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

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

Visual disturbances - Ask, "Does the light appear to be too bright? Is its color different than normal? Does it hurt your eyes? Are you seeing anything that disturbs you or that you know isn't there?"
0 - not present
1 - very mild sensitivity
2 - mild sensitivity
3 - moderate sensitivity
4 - moderate hallucinations
5 - severe hallucinations
6 - extremely severe hallucinations
7 - continuous hallucinations

Headache - Ask, "Does your head feel different than usual? Does it feel like there is a band around your head?" Do not rate dizziness or lightheadedness.

0 - not present
1 - very mild
2 - mild
3 - moderate
4 - moderately severe
5 - severe
6 - very severe
7 - extremely severe

Sulivan JT. Br J Addict. 1989.

Strategies for Use of Benzodiazepine

- **Loading dose** or "**Front-loading**"
  - Generally thought to be appropriate for initial severe presentations
    - i.e., CIWA-AR >19
  - Caution in those who might experience AE (elderly, severe liver disease, DDIs)

- **Fixed-dose** – effective, but high risk for "over-dosing"
  - Close monitoring for sedation/respiratory depression needed
  - No superiority vs. symptom-triggered, may be beneficial w/history of DTs/seizures
  - May be beneficial if symptoms do not align with scoring tools

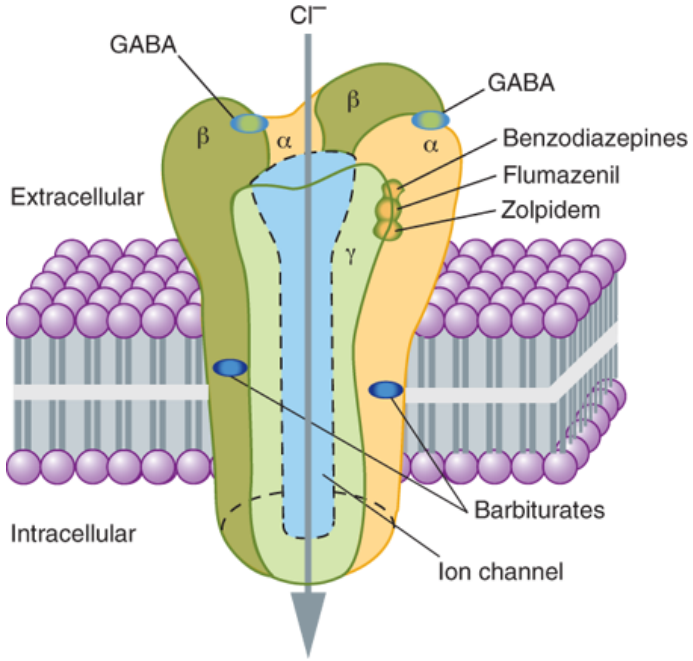
Barbiturates -Phenobarbital

- Binds to inhibitory GABA receptor -> increase <u>time</u> chloride channels are open (synergistic effect w/BZDs)
  - Secondary mechanism – inhibits the excitatory (up-regulated) NMDA receptor
  - No paradoxical agitation (?or delirium)

- Rapid onset (<5 minutes) with IV administration
- Long half-life/duration of action (2-5 days)
  - Some accumulation of doses within 24-48 hours

- Single-compartment model or "linear dose/concentration"

- Therapeutic drug monitoring available
  - Epilepsy = 15-40 mcg/mL
  - Ataxia/nystagmus = ~50 mcg/mL
  - Coma/stupor = >65 mcg/mL



Source: Bertram G. Katzung, Todd W. Vanderah:
Basic & Clinical Pharmacology, Fifteenth Edition
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Tangmose K. Dan Med Bull. 2010.

Phenobarbital Clinical Pearls

- Organ Dysfunction
  - Metabolized in liver (~60-80%), but also eliminated unchanged in kidneys
  - Half-life increases in cirrhosis
    - Kidney compensates to increase excretion
  - Does not result in higher peaks; half-life/duration increases (i.e., longer "self-taper")

"Changes [to PB metabolism in liver disease] are modest .. because excretion of unchanged PB via the kidneys tends to moderate the importance of impaired hepatic function."

THE EFFECT OF LIVER DISEASE IN MAN ON THE DISPOSITION OF PHENOBARBITAL[1,2]

JOHN ALVIN, TOM McHORSE, ANASTACIO HOYUMPA, MILTON T. BUSH AND STEVEN SCHENKER

Departments of Pharmacology and Medicine, Vanderbilt University School of Medicine and Veterans Administration Hospital, Nashville, Tennessee

Accepted for publication July 8, 1974

ABSTRACT

ALVIN, JOHN, TOM MCHORSE, ANASTACIO HOYUMPA, MILTON T. BUSH AND STEVEN SCHENKER: The effect of liver disease in man on the disposition of phenobarbital. J. Pharmacol. Exp. Ther. **192:** 224–235, 1975.

The disposition of phenobarbital (PB) was studied in normal individuals and in patients with cirrhosis or acute viral hepatitis to determine 1) if there is significant impairment of PB metabolism in hepatic disease and 2) to what extent such abnormal disposition of the drug affects its disappearance from blood. The diagnosis of liver disease was based on characteristic clinical findings, biochemical liver "function" tests and liver biopsy when necessary. All individuals had normal renal function and were free of other drug and alcohol intake for at least 3 weeks. With radiotracer methodology, PB and its principal metabolites, *p*-hydroxyphenobarbital (PBOH) and conjugated PBOH (PBOC), were monitored in blood and urine for 5 days after a single dose of ^{14}C-PB administered intraduodenally. PB blood half-life ($T_{1/2}$) in the control group was 86 ± 3 hours (S.E.). In cirrhotics the $T_{1/2}$ was prolonged to 130 ± 15 hours ($P < .001$) and this was accompanied by a 50% reduction in urinary PBOC excretion ($P < .05$). Urinary excretion of PB and PBOH was unaltered by cirrhosis. In patients with acute viral hepatitis, PB $T_{1/2}$ was not significantly prolonged and urinary excretion of PB and its metabolites was in the normal range ($P > .05$). No PBOH and only traces of PBOC were detected in the blood of either control individuals or patients with liver disease. Urinary excretion of unchanged PB was an important elimination pathway of the drug in all groups. As a result of this, PB $T_{1/2}$ in cirrhosis was only moderately prolonged.

Phenobarbital Clinical Pearls

- Drug-Drug Interactions
  - Minor substrate of CYP 2C19/2C9/2E1
  - Induces
    - CYP 3A4 (strong)
    - CYP 1A2/2A6/2B6/2C9 (weak)
    - UGT1A1 (weak)

- Induction generally occurs 1 week after initiation (maximal at 2-3 weeks); de-induction 1 week after discontinuation
    - Unclear and potentially insignificant effect of short period of exposure
    - Assess risk/benefit of individual drug interactions
      - Consult drug information resources and/or clinical pharmacist

Example Phenobarbital Protocol

Initial load + small PRN doses

Vs.

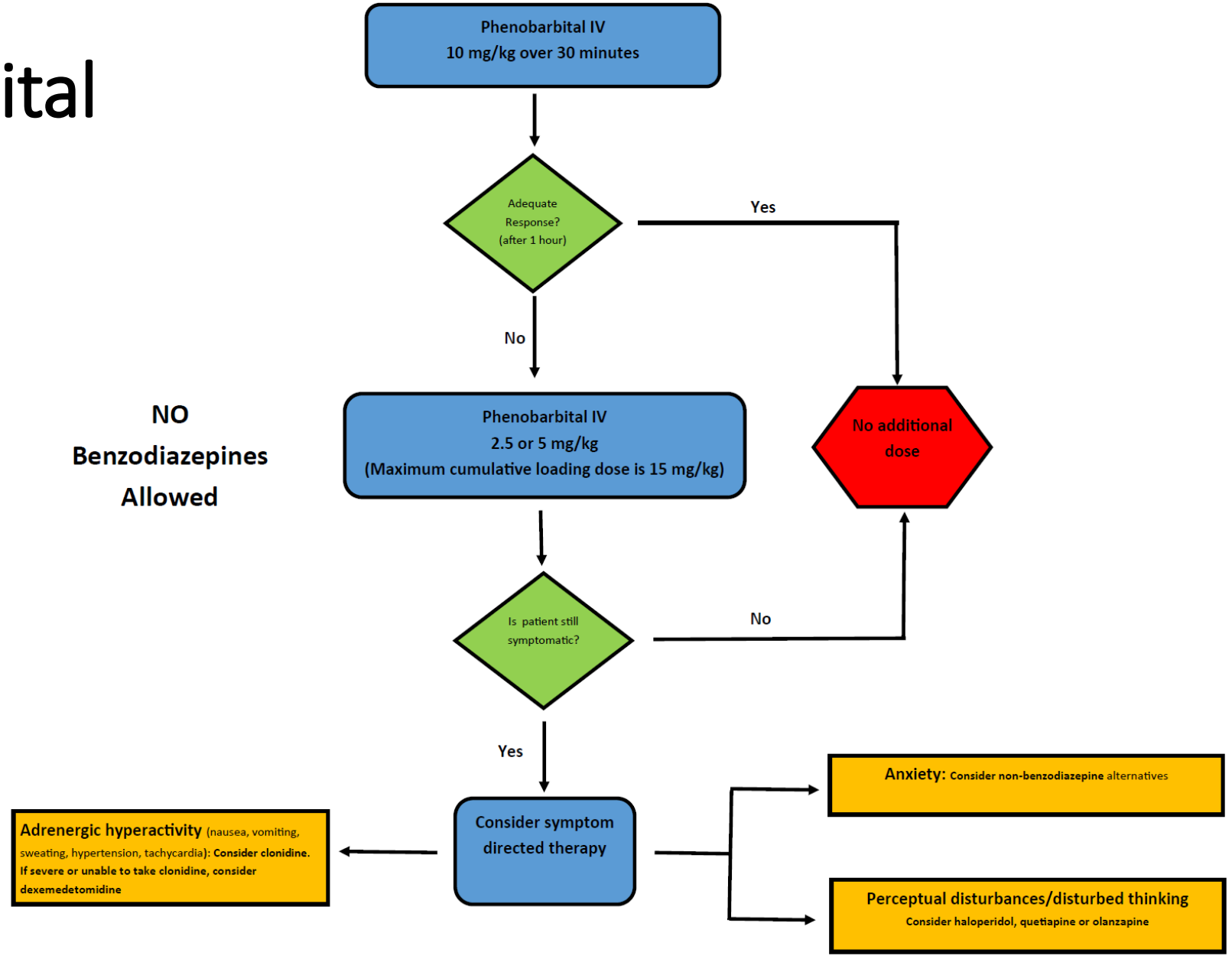
Symptom-trigger PRN doses
(65mg vials, usually stocked in unit)

~10mg/kg dose *generally* produces a peak concentration of 10-15 mcg/mL
(subtherapeutic for epilepsy indication)

General max dose is 15/20/25 mg/kg

Higher dosing requirements prompts investigation of other causes (or adjuncts)

NO Benzodiazepines Allowed



Comparing the options

Benzodiazepines

- Symptom triggered > fixed dosing
  - Decreased dosage, Decreased time on MV, Decreased ICU LOS

- Multiple agents with varying onset/duration
  - Provider familiarity
  - Comfort in all patient care settings

Hammond D. Hospital Pharmacy. 2017.

Comparing the options

Benzodiazepines

- Symptom triggered > fixed dosing
  - Decreased dosage, Decreased time on MV, Decreased ICU LOS
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  - Provider familiarity
  - Comfort in all patient care settings

Phenobarbital

- Effective for BZD "nonresponsive" AWS
- Severe AWS often requires intubation 2/2 large BZD doses
  - Front-loading PHB instead? Does it mitigate agitation/delirium/resp depression?
- Limited data on PHB monotherapy
- ?use outside of ED or ICU

Hammond D. Hospital Pharmacy. 2017.

Current Evidence

- 2023 SR/MA of BZD vs PHB presenting to ED, treated in ICU/ED
    - PHB "used alone or with other pharmacological agents"
  - 12 studies (1934 patients); mostly observational, significant heterogeneity
  - No difference in risk of intubation (RR 0.70, 95% CI 0.36-1.38)
  - Similar rates of seizures (RR 0.70, 95% CI 0.29-1.89)
  - No difference in ICU/hospital LOS

- Similar conclusions from a 2017 SR/MA by Hammond
  - Slightly more favorable outcomes for PHB - included broader scope of patients

Pourmand A. Am J Emerg Med. 2023.
Hammond DA. Hosp Pharm. 2017.

Current Evidence

2023 Alwakeel, Pre/Post study

Medical ICU

- BZD: CIWA-AR – PRN Lorazepam/Diazepam
- PHB: 260mg PHB load + 130mg q15-30min PRN (max 15mg/kg)

No medication cross-over in ICU
(unknown prior to ICU admission)

Regression analysis – 40% (95% CI 25.8-53.5) decrease in ICU LOS with PHB

Outcomes	Phenobarbital (n = 51)	Benzodiazepines (n = 51)	*p*[d]
Primary outcome			
ICU LOS[a] (d)	1.5 (1.2–2.4)	2.3 (1.4–4.8)	**0.009**
Secondary outcome			
Hospital LOS[a] (d)	3 (2.7–4)	6 (4–10)	**< 0.001**
Clinical Institute Withdrawal Assessment Alcohol Scale-Revised score control			
Maximum during MICU stay[a]	16 (12–22)	21 (15–27)	**0.009**
MICU discharge[a]	3 (2–5)	5 (3–8)	**0.010**
Safety			
Hypotension[b]	0 (0)	1 (2)	1.000
Agranulocytosis[b]	0 (0)	1 (2)	1.000
Sitter[b]	16 (31.4)	13 (25.5)	0.510
Restrain[b]	19 (37.3)	29 (56.9)	**0.047**
Need for mechanical ventilation[b]	1 (2)	10 (19.6)	**0.023**
MICU readmission[b]	3 (5.9)	3 (5.9)	1.000
Adjunct medications[c]	0.7 (0.5–1)	2.5 (2–3)	**< 0.001**
Dexmedetomidine[b]	13 (25.5)	24 (47.1)	**0.023**
Gabapentin[b]	6 (11.8)	39 (76.5)	**< 0.001**
Haloperidol[b]	11 (21.6)	31 (60.8)	**< 0.001**
Clonidine[b]	8 (15.7)	27 (52.9)	**< 0.001**
Valproic acid[b]	0 (0)	6 (11.8)	**0.027**
Cumulative dosage in MICU, mg			
Lorazepam equivalent[c]	0 (0–0)	21 (15–28)	**< 0.001**
Phenobarbital[c]	520 (390–520)	0 (0–0)	**< 0.001**

Alwakeel M. Crit Care Explor. 2023.

Current Evidence

2023 Malone Pre/Post study

ED->ICU; 4-day PHB course

Load: 6-10 mg/kg IBW (3 IM injections 3hrs apart)

Daily maintenance: 60mg PO q12 x2->30mg PO q12 x3

PRN Breakthrough: 65mg IM/IV q6hr

Vs.

BZD = CIWA-Ar PRN dosing

Similar cohorts, but PHB had higher admission BAL

Total dose in study:

Medication	Median	Mean
Phenobarbital	968 mg	803 mg
Lorazepam equivalents	86 mg	40 mg

Clinical Outcomes	Phenobarbital; *n* = 76	Benzodiazepine; *n* = 71	*p*-Value
Primary outcome			
Intubation (after initiation of AWS protocol); *n* (%)	15 (20)	36 (51)	<0.001
≥6 L of oxygen; *n* (%)	10 (13)	28 (39)	<0.001
Secondary outcomes			
Pneumonia incidence; *n* (%)	15 (20)	33 (47)	<0.001
Seizure incidence; *n* (%)	5 (7)	6 (9)	0.759
Median seizures; (min; max)	0 (0; 3)	0 (0; 6)	0.677
Median LOS in days (min; max)			
ICU	2 (0; 11.2)	4.2 (0.7; 30)	<0.001
Hospital	5.3 (0.3; 20.7)	9.9 (1.4; 63.7)	<0.001
Median additional medications for delirium; (min; max)	0 (0; 3)	1 (0; 3)	<0.001
Dexmedetomidine	12 (16)	40 (56)	<0.001
Haloperidol	16 (21)	28 (39)	0.019
Quetiapine	8 (11)	18 (25)	0.029
Mode RASS			
0–9 h (min; max)	0 (−4; 3)	-1 (−5; 4)	0.525
9–24 h (min; max)	0 (−5; 3)	−2 (−5; 4)	0.002
24–48 h (min; max)	0 (−5; 1)	−1 (−5; 3)	<0.001
48–96 h (min; max)	0 (−5; 1)	0 (−5; 3)	0.357

Malone D. Neuropsychopharmacology Reports. 2023.

Adjunctive Therapy

- Dexmedetomidine
  - Alpha-2 agonist - decreased sympathetic overdrive
    - More selective for Alpha-2 vs Alpha-1 than clonidine (1620:1 vs. 220:1)
  - "Cooperative sedation" without need for intubation – BZD-sparing effect
  - No GABA activity – does not prevent seizures or DTs!!

- Propofol
  - Enhances inhibitory GABA, decreases excitatory NMDA. Minimal literature support

Jesse S. Acta Neurologica Scandinavica. 2016.

Adjunctive Therapy (continued)

- Anti-epileptics (carbamazepine, valproate, gabapentin, levetiracetam..)
  - Potential role for prevent seizures or DTs
    - Potentially neuroprotective by decreasing excessive neuronal activity
  - Reports demonstrate widespread used – Cochrane review of 56 studies found no benefit

- Antipsychotics
  - Potentially reduce withdrawal symptoms, especially in protracted courses
  - AEs: Increase QT interval, lower seizure threshold

Jesse S. Acta Neurologica Scandinavica. 2016.

Adjunctive Therapy (continued)

- Thiamine (first, and then glucose)
  - Prevents and treats Wernicke's encephalopathy
    - Often difficult to differentiate from AWS/DTs
  - Prevents thiamine-related cardiomyopathies
  - Broadly recommended, despite lack of concrete evidence
    - Uncertainty with dosing (100-500mg dose, every 6-24 hours)

- Magnesium
  - Could low serum levels precipitate "hyper-excitability"?
  - No evidence for support per 2013 Cochrane Review

- Multivitamins

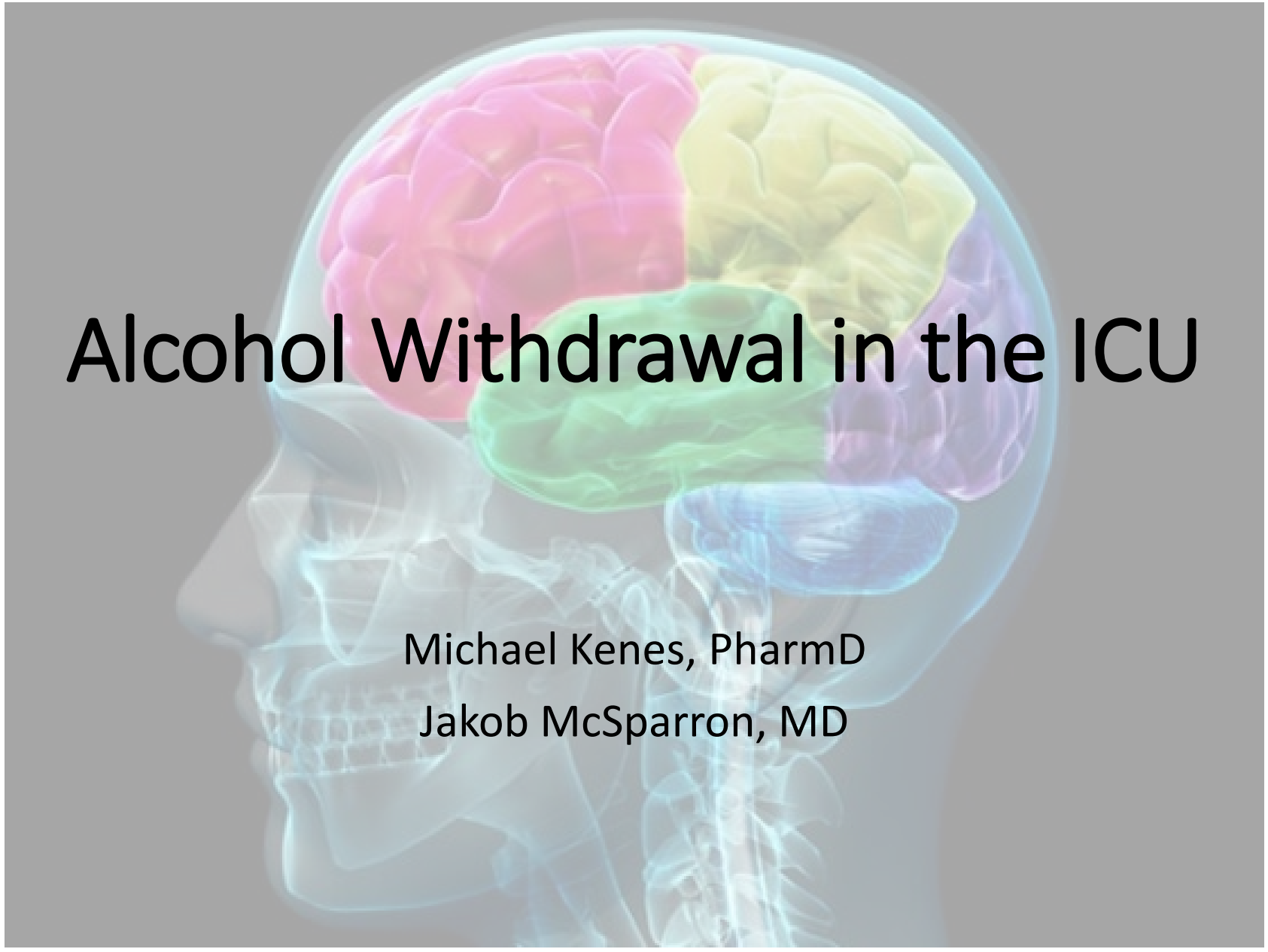
Schuckit MA. NEJM. 2014.
Sarai M. Cochrane Syst Rev. 2013.

Current Unknowns

- Transitioning from one class to another
  - "Failure of BZD" / dose threshold?
- Comfort with liver dysfunction
  - PK demonstrates general safety; clinical data currently lacking
- When to discharge from ICU
- Refractory withdrawal cases

Conclusions

- Alcohol withdrawal is common in in the ICU
- Abrupt cessation in alcohol consumption → deficient GABA activity and excessive NMDA activity → CNS hyperexcitation
- Benzodiazepines (GABA) and Phenobarbital (GABA and NMDA) both treat delirium
- Adjunctive agents may be necessary for specific symptoms



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