Phenobarbital for Moderate to Severe Alcohol Withdrawal in the Acute Care Setting

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Disclosure

- Today's presenters have nothing to disclose

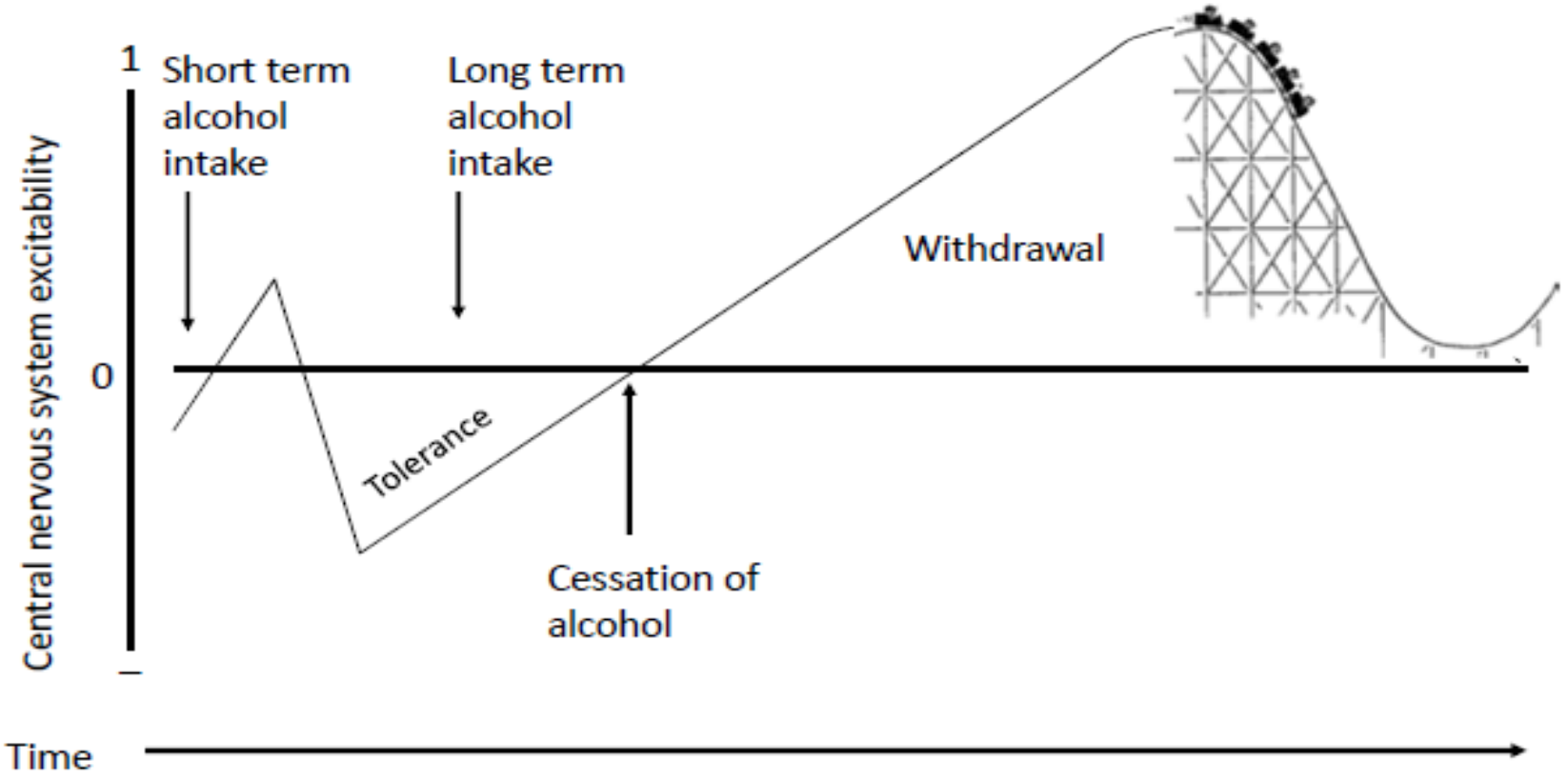
Objectives

- Explain patient management and treatment goals when treating moderate to severe alcohol withdrawal symptoms with phenobarbital
- Describe the mechanism of action of phenobarbital in treating patients with alcohol withdrawal symptoms
- Describe potential protocols to decrease the amount of dexmedetomidine and benzodiazepines that are used in their institutional settings for treating patients with alcohol withdrawal symptoms

Alcohol Abuse

- Approximately 7% of US population abuses or is dependent on alcohol.
  - 10% of patients will experience seizures
  - 5% experience delirium tremens
- 20% of patients admitted to the in-patient units
- Patients often seek medical attention in Emergency departments for complications directly related to alcohol use.
  - 16% surgical patients
  - 31% of trauma patients
    - 25-35% MVAs

Effects of Alcohol Exposure and Withdrawal



Adapted from: McKinley MG. *Crit Care Nurse*. 2005 Jun;25(3):40-2, 44-8

Symptoms of Alcohol Withdrawal

Symptoms	Hours
Minor symptoms: Insomnia, tremulousness, mild anxiety, GI upset, headache, diaphoresis, palpitations, anorexia	6 – 12 hours
Alcoholic hallucinosis: visual, auditory, or tactile hallucinations	12 – 24 hours
Withdrawal seizures: generalized tonic-clonic seizures	24 – 48 hours
Alcohol withdrawal delirium (delirium tremens): hallucinations (predominately visual), disorientation, tachycardia, hypertension, low-grade fever, agitation, diaphoresis	48 – 72 hours

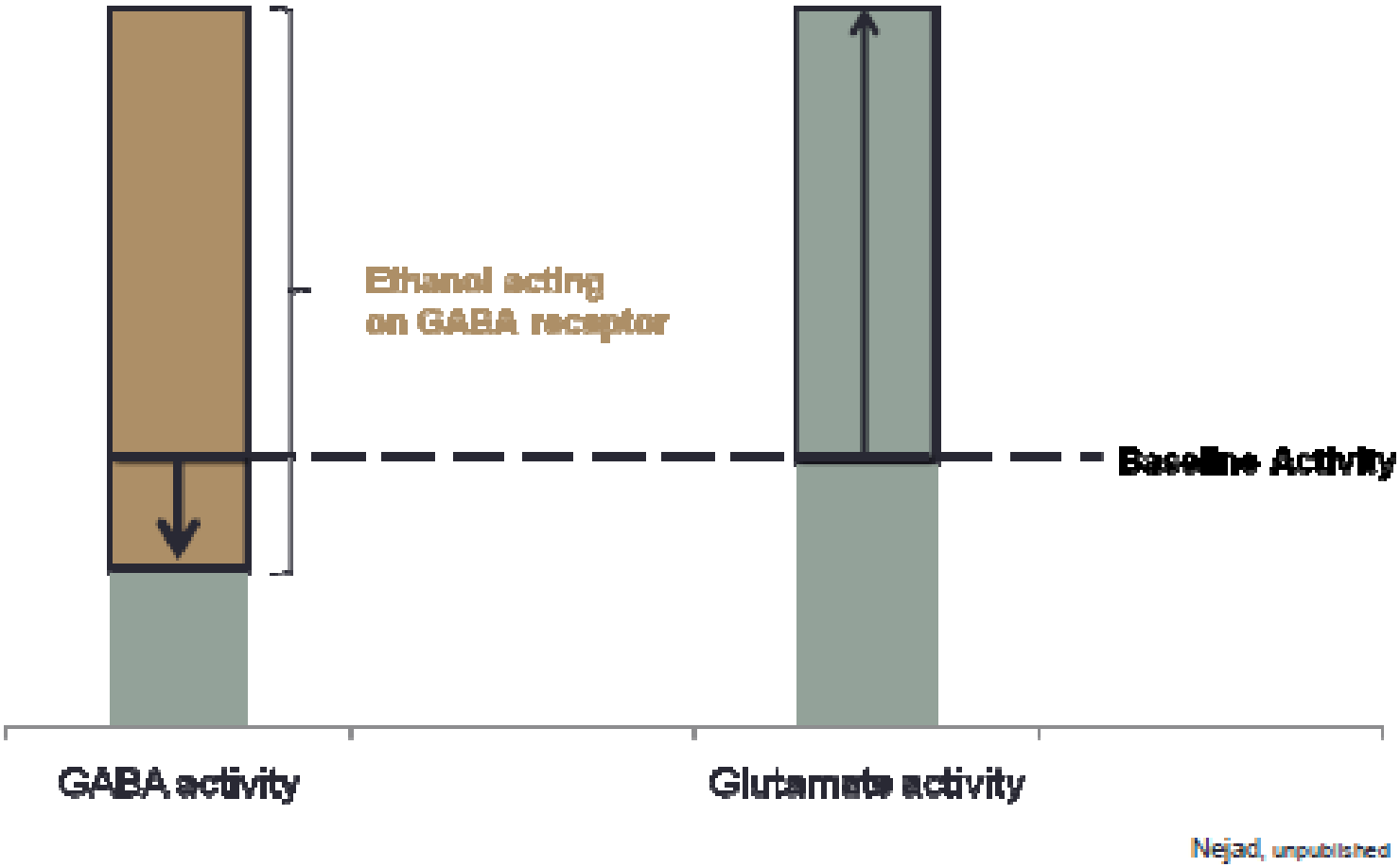
CNS Alcohol Withdrawal Physiology: GABA vs. Glutamate

- Two major types of neurotransmitter systems in the CNS:
  - γ- aminobutyric acid (GABA) → inhibitory of electrical activity
  - Glutamate → Excitatory impact on electrical activity
- > 80% of neurons in the brain use GABA or glutamate
- Alcohol **agonizes** GABA receptors and **blocks** glutamate receptors

Stehman CR, et al. *Am J EmergMed*. 2013 Apr;31(4):734-42
Fadda F, et Cosgrove KP, et al. *Neuropharmacology*. 2011 Jun;60(7-8):1318-25

CNS Alcohol Withdrawal Physiology: GABA vs. Glutamate

GABA and Glutamate – Chronic Alcohol Use



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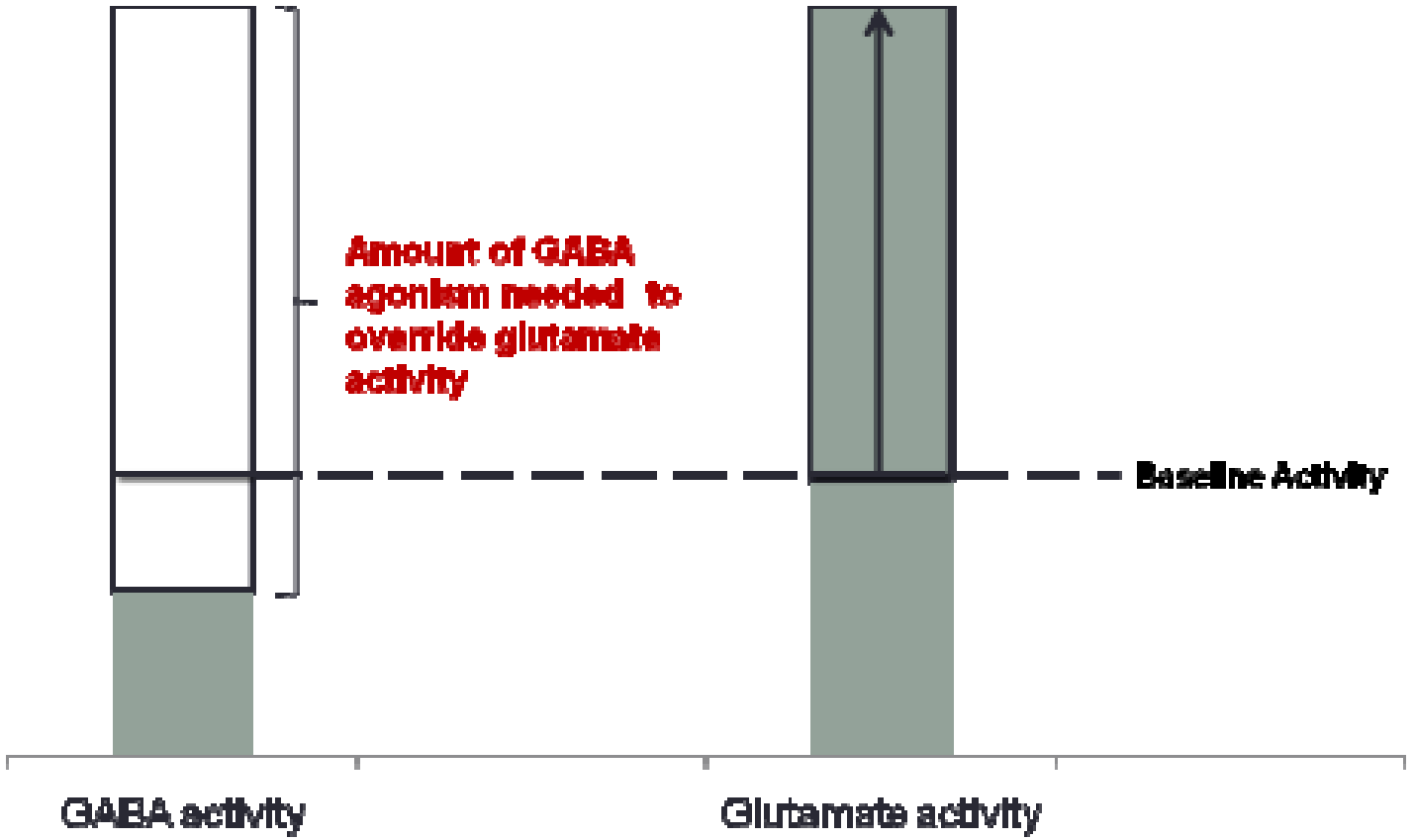
CNS Alcohol Withdrawal Physiology: GABA vs. Glutamate

GABA and Glutamate – Abrupt Cessation of Alcohol



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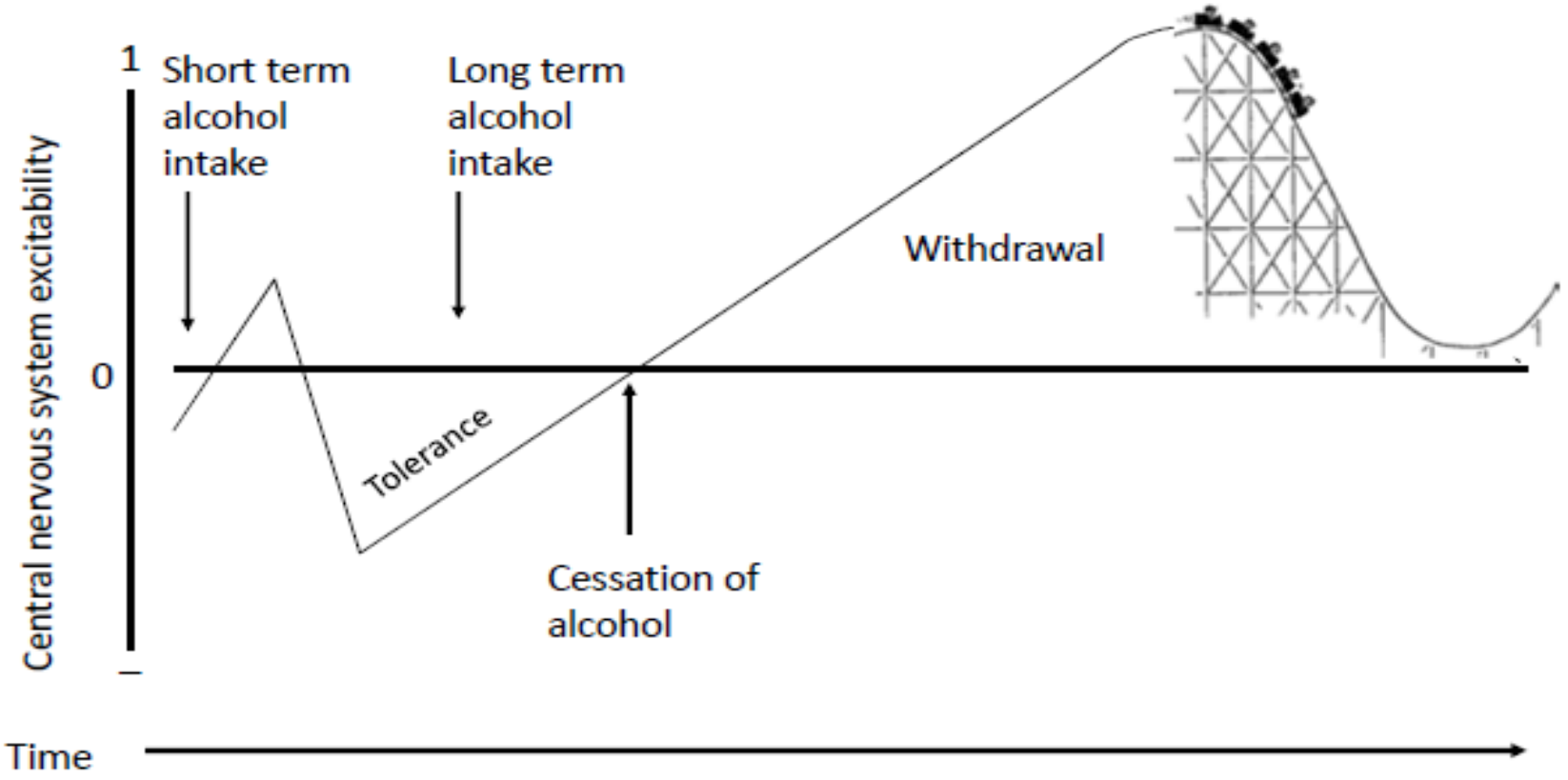

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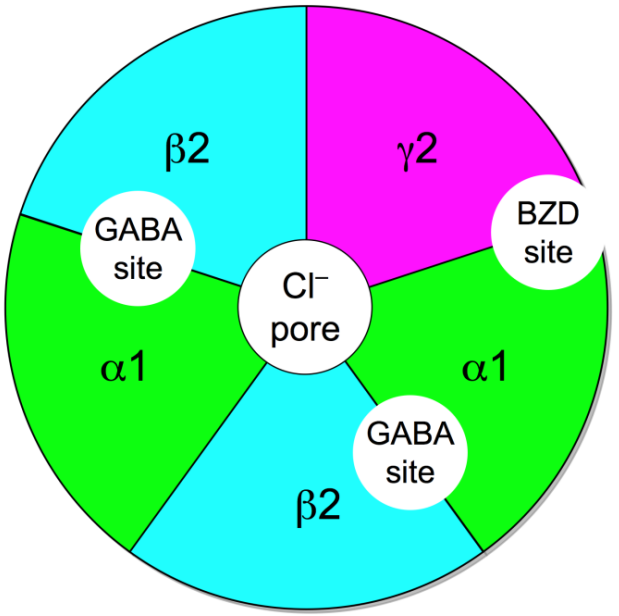
$GABA_A$ Receptor Pharmacology

- 16 different $GABA_A$ receptors → 9 in brain based upon subunit composition
- GABA related symptoms:
  - Sweating, tremors, anxiety and sleep alternations
- 1-4 Benzodiazepines
  - Require GABA to bind
  - Increase the frequency Cl channel opening
  - Affinity guided by α unit selectivity
- Barbiturates
  - Does NOT require GABA to bind
  - Increase time Cl channel is open
  - Attenuate BZD and GABA binding



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Sankar R. *CNS Drugs*. 2012 Mar 1;26(3):229-44.
Olsen RW, et al. *Neuropharmacology.* 2009 Jan;56(1):141-8.
Krystal JH, et al. *Arch Gen Psychiatry*. 2006 Sep;63(9):957-68.

Select GABA agonists for Alcohol Withdrawal

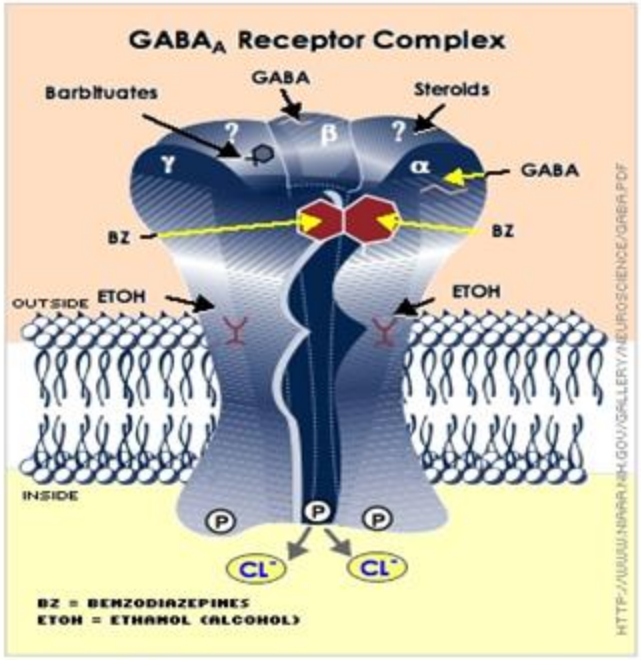
Variable	**Midazolam**	**Lorazepam**	**Phenobarbital**	**Propofol**
Area of Use	ICU	All	All	ICU
Route	IV	IV/PO	IV/IM/PO	IV
Typical Dose	1-3 mg q1hr	1-4 mg q4hrs	65-320 mg Q6hrs	0-5 mg/kg/hr
IV onset (min)	1-5	5-20	5	10-50 seconds
IM onset (min)	15	30	20	-
Duration	Short	Medium	Long	Really Short
Prolonged in renal failure	Yes	No	Yes	No
Prolonged in hepatic failure	Yes	Yes	Yes	No
Elimination T1/2	1-4 hrs	12-14 hrs	1.5-4.9 days	1.5-12.4 hrs
Active Metabolite	Yes	No	No	No
IV formulation toxicity	None	Propylene glycol	Propylene glycol	Lipid elimination

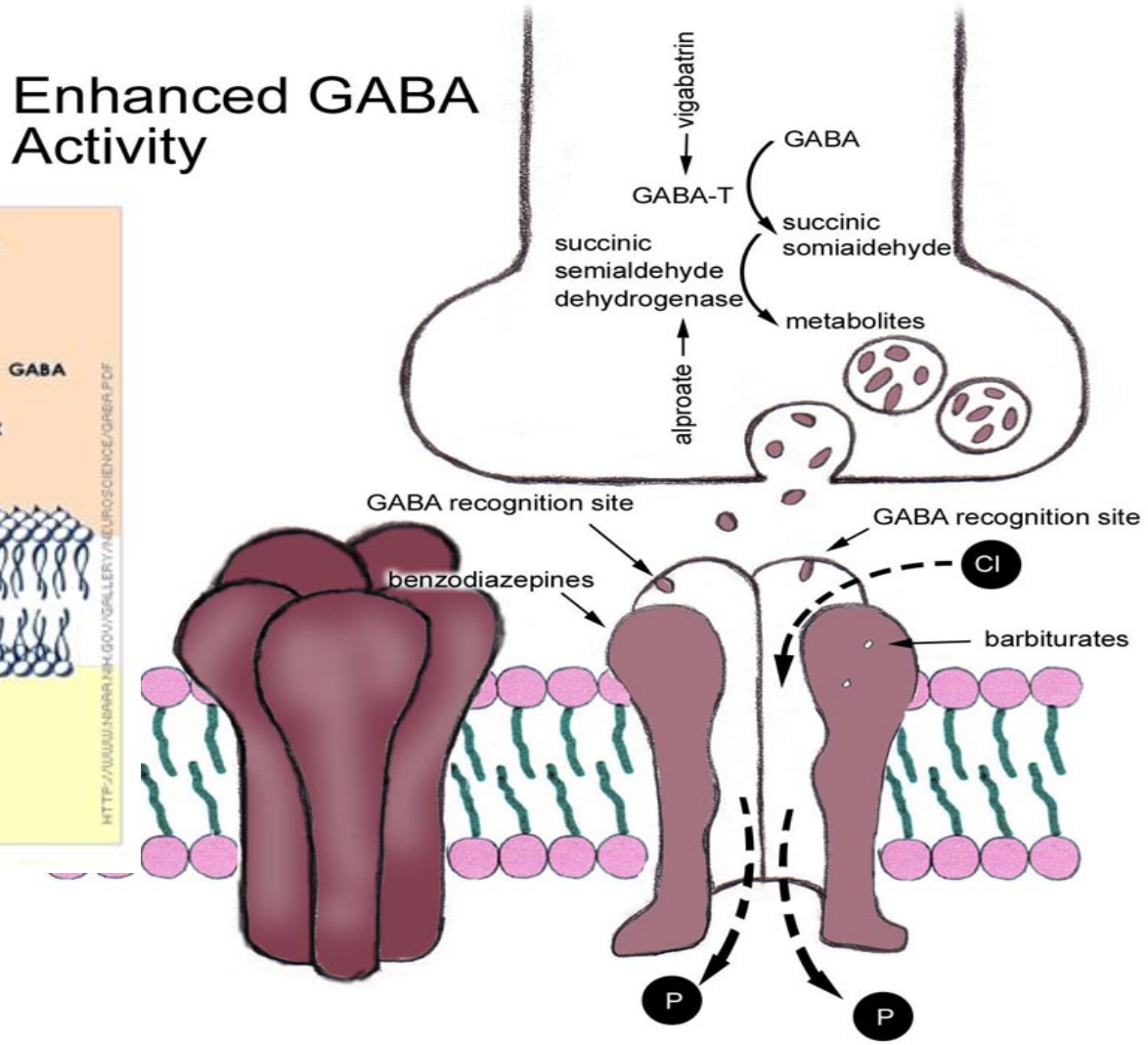
Prophylene Glycol Administration

Drug	Concentration	Amount of propylene glycol (mg/ml)	Daily propylene gycol exposure (g)*
Lorazepam	4	830	99.6
Phenobarbital	130	702.4	2.1

*Based on a lorazepam infusion of 20 mg/hr and phenobarbital dosage of 130 mg 3 times a day

Phenobarbital's Mechanism of Action





Pharmacokinetics of Phenobarbital

- Available in parenteral, intramuscular and enteral formulations
- Bioavailability of IM,IV and PO formulations is almost 100% complete
- Time to maximum plasma concentration
  - IV: 15 to 30 minutes
  - PO: 0.5 to 4 hours
  - IM: 2 to 8 hours
- Half-life is 1 to 4 days
- Possible induction of cytochrome 2B6 and 3A4

Side Effects

- CNS excitation or depression
- Respiratory depression
- Dermatitis
- Facial edema
- Headache
- Hypotension
- Nausea
- Bradycardia
- Agitation
- Confusion
- Insomnia
- Somnolence
- Hallucinations
- Vertigo

Contraindications / Reactions

- Contraindications
  - History of SJS/TEN
  - History of acute intermittent porphyria
  - History of rash with an AED
  - History of cirrhosis
- Adverse Reactions
  - Sedation
  - Respiratory depression
  - Rash/SJS/TEN
  - Exacerbation of acute or intermittent porphyria
- Chronic Use
  - Bone loss
  - Hematologic

Published Literature About Phenobarbital Dosing

Use of Phenobarbital as an Adjunctive Therapy

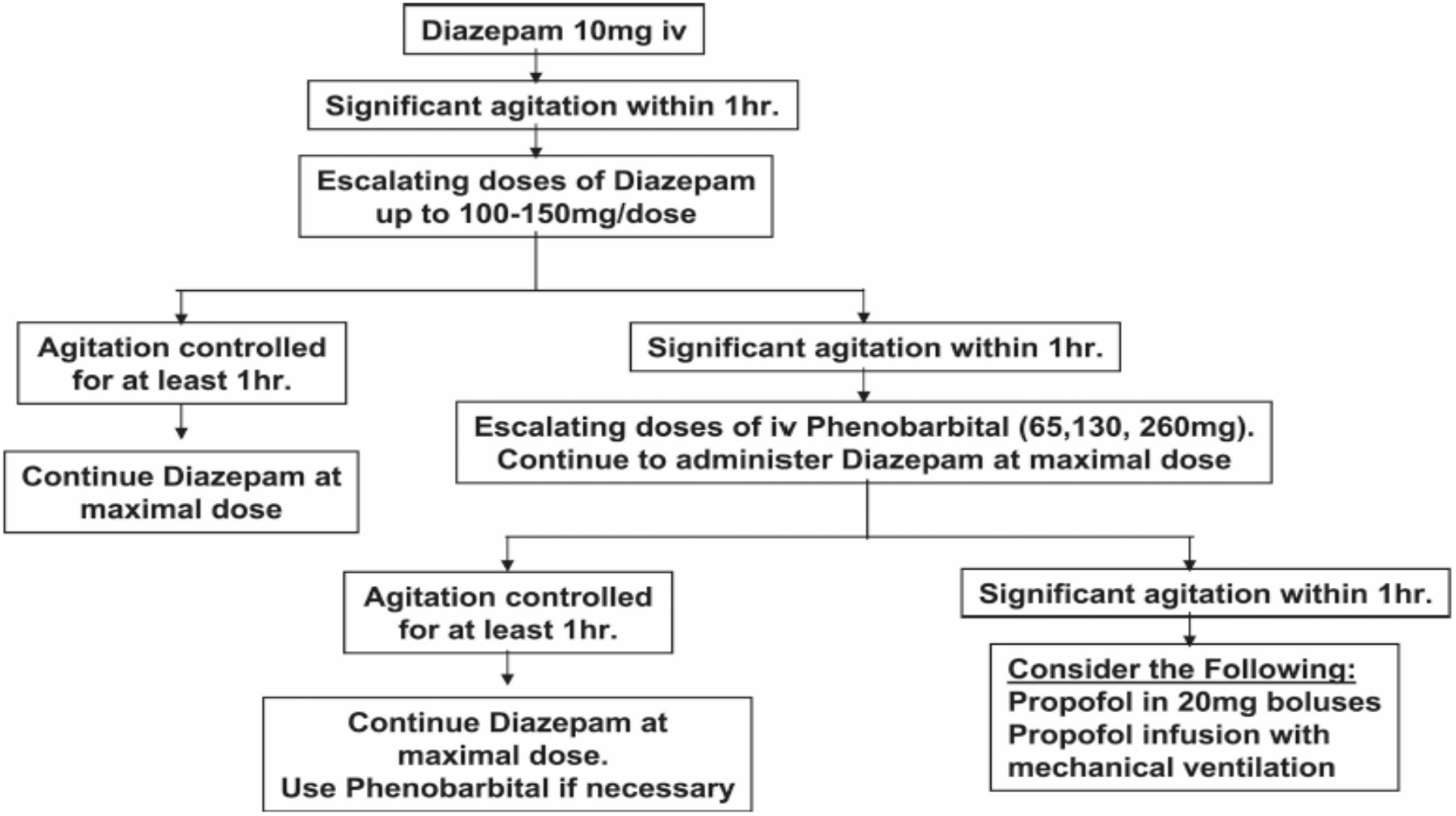
- 51 patients were randomized to receive phenobarbital versus 51 placebo
- Patients received a single dose of i.v. phenobarbital had a decreased ICU admission rate
  - Phenobarbital vs. placebo, 8% vs. 25%, difference 17% [95% confidence interval (CI) 4–32%]
- Phenobarbital resulted in decrease in :
  - Use of continuous lorazepam infusion
    - 4% vs. 31%; difference 27% [95% CI 14–41%]
  - Decreased total lorazepam required
    - 26 vs. 49 mg; difference 23 mg [95% CI 7–40]
- There were no differences in:
  - Telemetry admission
  - Floor ward admission
  - Median ICU
  - Total hospital LOS

Rosenson et al. Journal of Emergency Medicine, Vol .44, No.3, pp. 592-598, 2013

Use of Phenobarbital as an Adjunctive Therapy

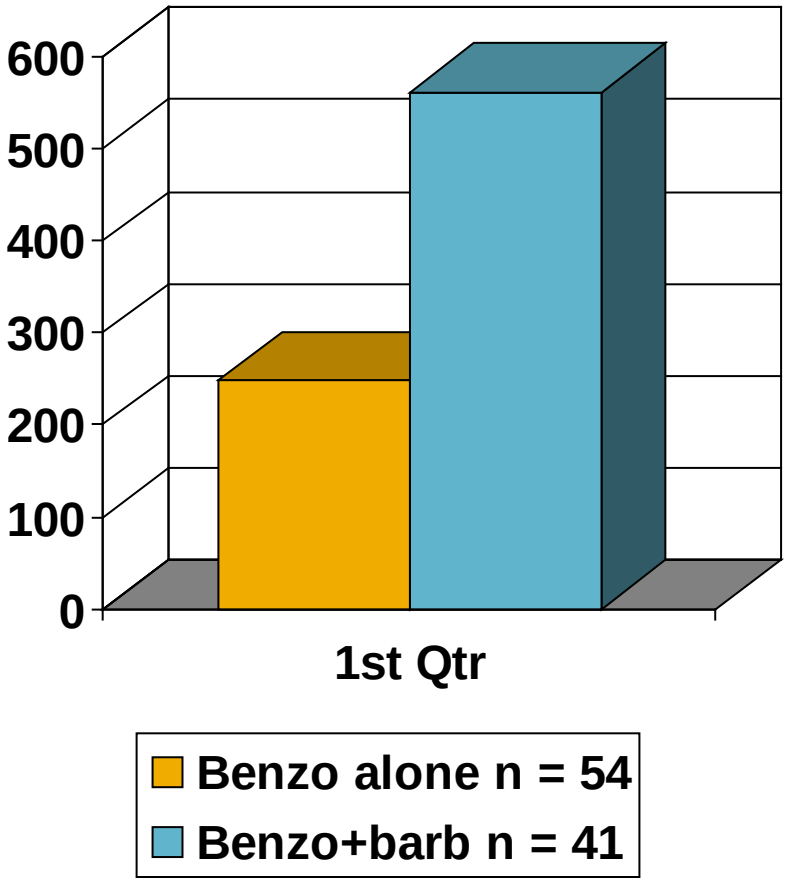
- Advantages
  - A single dose of 10 mg/kg IV phenobarbital resulted in decreased:
    - ICU admission rate
    - Use of continuous lorazepam infusion
    - Not associated with increased adverse events
- Disadvantages
  - Predominantly males
  - Single center study

Addition of Phenobarbital to Benzodiazepines in ICU Patients With DTs



Crit Care Med 2007;35:724-730

Addition of Phenobarbital to Benzodiazepines in ICU Patients With DTs



Significant patient characteristics/metrics/outcomes			
Variable	**Benzo alone (n = 54)**	**Benzo+ Barb (n = 41)**	**P Value**
Haloperdol use	2 (4%)	0	*NR*
Phenobarbital use	9 (17%)	24 (58%)	*p <0.01*
Intubation requirement	26 (47.3%)	9 (21.9%)	*p <0.01*
Days intubated	6.4 ± 1.6	3.1 ± 1.3	*p = 0.01*
Nosocomial Pneumonia intubated (%)	55.5	12.5	*p = 0.02*

Crit Care Med 2007;35:724-730

Addition of Phenobarbital to Benzodiazepines in ICU Patients With DTs

- Advantages
  - Appear to augment benzodiazepines' efficacy at the $GABA_A$ receptors in the brain
  - Inhibit stimulatory glutamate receptors
  - Escalating doses of benzos + Phenobarbital reduce the need for mechanical ventilation
- Disadvantages
  - Single center study
  - Narrow therapeutic window
  - Potential to induce respiratory depression

Taper Dosing of Phenobarbital

- Dosing Schedule
  - Day 1: 60 mg PO Four times a day
  - Day 2: 60 mg PO Three times a day
  - Day 3: 60 mg PO Twice daily
  - Day 4: 30 mg PO Twice daily

The American Journal on Addictions, 15:76-84, 2006.
Am J Addict 1998;189-197

Phenobarbital Treatment in Patients resistant to Benzodiazepines for AW

- Definition of Benzodiazepine Resistance:
  - A need for more than 10 mg of lorazepam in 1 hour
- Phenobarbital improved symptom control, minimized the potential for propylene glycol toxicity and was not associated with respiratory depression and facilitated successful weaning of benzodiazepine.

Pharmacotherapy 2009;29(7):875-878

When to Use Phenobarbital in Alcohol Withdrawal

- Patients with:
  - A history of tremors or seizures
  - Apparent non-response to benzodiazepines or history of benzodiazepine resistance
  - Active DTs or severe withdrawal symptoms
  - Altered mental status and/or high or medium risk for delirium
- Patients at risk or with respiratory compromise in which you may wish to avoid benzodiazepines

Alcohol Withdrawal Orderset

Medium Risk for Alcohol Withdrawal

- Active Alcohol dependence plus 2 of the following:
  - 2 days or more since last drink
  - Elevated BAL on admit
  - Autonomic dysfunction with Blood Alcohol Level > 0.1 g/dL
  - Elevated MCV and/or AST/ALT ratio
  - Heavier and longer drinking history
  - Burn related injuries
  - Falls, particularly with long bone fractures

High Risk for Alcohol Withdrawal

- Past DTs +/- past seizures AND
  - + recent alcohol use (≥2weeks)
  - Active symptoms of AWS
  - Positive BAL, elevated MCV, elevated AST/ALT ratio

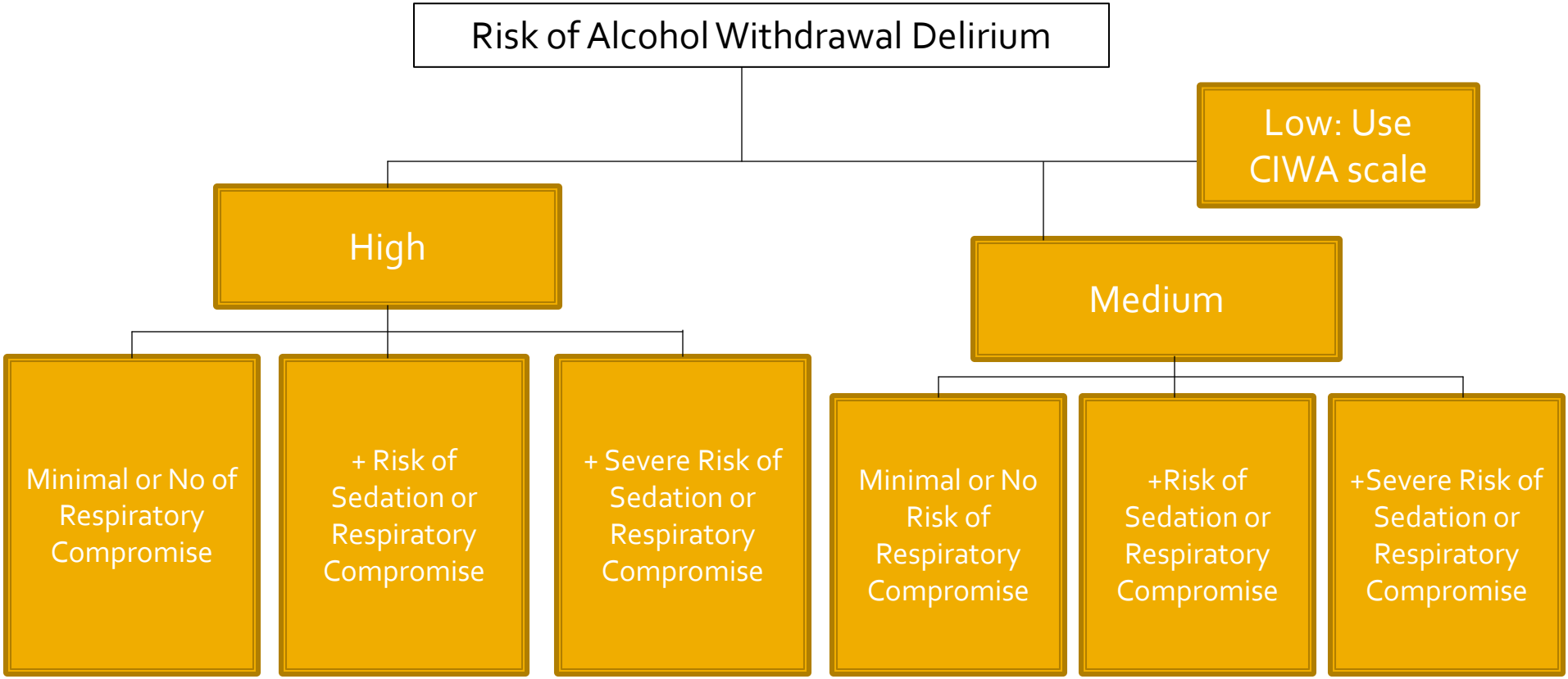
Risk of Sedation

- Age > 65 years old
- Hepatic dysfunction
- Narcotics
- Head injury – Neuro checks
- Recent administration of Benzodiazepines
- Current administration of sedatives

Risk of Respiratory Compromise

- Pneumonia
- Rib fractures
- Chest tube
- Pulmonary contusion
  - Caused by chest trauma => fluid accumulation
  - Leads to hypoxia
- C-collar/brace

Algorithm for Loading Dose



Phenobarbital Protocol

- Weight-based dosing ranging from 6-15 mg/kg
- Dosing is broken up into 3 loading doses and a taper regimen
  - Loading Dose: 1 dose given q3h for 3 doses
    - 1st dose: 40%
    - 2nd dose: 30%
    - 3rd dose: 30%
  - Maintenance dose (decreasing by approx. 50% every stage)
    - D#2+3: Stage 1
    - D#4+5: Stage 2
    - D#6: Stage 3
    - D#7: Stage 4

Pilot Study Data

- Patients were retrospectively reviewed from November 1, 2016 to April 30, 2017
- 28 patients were initiated on the Phenobarbital protocol
- 14 patients utilized Precedex for control of sedation/agitation/delirium
- 27 patients utilized benzodiazepines
- 18 patients had documented CIWA scores >15 prior to starting Phenobarbital
- 4 patient experienced ADRs

Pilot Study Results

- **64%** patients had Precedex discontinued within 24h from starting Phenobarbital
  - 3 patients started Precedex after Phenobarbital was initiated
- **55%** patients discontinued benzodiazepine use upon initiation of Phenobarbital
- **94%** patients were controlled once Phenobarbital protocol was initiated
  - 7 patient continued Phenobarbital + Benzo
  - 2 Patient continue Phenobarbital + Precedex
- 3 patients received q6h dosing
  - 2 patients had therapy discontinued early

Full Course of Therapy

- **75%** patients completed the full course of therapy
- **25%** patients stopped therapy prior to protocol completion
  - 2 patients had no desire to stop drinking
  - 1 patient had therapy stopped by provider due to lack of symptoms
  - 4 were due to ADRs
    - 1 developed a rash
    - 3 were due to sedation issues

Options to Optimize Treatment

- Consider Phenobarbital therapy prior to patients becoming uncontrolled on a CIWA protocol
- Reload the patient with empiric loading doses
- Consider q6h dosing
- Increase the Phenobarbital taper length
- Continue CIWA scoring, without dosing with Lorazepam

Patient Case #1

- 28 y.o. male, MS, is brought to the emergency room for an altered mental status.
- He called EMS reporting that someone was breaking into his house and Police and SWAT were standing outside watching.
- Patient has a past medical history of alcohol abuse and reports drinking 4 glasses of vodka daily.
- Patient stated that he had his last drink 3 days prior to admission as he planned to self detox.

Course of Treatment

- Started on the Hospital CIWA protocol
- Patient continue to have CIWA score >15 whose symptoms remained uncontrolled
- MS was started on the phenobarbital protocol
  - Classified as High risk of withdrawal and Severe risk of sedation/respiratory compromise
- CIWA treatment was continued throughout the time the patient was on phenobarbital
  - Continued to have CIWA scores >15
  - Received regular doses of Lorazepam

Patient Case #1

- Recommendations/Improvements
  - Review the Risk Assessment of the patient
  - Reload the patient vs. q6 hour dosing
  - Start phenobarbital earlier as the patient remained uncontrolled on high dose benzodiazepines

Patient Case #2

- 52 y.o male, GC, was shoveling snow when he arrested.
- ROSC was returned prior to arrival in the emergency room.
- Patient was rushed to the cath lab and stents were placed.
- In speaking with the patient's wife, the patient has a significant drinking history, 30 beers per day.
- Patient's last drink was only hours before the incident, and the last day without a drink is unknown.

Course of Treatment

- Patient was started on Precedex and phenobarbital protocol 48 hours after admission
  - Categorized as High risk of withdrawal, low risk for respiratory compromise
- Patient was uncontrolled on both agents as the taper began
  - Scheduled Lorazepam was started
  - Precedex and Phenobarbital continued
- Phenobarbital q6h dosing was initiated 36 hours after the loading dose
  - Precedex and scheduled Lorazepam were able to be rapidly weaned
- Phenobarbital q6h dosing was continued for 4 days and then patient taper off based on the protocol

Patient Case #2

- Recommendations/Improvements
  - Utilize the higher loading dose based on risk stratification
  - Reload the patient based on symptom improvement from the initial loading dose
  - Utilize phenobarbital q6h dosing before starting the taper

Patient Case #3

- 51 y.o. male, PW, was brought to the emergency room by EMS after police were called by neighbors.
- When police arrive, the patient appears to be shadow boxing in the mirror, reporting that he was fighting someone.
- While in the EMR the patient reports having auditory and visual hallucinations.
- CT of the head and CXR did not show any abnormalities.

Course of Therapy

- Patient was treated in the EMR with Lorazepam and Diazepam
  - Lorazepam was given based on CIWA in conjunction with additionally ordered doses
  - Patient's symptoms continued and remain uncontrolled
- Patient was continued on the CIWA protocol and Precedex was added to control symptoms
- Phenobarbital Protocol was initiated
  - Precedex was rapidly tapered after the loading doses
  - CIWA was discontinued within 24 hours
- PW was controlled successfully on phenobarbital alone
- PW was completed the last 2 days of therapy as an outpatient

Patient Case #3

- Recommendations/Improvements
  - Start phenobarbital protocol earlier
    - Patient was uncontrolled on high dose benzodiazepines
  - Utilize phenobarbital protocol instead of Precedex

Improvements

- Reviewed and revised PRH CIWA protocol
- Provided education to Providers and nursing staff
- Expanded availability of Phenobarbital Protocol Initiation
- Using PRN Phenobarbital for patients receiving high doses of benzodiazepines in non-ICU settings in addition to protocol
- Utilized RASS and CIWA scoring to monitor Phenobarbital

Questions?

If there are questions that remain unanswered please email us:

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Thank you

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