Towards a Better Understanding of AWS & AUD Management

Shamim Nejad, MD, FASAM, FACLP
Medical Director, Psychiatry Consultation & Addiction Consultation Services
UW Medicine - Valley Medical Center

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Disclosure: Shamim Nejad, MD

With respect to the following presentation, there has been no relevant (direct or indirect) financial relationship between the party listed above (and/or spouse/partner) and any for-profit company which could be considered a conflict of interest.

Objectives

- **Alcohol Withdrawal Syndromes**
  - **Recognition and management of alcohol withdrawal syndromes (AWS) within the general hospital setting**
  - **Pharmacotherapy for alcohol use disorder (AUD)**

Alcohol Withdrawal Syndromes and Management

Usual Treatment Overview of AWS

- **Supportive Care**

- **Wernicke's Treatment/Prophylaxis**
  - Signs: thiamine 500mg IV TID indefinitely
  - Risk: thiamine 100mg IV/IM BID x3 days

- **Pharmacologic management**
  - Benzodiazepines
  - Phenobarbital
  - Dexmedetomidine
  - (Propofol)
  - (Continuous infusions of lorazepam or midazolam)
  - (Ethanol)

- **Benzodiazepine Administration Strategies**
  - Active Symptoms
    - Symptom Triggered
    - Fixed schedule **+ PRN/Symptom-triggered**
  - Prophylaxis
    - Front-loading
    - Fixed dose

- **Augmentation agents**
  - Beta Blockers
  - Clonidine
  - Haloperidol

Issues Surrounding AWS in the Hospital

- Issues specific to benzodiazepines
- Issues in recognizing high-risk patients for *complicated* alcohol withdrawal at time of presentation and/or admission
- Issues specific to CIWA-Ar (symptom triggered protocols)
  - Clinical Institute Withdrawal Assessment Alcohol Scale, revised

Benzodiazepines for AWS in the General Hospital

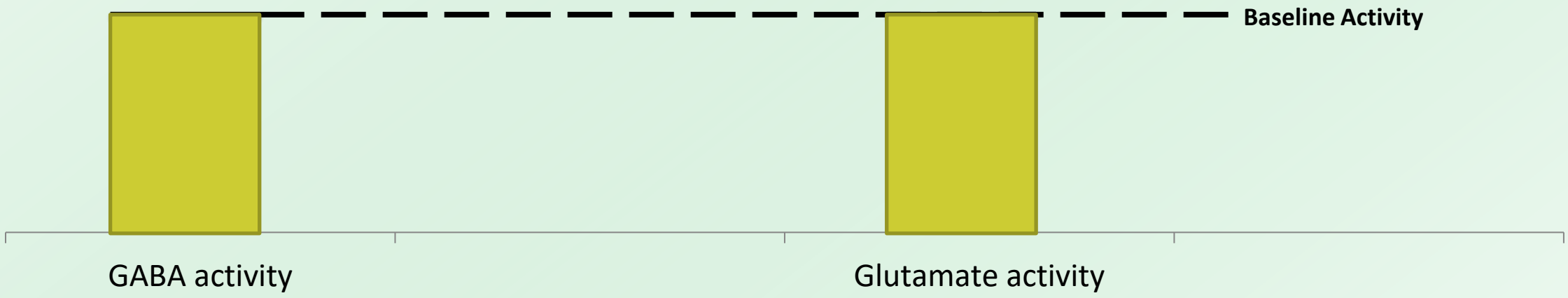
- Benzodiazepines should work fine for the majority of patients who are at risk for *uncomplicated* alcohol withdrawal

- Limitations of benzodiazepines in AWS seen:
  - In patients with moderate to high risk for AWS
  - In patients with pre-existing history of *complicated* AWS:
    - Alcohol withdrawal delirium
    - Alcohol withdrawal seizures
    - Alcohol withdrawal hallucinosis

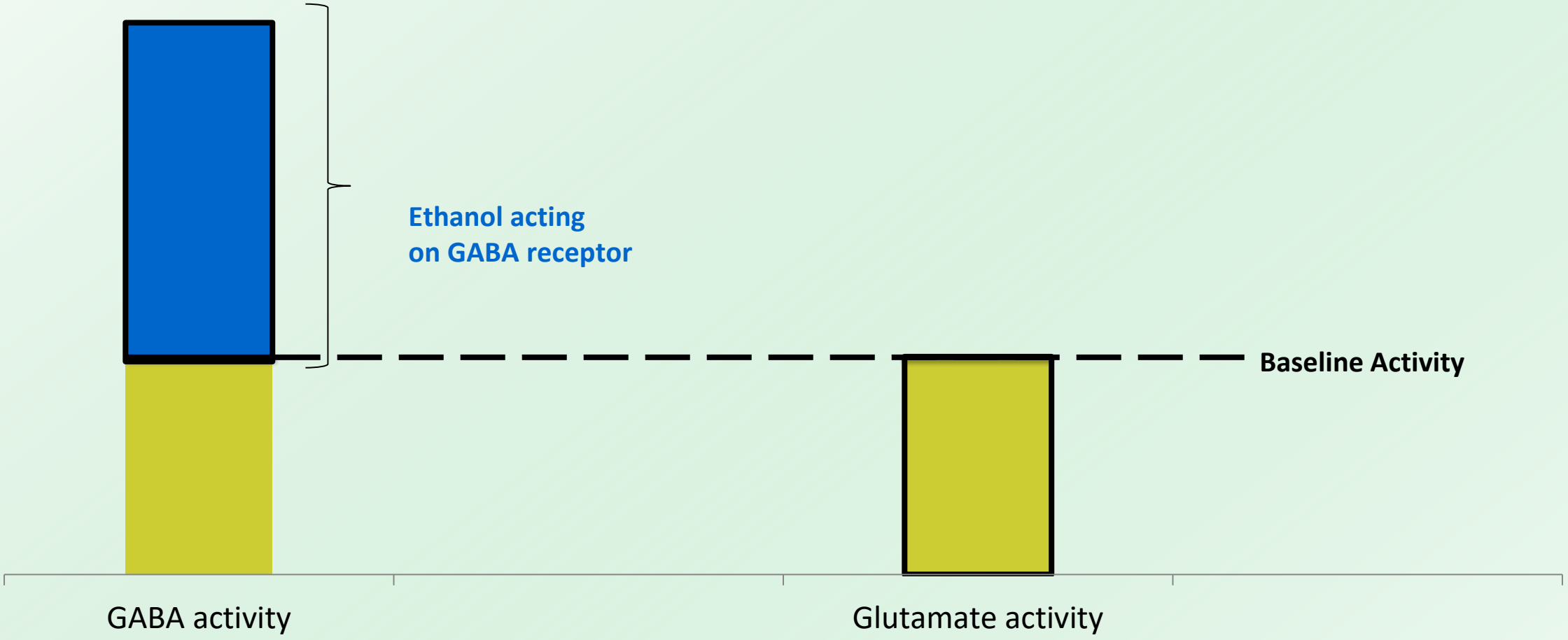
- In patients with active delirium symptoms from other medical etiologies outside of AWS or those patients with anticipated lower delirium threshold due to concomitant traumatic injury, medical illness(es), or other neurodegenerative process(es)

Neurotransmitters in AWS Made ‘Simple’

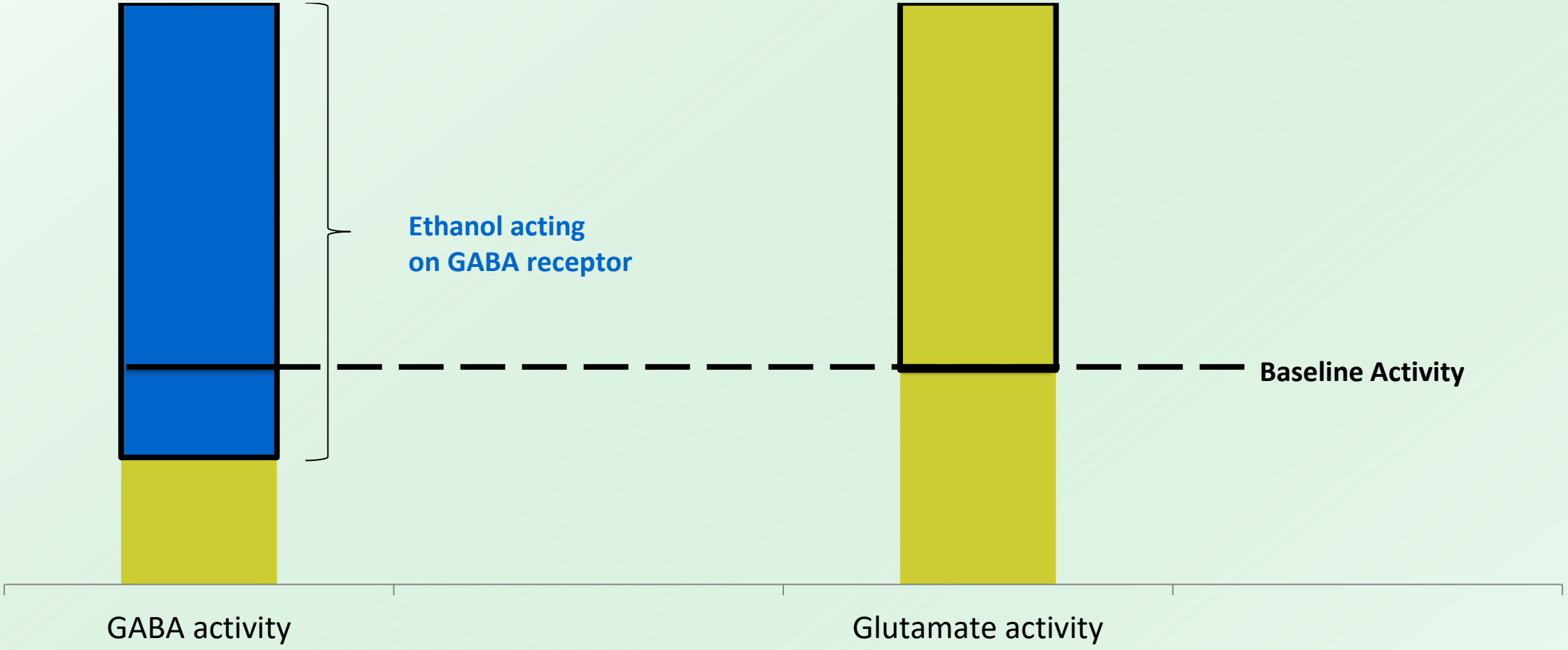
GABA and Glutamate – Intermittent Alcohol Use



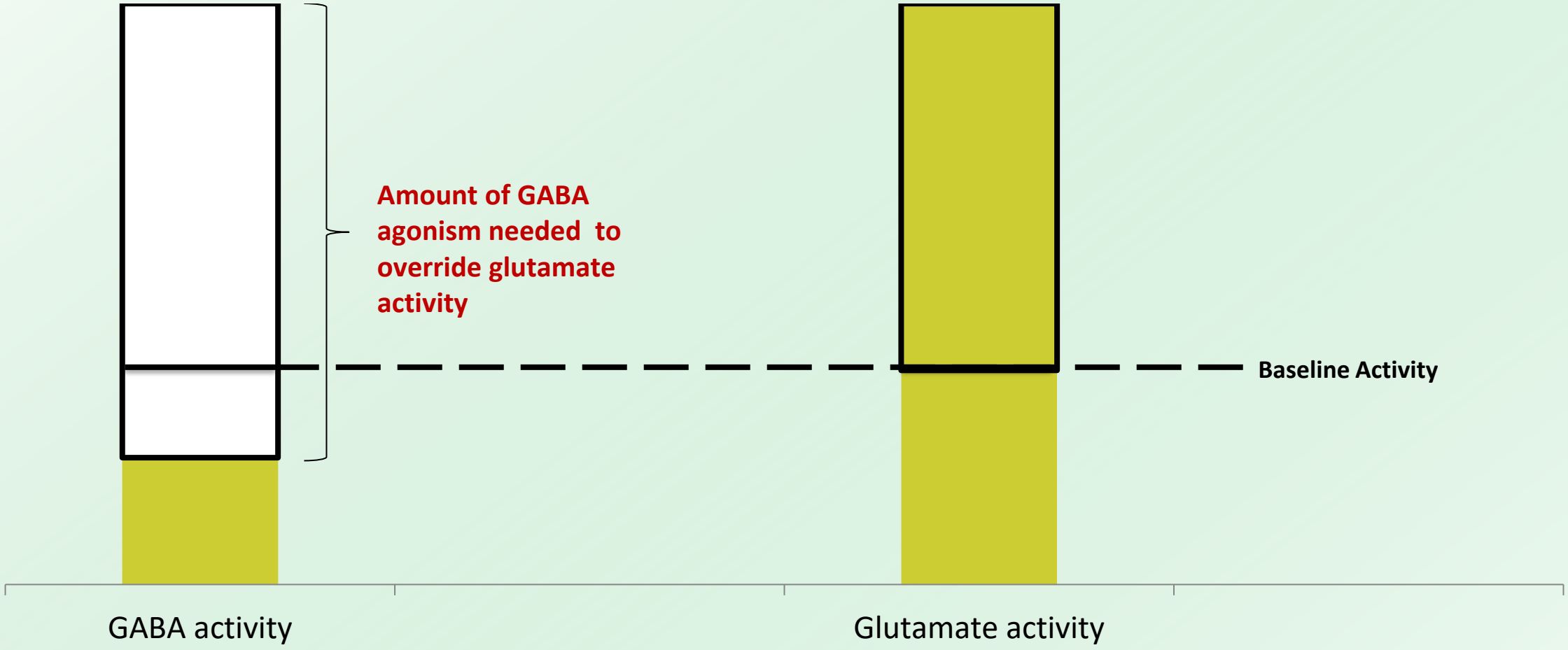
GABA and Glutamate – Acute Alcohol Use



GABA and Glutamate – Chronic Alcohol Use

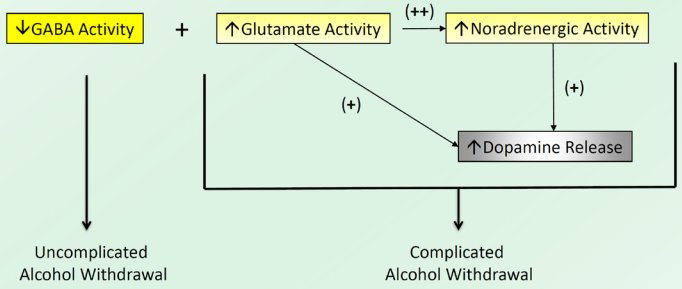


GABA and Glutamate – Abrupt Cessation of Alcohol Use

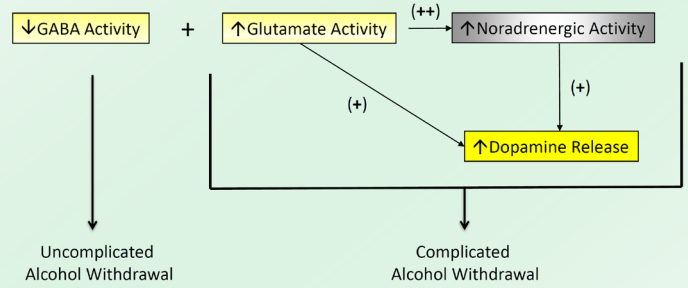


Neurotransmitters in AWS Made 'Simple'

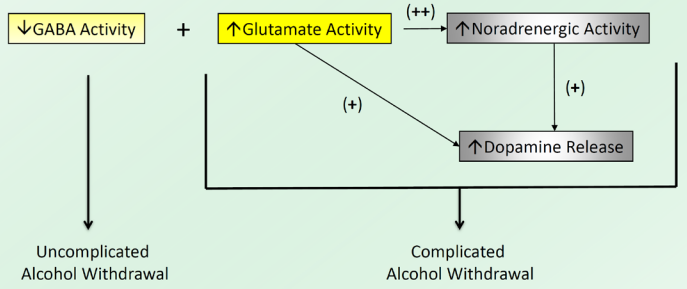
Uncomplicated Alcohol Withdrawal



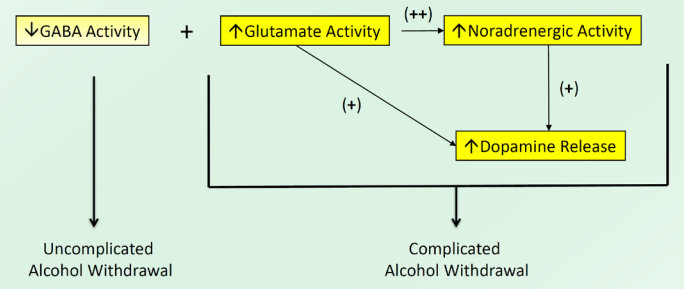
Alcoholic Hallucinosis



Alcohol Withdrawal Seizure



Alcohol Withdrawal Delirium



Stages	Clinical Findings	Onset*
Early or Uncomplicated	Anxiety, ***fine*** tremor (anxiety related), tachycardia (anxiety related), headache, palpitations, anorexia, GI upset, general malaise	6-36 hrs
Seizure	Generalized, tonic-clonic seizures, status epilepticus (rare)	6-48 hrs
Alcoholic Hallucinosis	Visual, auditory, and/or tactile hallucinations	12-48 hrs
Delirium Tremens	Agitation, delirium, tachycardia (noradrenergic related), hypertension, fever, diaphoresis, ***coarse*** tremor	48-96 hrs

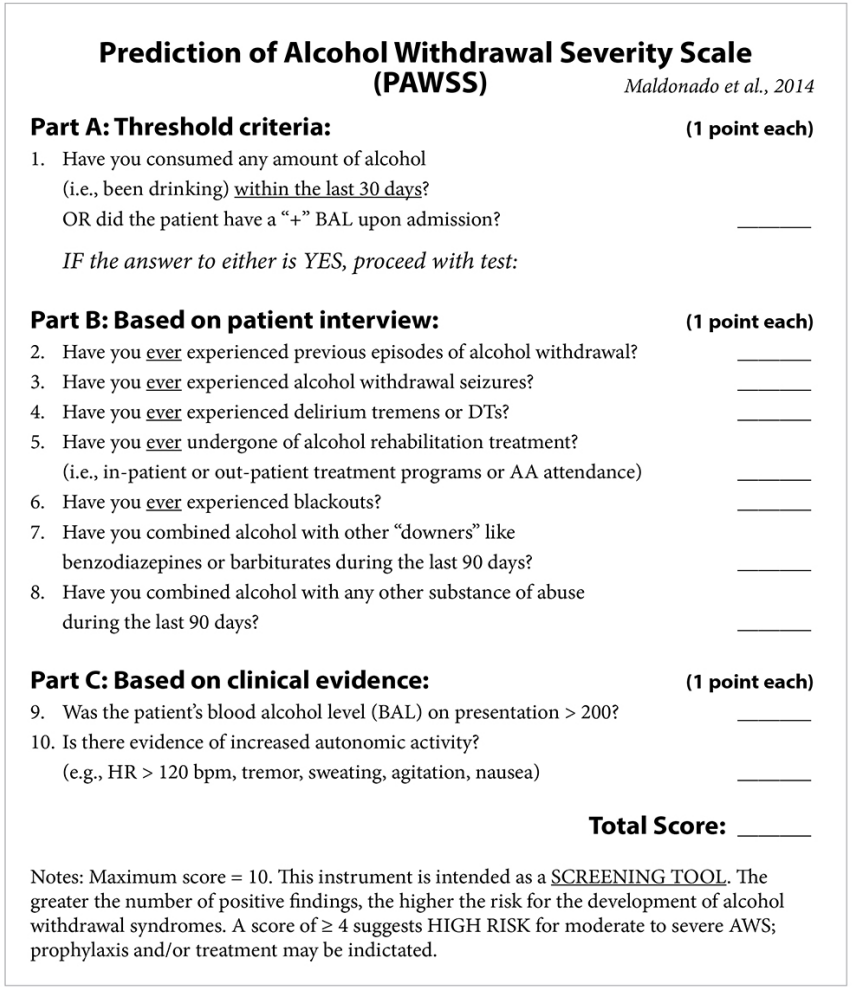
Recognizing Patients at Higher Risk for for SAWS

- **Why?**
  - These are the patients that go into *complicated* withdrawal
  - Generally, these are the patients you may want to be more aggressive pharmacologically and even consider prophylaxis *before* withdrawal symptoms
    - These are patients in which you generally want to avoid having go into significant withdrawal as you may not be able to 'catch up' in time
  - These are the patients who historically do NOT do well with symptom triggered protocols

- **Risk factors for AWD:**
  - History of past seizure or delirium tremens
  - Seizure in the field or in ED prior to admission
  - Acute concurrent medical illness
  - More days since last drink (2 or more days)
  - Elevated admission blood alcohol
  - Heavier and longer drinking history
  - Signs of autonomic hyperactivity with BAL of $\geq$ .1g/dL
  - AGE>40
  - Burn related injuries
  - Falls, particularly with long bone fractures
  - Elevated MCV, AST (? CDT)
  - On one study – MVA had negative predictive value

Ferguson J, et al. Risk Factors for Delirium Tremens Development. J Gen Int Med, 1996; 11: 410-14
Kraemer et al. Impact of Age on Severity, Course and Complications of Alcohol Withdrawal. Arch Int Med, 1997; 157: 2234-41.
Lukan et al. Risk Factors for Delirium Tremens in Trauma Patients. J Trauma, 2002; 53(5): 901-906.
Palmstierna T. A model for predicting alcohol withdrawal delirium. Psychiatr Serv 2001;52:820–3.

Prediction of Alcohol Withdrawal Severity Scale (PAWSS)



Prediction of Alcohol Withdrawal Severity Scale (PAWSS)

Maldonado et al., 2014

Part A: Threshold criteria: **(1 point each)**

1. Have you consumed any amount of alcohol (i.e., been drinking) within the last 30 days? OR did the patient have a "+" BAL upon admission? _____

IF the answer to either is YES, proceed with test:

Part B: Based on patient interview: **(1 point each)**

2. Have you ever experienced previous episodes of alcohol withdrawal? _____
3. Have you ever experienced alcohol withdrawal seizures? _____
4. Have you ever experienced delirium tremens or DTs? _____
5. Have you ever undergone of alcohol rehabilitation treatment? (i.e., in-patient or out-patient treatment programs or AA attendance) _____
6. Have you ever experienced blackouts? _____
7. Have you combined alcohol with other "downers" like benzodiazepines or barbiturates during the last 90 days? _____
8. Have you combined alcohol with any other substance of abuse during the last 90 days? _____

Part C: Based on clinical evidence: **(1 point each)**

9. Was the patient's blood alcohol level (BAL) on presentation > 200? _____
10. Is there evidence of increased autonomic activity? (e.g., HR > 120 bpm, tremor, sweating, agitation, nausea) _____

Total Score: _____

Notes: Maximum score = 10. This instrument is intended as a SCREENING TOOL. The greater the number of positive findings, the higher the risk for the development of alcohol withdrawal syndromes. A score of ≥ 4 suggests HIGH RISK for moderate to severe AWS; prophylaxis and/or treatment may be indictated.

FIGURE 2. Prediction of Alcohol Withdrawal Severity Scale developed by Maldonado and colleagues.[36]

Maldonado et al. Prospective Validation Study of the Prediction of Alcohol Withdrawal Severity Scale (PAWSS) in Medically Ill Inpatients: A New Scale for the Prediction of Complicated Alcohol Withdrawal Syndrome, *Alcohol and Alcoholism*, 50(5): 2015, 509–518

Recognizing Patients at Higher Risk for AWS

RISK OF SAWS*

+4 Points

- Active severe SAWS (CIWA ≥ 20)
- History of ICU admissions for SAWS
- History of alcohol withdrawal seizures or delirium tremens (DTs)
- BAL >0.1 g/dL with signs of withdrawal AND elevated MCV or AST:ALT ratio

+1 Point

- Recent and chronic active alcohol use
- Binge drinking about 3x per week (men: >5 or women: >4 drinks in 2hrs)
- BAL >0.1 g/dL with signs of withdrawal
- Elevated MCV or AST:ALT ratio
- History of alcohol related injuries (falls, head injury, bone fractures, etc.)
- Age >40

- **Medium Risk for AWS (>2 points):**
- **High Risk for AWS (≥4 or more points):**

Nisavic M, Nejad SH, Isenberg BM, Bajwa EK, Currier P, Wallace PM, et al. Use of phenobarbital in alcohol withdrawal management—a retrospective comparison study of phenobarbital and benzodiazepines for acute alcohol withdrawal management in general medical patients. Psychosomatics 2019;60:458–467.

Nejad S, Nisavic M, Larentzakis A, Dijkink S, Chang Y, Levine AR, et al. Phenobarbital for acute alcohol withdrawal management in surgical trauma patients—a retrospective comparison study. Psychosomatics 2020;61:327–335.

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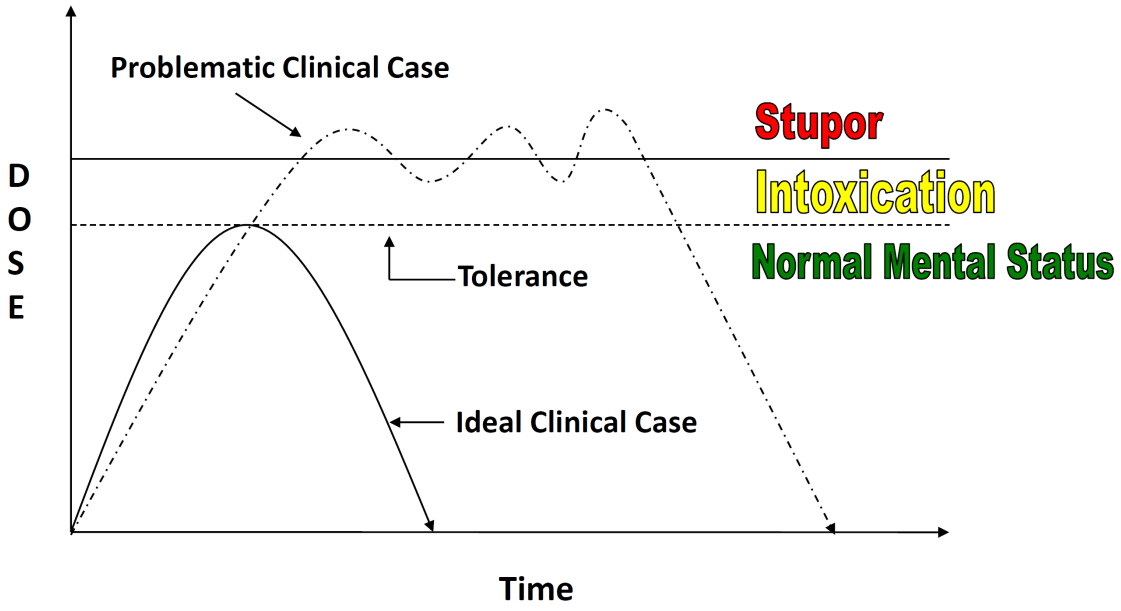
Benzodiazepine Monotherapy



- BZD excess seen often – regardless of symptom-triggered protocol, 'fixed-dosing' protocol, loading-dose protocol, etc.
- Anytime when patients receive benzodiazepines when symptoms not necessarily due to AWS
  - There is a significant difference between nursing experience between detoxification facilities versus the general hospital (!)
- Also seen when:
  - Patients are given too high of a dose
  - Too frequent of a dose
  - Underlying medical condition(s) are associated with lower tolerance for BZDs

Edited, Nick Kontos personal communication

Rating Scales in AWS

- CIWA-Ar (Clinical Institute Withdrawal Assessment for Alcohol – Revised)
- BAWS (Brief Alcohol Withdrawal Scale)
- AWS (Alcohol Withdrawal Symptoms rating scale)
- SAWS (Short Alcohol Withdrawal Scale)
- SAS (Severity Assessment Scale)
- SHOT (Sweating Hallucinations Orientation and Tremor)
- OAWS (Objective Alcohol Withdrawal Score)

STP Using CIWA-Ar: Things To Consider

- Patient Location
- Mental status
- Level of medical comorbidity
  - Do current medical etiologies and physiological sequelae complicate specificity and sensitivity of STP (e.g., CIWA-Ar)?
  - Does use of a STP increase the medical risk due to current active medical issues (e.g., current MI, CVA, etc.)?
- Current severity of alcohol withdrawal
  - *CIWA-Ar score of ≥20 is a general contraindication to remain in a STP protocol*
    - *Switch to fixed dose benzodiazepine administration*
    - *Switch to non-BZD strategy*
- History of previous or repeated *complicated* alcohol withdrawal
- When used, remember that most protocol order sets are only a 'starting point,' and you may need to adjust dose and route to be relevant to your patient
- **Alternative protocol should be available if there are contraindications to CIWA-Ar use**

CONTRAINDICATIONS TO CIWA-Ar

- Current delirium/encephalopathy/AMS
- History of alcohol withdrawal delirium (delirium tremens)
- History of alcohol withdrawal seizures (or primary seizure disorder)
- History of ICU admission for SAWS
- Risk for or current active opioid withdrawal
- Active psychosis
- Severe anxiety disorder

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Hecksel KA, Bostwick JM, Jaeger TM, Cha SS. Inappropriate use of symptom-triggered therapy for alcohol withdrawal in the general hospital. Mayo Clin Proc. 2008 Mar;83(3):274-9.

Non-Benzodiazepine Based Protocol - Phenobarbital

- When to consider:
  - Active DT's or severe withdrawal symptoms
  - Patient with contraindications to CIWA-Ar or STP
  - Patients with a history of delirium tremens and seizures
  - Patients with altered mental status and/or high risk for delirium (most ICU patients, surgical patients, patients with severe SIRS, etc)
  - Patients with apparent non-response to benzodiazepines or history of benzodiazepine resistance
  - Patients at risk for paradoxical disinhibition:
    - Acute and chronic TBI
    - Neurodegenerative disorders
    - History of alcohol related black-outs and/or assaultive behavior
  - Patients at risk or with respiratory compromise in which you may wish to avoid benzodiazepines

Historical Aspects - Phenobarbital

- First synthesized in 1911 by Hörlein and commercialized by F Bayer and Co as *Luminal* in the same year
- **It is the most widely used AED in the world**
- **Has been used for the treatment of alcohol withdrawal since the early 1910s following its development**
  - Utilization in AWS decreased with the introduction of diazepam in 1959
  - Phenobarbital is still utilized as the sole agent for detoxification in many state funded treatment centers
- Utilized for treatment of benzodiazepine detoxification

Phenobarbital for Treatment of AWS

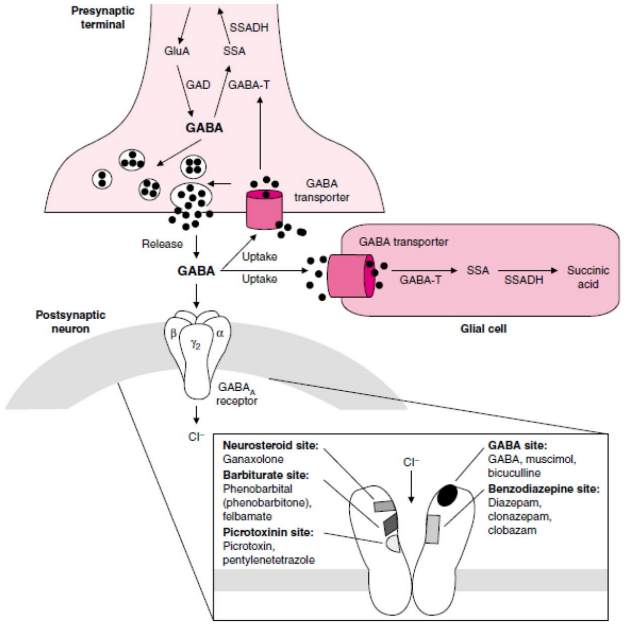
Reference	Pts. (N)	AWS Severity	Control	Outcome Measures	Results
Young (1987)	62	Moderate	None	Seizures (n) Delirium (n) Discharge from ED (%)	0 4 92%
Ives (1991)	+70	Unknown	None –observational noncomparitive report	Seizures (%) ↓ Delirium (%)	No 'undue consequences'
Rosenthal (1998)	32	Mild-moderate	Valproate	MSSA Score Phenobarbital Dose (n)	Change not significant VPA: 20 Control: 39 p<0.05
Mariani (2006)	27	Moderate	Gabapentin	Change in CIWA-Ar Score Phenobarbital Doses (n)	Difference not significant Gabapentin: 8 Phenobarbital: 5 p<0.45
Hendey (2011)	44	Moderate	Lorazepam	Change in CIWA-Ar Score upon ED disposition	Difference not significant
Rosenson (2013)	102	Unknown	Lorazepam +/- placebo	Level of admission LOS Adverse events	ICU admissions Decreased LOS None
Hsu (2016)	250	Severe	Lorazepam	Change in CIWA-Ar Score Hospital LOS ICU LOS	31% shorter duration in AWS in PB group 13% shorter ICU LOS in PB group
Nisavic et al (2019)	562	Moderate to Severe	Lorazepam	Seizures Hallucinosis AWD Hospital LOS ICU LOS	No difference between groups despite PB group having higher AWS risk history
Nejad et al (2020)	85	Moderate to Severe	Lorazepam	Seizures Hallucinosis AWD Uncomplicated AWS Hospital LOS	48.2% of BZD group developed AWD 73.1% of BZD group developed uncomplicated AWS 19.2% of BZD group developed medication adverse side effects None observed in PB group
Bosch et al (2021)	485	Not stated	Lorazepam	Need for mechanical ventilation ICU LOS Hospital LOS	Decrease in need for MV Decrease in LOS Decrease in use of restraints

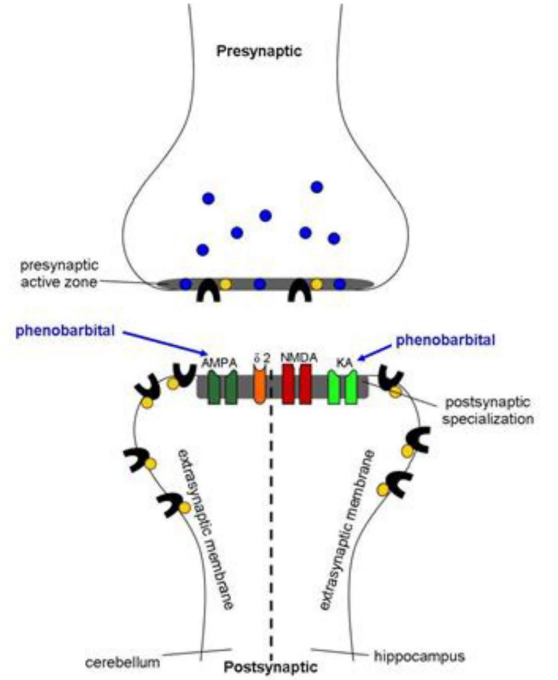
Institutions Where Phenobarbital Protocol Used and Disseminated:

- MGH
- NSMC
- Newton Wellesley Hospital
- BIDMC
- Martha's Vineyard Hospital
- Cooley Dickinson Hospital
- Holyoke Medical Center
- Elliot Hospital (New Hampshire)
- Eastern Maine Medical Center
- Long Island Jewish Medical Center
- University Hospital East (OSU)
- University of Southern Florida
- UW Medicine - Harborview Medical Center (modified)
- Swedish Medical Center (modified)
- Evergreen Medical Center (modified)
- UW Medicine – Valley Medical Center (modified)
- MedStar – Washington Hospital Center (modifed)

Phenobarbital

- Has GABA agonism AND decreases glutamate activity *ionotropically*
- Research does not demonstrate decreased receptor sensitivity as seen with benzodiazepines in patients with AUD
- ***Minimal changes in mental status and no observed paradoxical disinhibition***
- Pharmacokinetics are extremely reliable
  - Able to target specific serum levels (which are meaningful clinically)
  - Does ***NOT*** have a narrow therapeutic index
  - Longer-acting
- **Serum levels have clinical significance (!)**
  - Serum level of >10 (>90% coverage)
  - Serum level of ≥12 ((95% coverage)
  - Serum level of ≥15 (99% coverage)
  - When serum level is ≥12 it is essentially diagnostic that there are other etiologies for agitated delirium outside of AWS alone





Abbreviations: KA, kainite receptor; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; NMDA, N-methyl-D-aspartate; δ 2, δ2 glutamate receptor.

Clegg A & Young JB. Which medications to avoid in people at risk of delirium: a systemic review. Age Ageing. 2011; 40(1):23-29.
Sanna et al. Changes in GABAA receptor gene expression associated with selective alterations in receptor function and pharmacology after ethanol withdrawal. J of Neuroscience. 2003; 23(37):11711-11724.

When to Consider Phenobarbital

- Patients with a history of delirium tremens and seizures
- Patients with apparent non-response to benzodiazepines or history of benzodiazepine resistance
- Active DT's or severe withdrawal symptoms
- Patients with altered mental status and/or high risk for delirium (most ICU patients, surgical patients, patients with severe SIRS, etc)
- Patients at risk for paradoxical disinhibition:
  - Acute and chronic TBI
  - Neurodegenerative disorders
  - History of alcohol related black-outs and/or assaultive behavior
- Patients at risk or with respiratory compromise in which you may wish to avoid benzodiazepines
- Patient with contraindications to CIWA-Ar or STP

Phenobarbital Based Protocol

MODERATE RISK OF AWS:

AT LEAST TWO:

- Recent and chronic active alcohol use
- Binge drinking >5 drinks (men) or >4 drinks (women) in 2 hours about 3x per week
- Elevated MCV and/or AST:ALT ratio
- History of alcohol related injuries (falls, head injury, long bone fractures, etc.)
- Age ≥40
- BAL >0.1 g/dL while showing signs of alcohol withdrawal

HIGH RISK OF AWS:

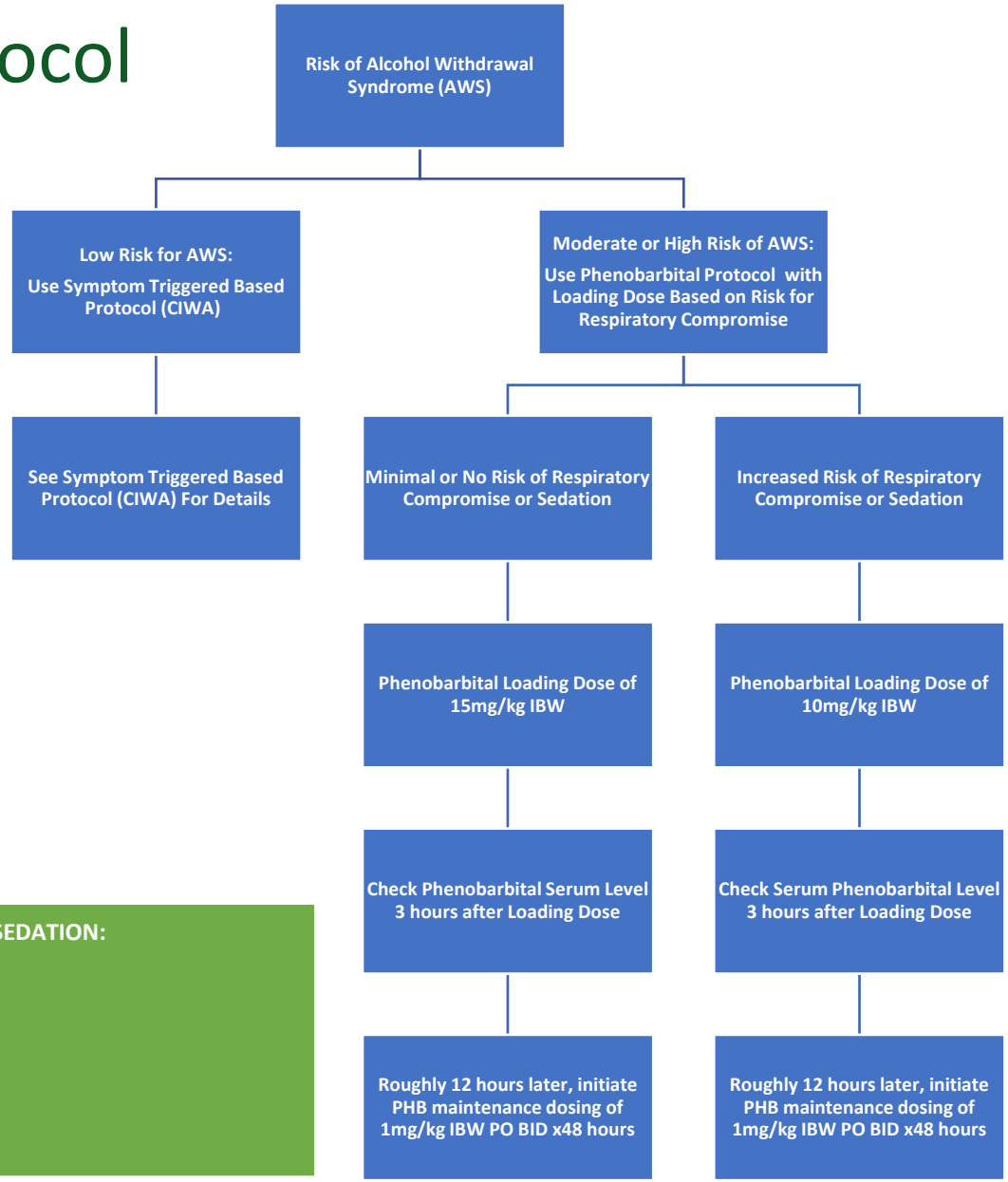
ANY ONE:

- History of ICU admissions for SAWS
- History of alcohol withdrawal seizures or delirium tremens (DTs)
- Current active signs of severe alcohol withdrawal at time of presentation
- BAL >0.1 g/dL while showing signs of alcohol withdrawal AND elevated MCV and/or AST:ALT ratio

RISK OF RESPIRATORY COMPROMISE OR SEDATION:

ANY ONE:

- Greater than 10mg of lorazepam equivalents in the last 12 hours
- Current PNA or other respiratory issue
- Rib fractures or chest wall injury
- Current opiate administration
- Administration of general anesthesia in the last 12 hours
- Cirrhosis or Child-Pugh Score of >8



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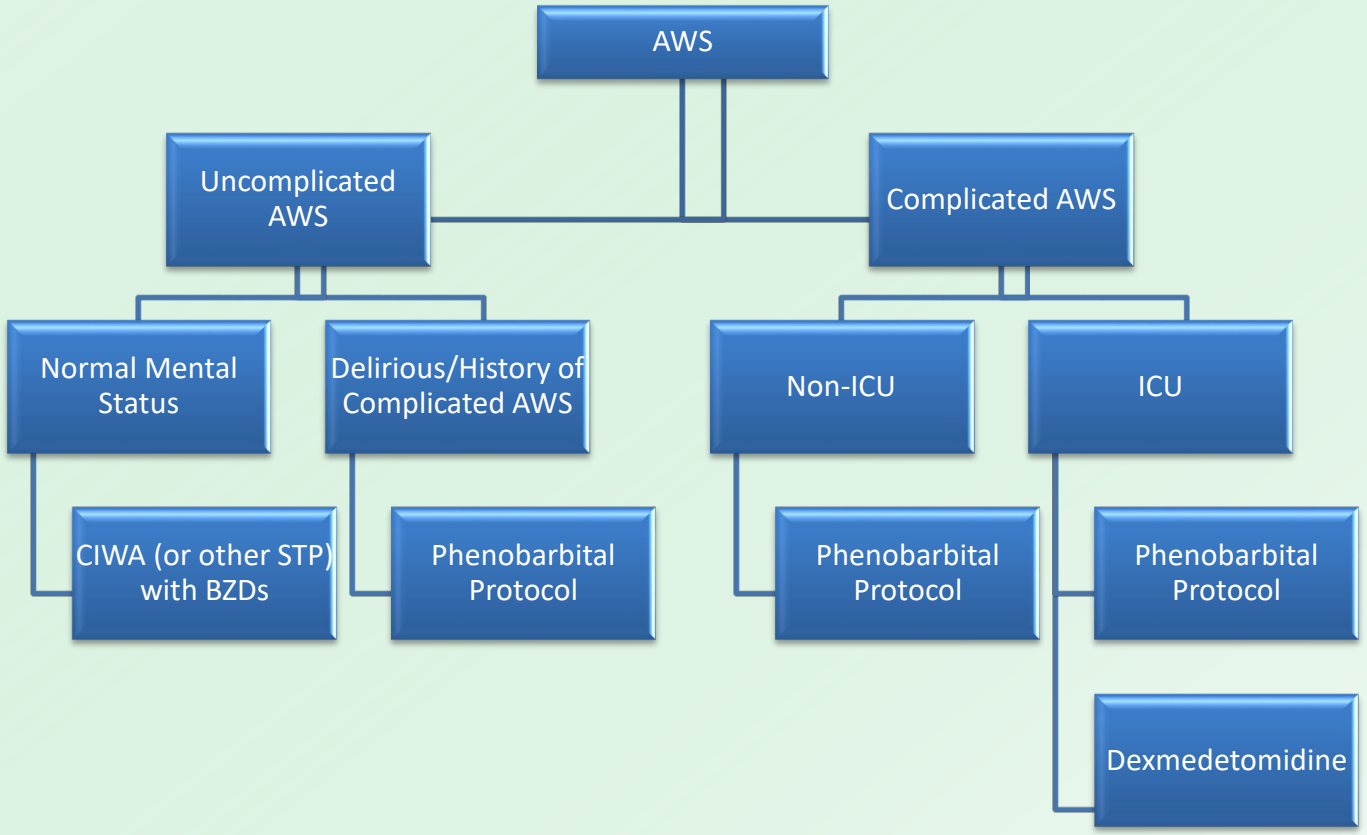
General AWS Pathway Considerations

- Dexmedetomidine
  - Ideal for AWS management
  - Need to be in the CCU/ICU
  - Similar to phenobarbital, when rate is ≥0.8mcg/kg/hr it is essentially diagnostic that there are other etiologies outside of AWS alone if ongoing agitation symptoms



Recommendations

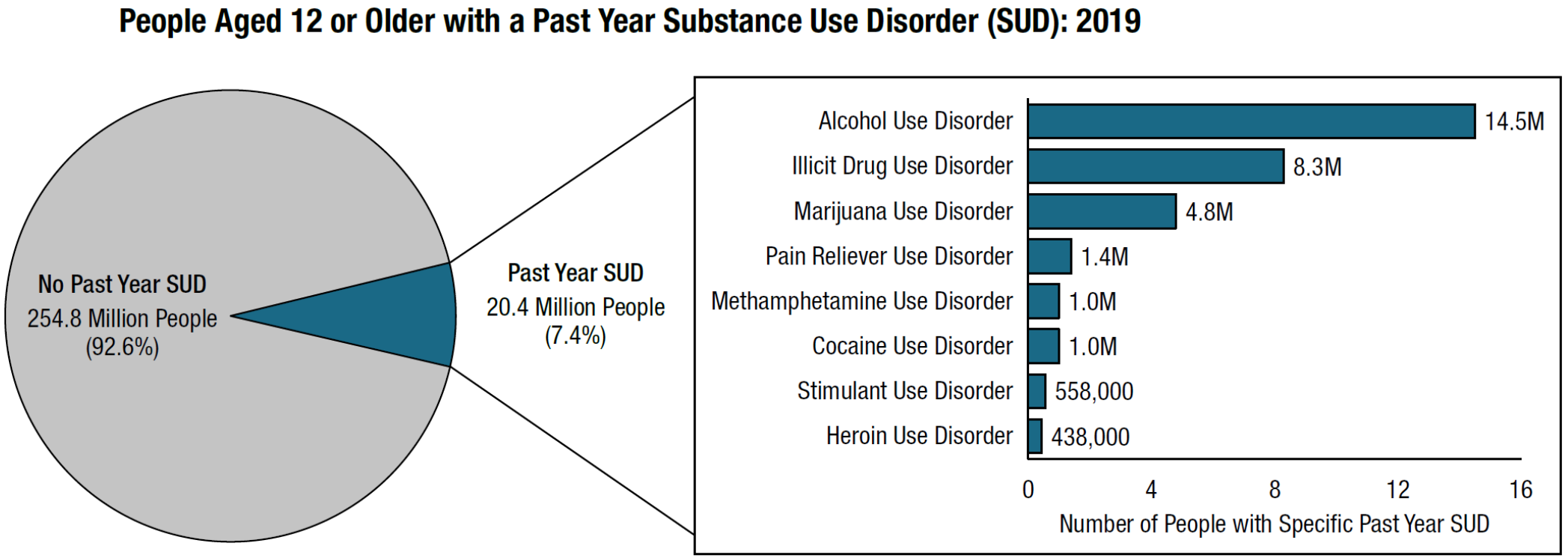
- Early in hospital course, utilize history, labs, and epidemiologic data to help guide risk assessment for development of *complicated* and *uncomplicated* alcohol withdrawal

- Active medical illness and PMH, along with current AWS and past detoxification history can help guide you to management strategy: STP using CIWA-Ar vs fixed dose vs non-BZD protocols (e.g., phenobarbital) vs dexmedetomidine

- Use understanding of pathophysiology of AWS and current symptoms being observed to help guide augmentation strategies for more complicated alcohol withdrawal cases, particularly in those patient with concomitant active medical and surgical illness

Pharmacotherapy for Alcohol Use Disorder

Prevalence of Alcohol Use Disorder



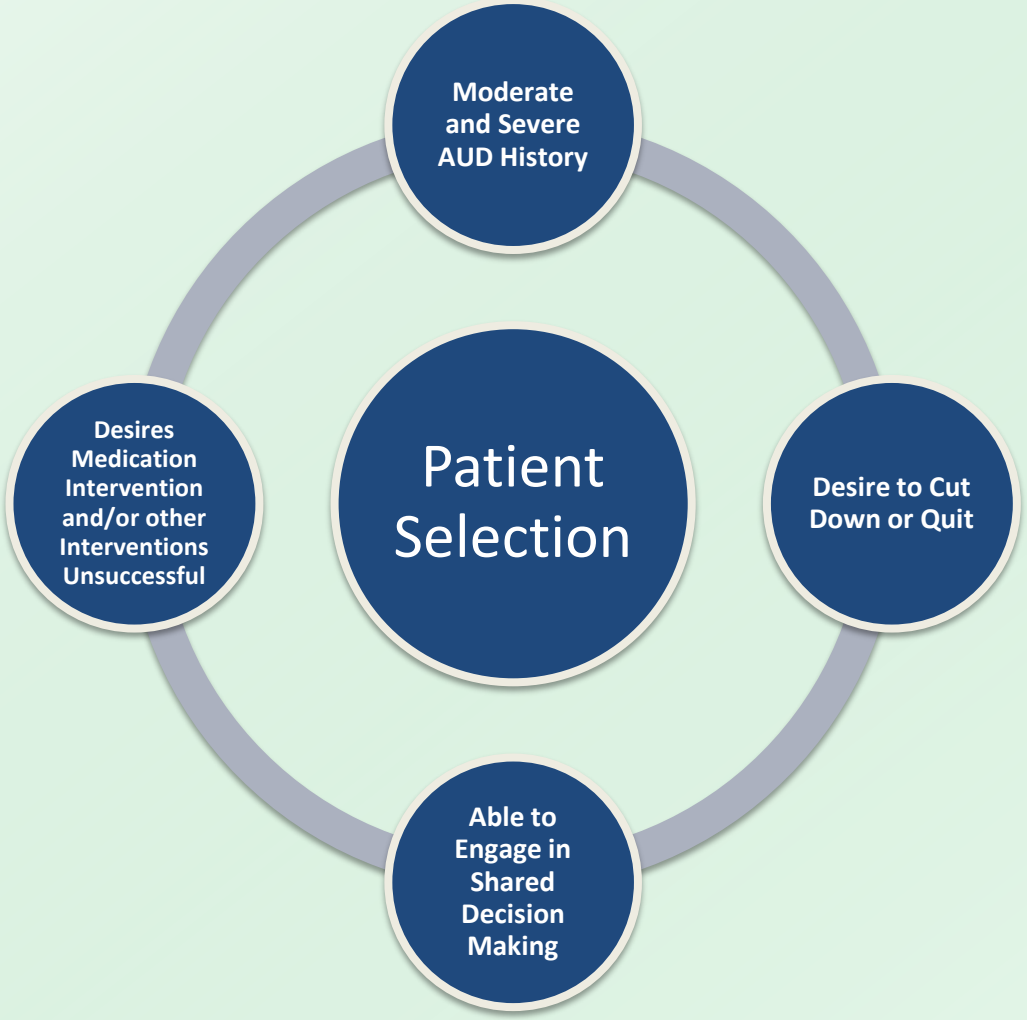
National Survey on Drug Use and Health, Annual Survey Report 2019

Severe Cost of AUD

- 95,000 people/year die from alcohol-related causes
  - 3.7% cause by chronic related conditions
  - 46.3% caused by acute related conditions
- 3rd leading cause of death in US
- 30% of homicides, 22% suicides, 33% MVAs
- Annual estimated cost of alcohol use is up to $250 BILLION

Esser MB, Sherk A, Liu Y, et al. Deaths and Years of Potential Life Lost From Excessive Alcohol Use — United States, 2011– 2015. MMWR Morb Mortal Wkly Rep 2020;69:1428–1433.
Substance Abuse and Mental Health Services Administration (SAMHSA). 2019 National Survey on Drug Use and Health (NSDUH). Table 2.1B—Tobacco Product and Alcohol Use in Lifetime, Past Year, and Past Month among Persons Aged 12 or Older, by Age Group: Percentages, 2018 and 2019.
Sacks JJ, Gonzales KR, Bouchery EE, et al. 2010 National and State Costs of Excessive Alcohol Consumption. Am J Prev Med 2015; 49:e73.
https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6101a4.htm?s_cid=mm6101

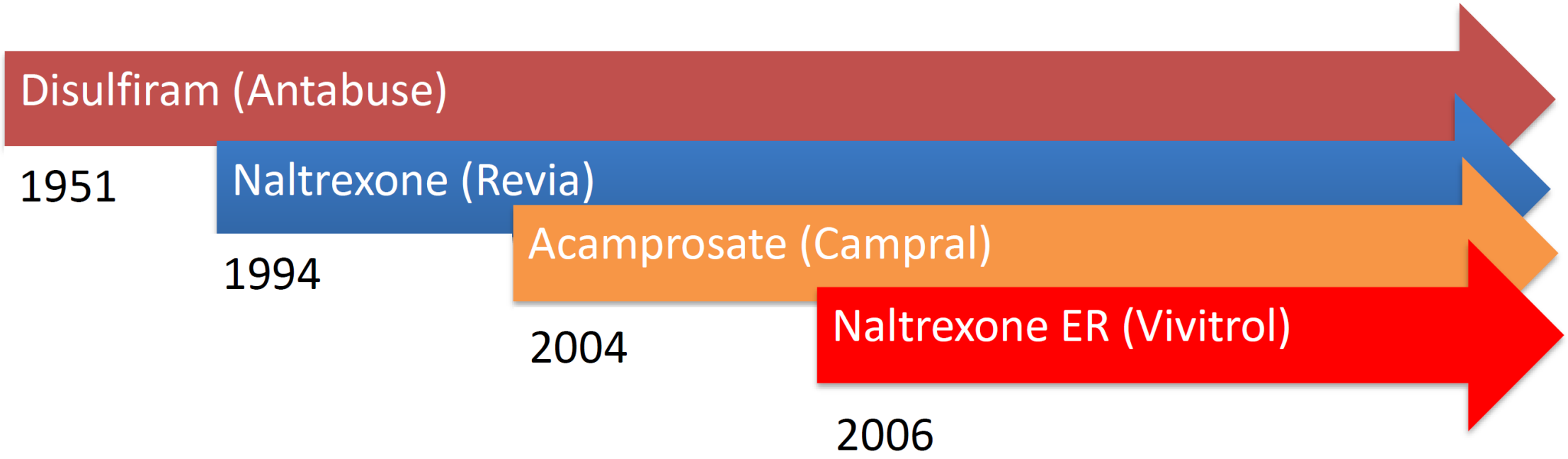
AUD Pharmacotherapy



General Mechanisms of Action for AUD

Try to Block or Reduce	• Block or Reduce reinforcing effects from alcohol use
Reduce	• Reduce Post-Acute Withdrawal Symptoms
Discourage or Provide Negative Effects	• Discourage alcohol use by aversion or inducing side-effects if alcohol ingested

FDA Approved Pharmacologic Treatments



Naltrexone

Mechanism of Action	Mu-opioid receptor antagonist
Indication	Alcohol Use Disorder Opioid Use disorder
Clinical Evidence	Reduced likelihood of returning to any and/or heavy drinking Fewer drinking days overall Reduced subjective experience of 'craving'
Pre-treatment Work-Up	Hepatic function
Dosing	Oral: 25mg PO daily x3 days, then 50mg PO daily IM Injection: 380mg IM every 4 weeks
Potential Side Effects	Abdominal pain (11%); diarrhea (13%); nausea (29%); dizziness (13%)
Contraindications	Opioid Use Child-Pugh Class C
Special Considerations	Be cautious when using in patients with acute hepatitis or liver failure **Be abstinent from all opioids for 7-14 days prior to taking naltrexone to avoid precipitated opioid withdrawal** May be preferable to acamprosate in patients with comorbid alcohol and opioid use disorder

Naltrexone – Decreased Drinking and Increased Abstinence

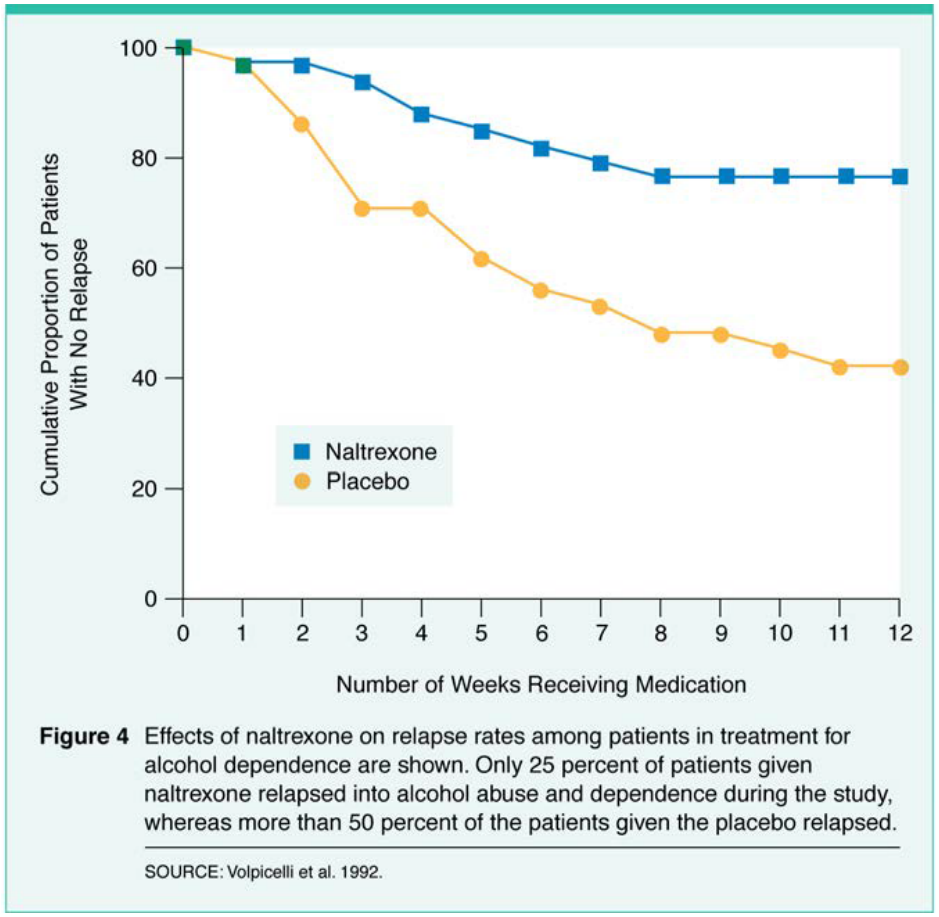
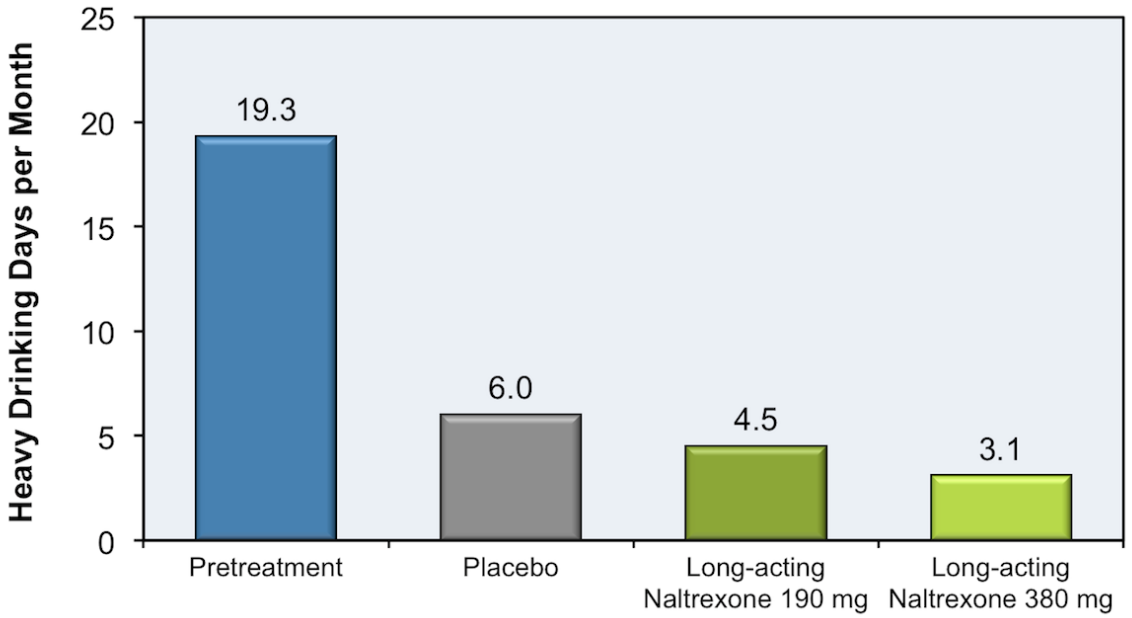


Figure 4 Effects of naltrexone on relapse rates among patients in treatment for alcohol dependence are shown. Only 25 percent of patients given naltrexone relapsed into alcohol abuse and dependence during the study, whereas more than 50 percent of the patients given the placebo relapsed.

SOURCE: Volpicelli et al. 1992.



Volpicelli et al, JAMA Psychiatry 1992. Naltrexone and the treatment of Alcohol Dependence
Garbutt et al. JAMA.2005 Apr 6;293(13):1617-25.

Naltrexone Take Home

- Can be used in patients who are still drinking
- Can be used for patients for abstinence and to decrease use/consequences
- No empirical evidence on frequency of LFT monitoring
  - Transaminitis is often due to other etiologies (alcohol, HCV, etc)
- It has opioid pain blockage – can utilize wallet card as an alert
- Many do well with oral dosing however can utilize ER injection to help with adherence

Acamprosate

Mechanism of Action	Glutamate receptor modulator
Indication	Alcohol use disorder
Clinical Evidence	Decreased likelihood of returning to drinking after achieving abstinence; Fewer drinking days
Pre-treatment Work-Up	Measure serum creatinine
Dosing	666mg PO TID *Can consider 333mg TID x3 days then 666mg TID if concerns for GI upset
Potential Side Effects	Diarrhea (17%)
Contraindications	Contraindication if CrCl <30ml/min Dose reduction if 30< CrCl >50ml/min
Special Considerations	Start treatment as soon as possible after the patient archives abstinence and continue treatment even if the patient relapses

Acamprosate Efficacy

- Naltrexone better for reducing drinking and acamprosate better for abstinence
- Improvements may be expected:
  - Time to first relapse (6 months versus 3 months)
  - Total number of days abstinence (270 days versus 135 days)
  - Time to first drink
  - Craving may decrease
- Length of treatment:
  - One year, whether drinking or not

Rosner S. Leucht S, et al. J Psychopharmacol 2008; 22:11
Verheul R et al. Predictors of acamprosate efficacy; Psychopharmacology 2005;178:167

COMBINE Trial

- Compared efficacy of 9 different treatment combinations
  - Acamprosate, naltrexone, or combination of both
  - Behavioral interventions included medical management (MM) and combined behavioral intervention (CBI)
  - Placebo conditions included pills and no medications

- Outcomes:
  - Patients receiving medical management with naltrexone, CBI, or both showed substantial reduction in drinking
  - Acamprosate showed no evidence of efficacy, with or without CBI
  - No combination produced better efficacy than naltrexone or CBI alone

Anton et al, Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence. JAMA.2006 May 3;295(17):2003-17.

Acamprosate Take Home

- Consider in patients with decompensated liver disease
- Consider in patients intolerant of naltrexone
- Consider in patients on chronic opioids (or methadone)
- Best outcomes for abstinence post-detox
- TID dosing is a huge barrier for ANYONE

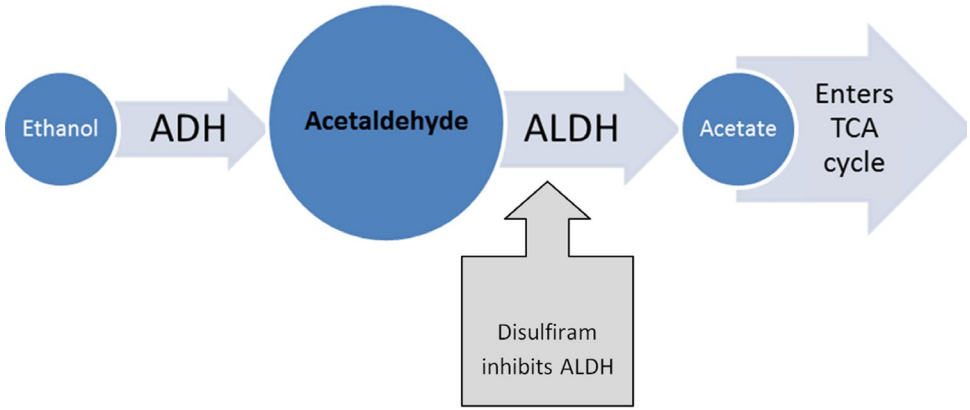
Treatment Efficacy of AUD for Acamprosate and Naltrexone

Naltrexone	Acamprosate	Aspirin	Metformin	Antimicrobial	Antihypertensive
NNT=12 Reduced Heavy Drinking	NNT=12 Return to Any Drinking	NNT=50 Prevention of CV Disease	NNT=14 Mortality Benefit After 10 years	NNT=16 Symptom Reduction for Otitis Media	NNT=67 Stroke Prevention
NNT=20 Complete Abstinence	NNT=9 Reduced Drinking				NNT=125 Mortality Prevention

- **<10% of patients with AUD receive medication treatment**
- **>70% of patients with hypertension receive medication treatment**

Jeremiah Fairbanks et al, Mayo Clinic Proceedings, Volume 95, Issue 9,2020
Merai R, et al. CDC grand rounds: a public health approach to detect and control hypertension.MMWR Morb Mortal Wkly Rep. 2016

Disulfiram



- Can consider when:
  - The patient has a goal of achieving abstinence
  - Prefers disulfiram or intolerant to or has not responded to naltrexone and acamprosate
  - The patient is capable of understanding the risks of alcohol consumption while taking disulfiram, and:
  - The patient has no contraindications to the use of this medication

- Efficacy
  - Evidence from RCT does not support long term use
  - Efficacy observed in supervised trial
  - Abstinence rate almost doubled (23% versus 15%) when monitored

Laaksonen E, Koski-Jannes et al. A randomized, multicentre, open label comparative trial of disulfiram, naltrexone and acamprosate. Alcohol Alcohol 2008 43:5

Disulfiram

Mechanism of Action	Inhibitor of aldehyde dehydrogenase When the patient consumes alcohol while taking disulfiram, the accumulation of acetaldehyde causes a physical response such as tachycardia, flushing, headache, nausea, and vomiting
Indication	Alcohol use disorder
Clinical Evidence	Increased likelihood of achieving abstinence in patients for whom this is their goal
Pre-treatment Workup	ECG, physical exam, hepatic function
Dosing	First dose 12 hours after the last drink; 500mg PO each morning for 1-2 weeks, then 250mg PO each morning
Potential Side Effects	Elevations in hepatic enzymes (common) Potentially fatal acute hepatotoxicity (rare) Neuropathy and increased blood pressure
Contraindications	Recent myocardial infarction or coronary artery disease History of a seizure disorder History of pancreatitis
Special Considerations	Only for those seeking abstinence from alcohol Instruct not to consume alcohol within 12-24 hours of taking disulfiram Recommend involving a family or roommate as an observer of daily medication adherence Physical reaction can be precipitated by alcohol containing products (e.g., cold medicine, mouthwashes) and certain medications (e.g., sertraline oral concentrate, metronidazole, ritonavir)

Disulfiram Take Home

- Aversive strategy only
- Adherence is not great
- Consider for patients with goal of abstinence but either intolerant of or not interested in other daily medication strategies
- Consider as adjunctive strategy in high-risk situations, but generally not first line

Gabapentin

Original Investigation

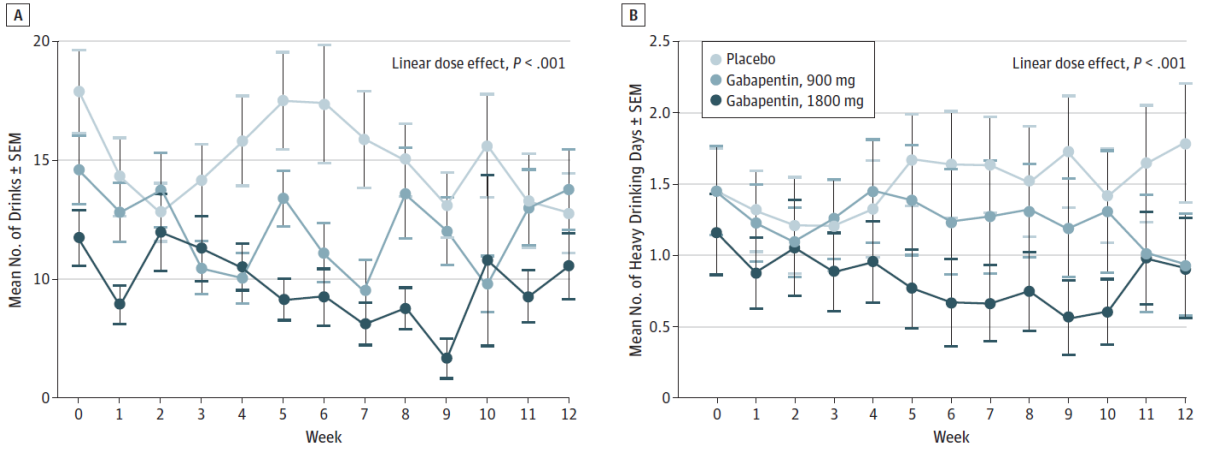
Gabapentin Treatment for Alcohol Dependence
A Randomized Clinical Trial

Barbara J. Mason, PhD; Susan Quello, BA, BS; Vivian Goodell, MPH; Farhad Shadan, MD; Mark Kyle, MD; Adnan Begovic, MD

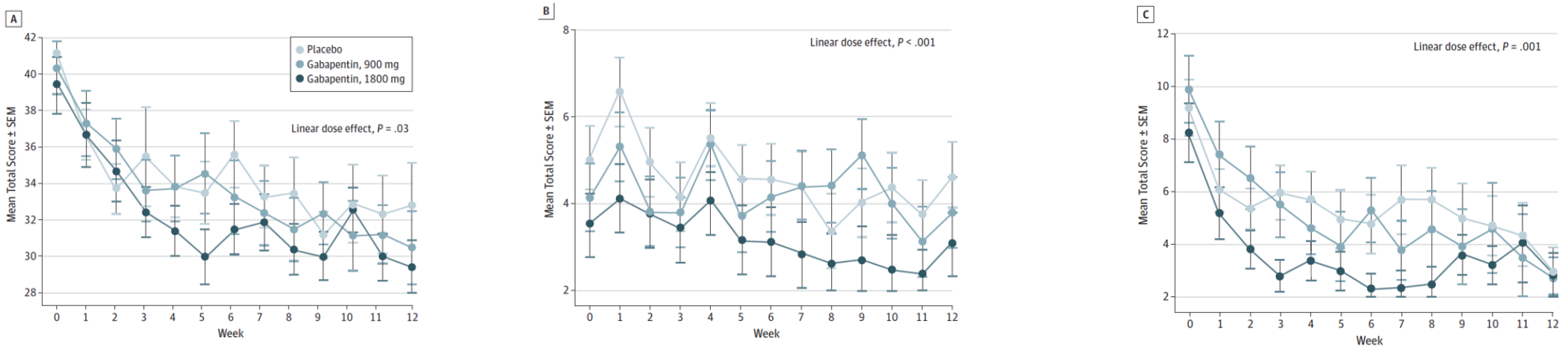
- A 12-week, double-blind, placebo-controlled, randomized dose-ranging trial of 150 men and women older than 18 years with current alcohol dependence, conducted from 2004 through 2010 at a single-site, outpatient clinical research facility adjoining a general medical hospital.
- Intervention was using oral gabapentin (dosages of 0 [placebo], 900 mg, or 1800 mg/d) and concomitant manual-guided counseling.
- Looking at outcome measure rates of complete abstinence and no heavy drinking(co-primary) and changes in mood, sleep, and craving (secondary) over the 12-week study.

Mason BJ, et al. *JAMA Intern Med*. 2014;174(1):70-77.

Gabapentin



A, Number of drinks per week; B, number of heavy drinking days per week. Error bars indicate SEM (N = 150).



A, Alcohol Craving Questionnaire; B, Pittsburgh Sleep Quality Index; C, Beck Depression Inventory II. Error bars indicate SEM (N = 150).

Mason BJ, et al. *JAMA Intern Med*. 2014;174(1):70-77.

Gabapentin

Mechanism of Action	• Ligand of α2δ calcium channel subunit (component of voltage-dependent calcium channels) • It is **NOT** a direct channel blocker but exerts effects by disrupting regulatory function of the α2δ and with other proteins • Potent activator of voltage-gated potassium channels KCNQ3 and KCNQ5 but unlikely to be dominant mechanism of its therapeutic effects • **Even though it is a structural GABA analogue, it does NOT bind to GABA receptors, does NOT convert into GABA or another GABA receptor agonist *in vivo*, and does NOT modulate GABA transport or metabolism**
Indication	Off-label use for AUD
Clinical Evidence	Improved rates of complete abstinence and no heavy drinking (particularly at higher dosing of 1800mg/daily); improved PAWS
Pre-treatment Workup	None
Dosing	Taper upwards to target of 900-1800mg (divided 3 times daily)
Potential Side Effects	Sedation; fatigue; headache; ataxia
Contraindications	Allergy to gabapentinoids (monitor for arm/leg edema)
Special Considerations	Need to taper down/off due to withdrawal risk Misuse potential, particularly for patients with OUD or stimulant disorders

Gabapentin Take Home

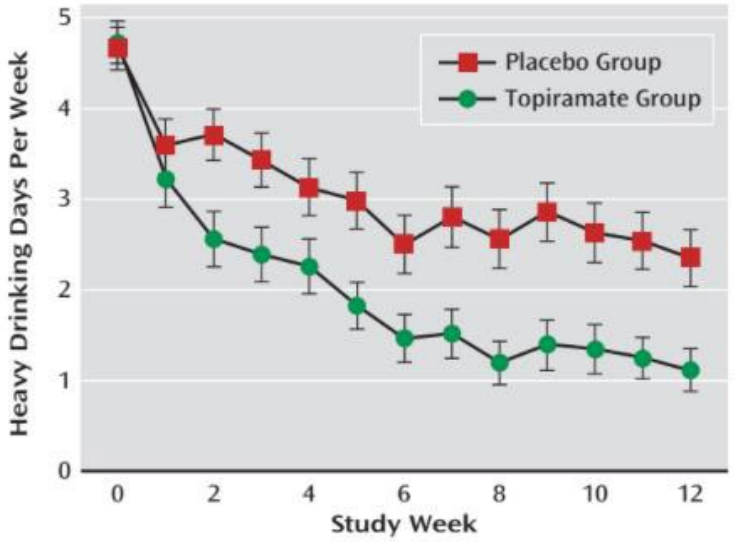
- Off label but emerging evidence for AUD
- Consider in patients who are immediately post-detox
- Consider in patients with ongoing use and/or post-acute withdrawal symptoms (anxiety, insomnia, cravings)
- Need to taper

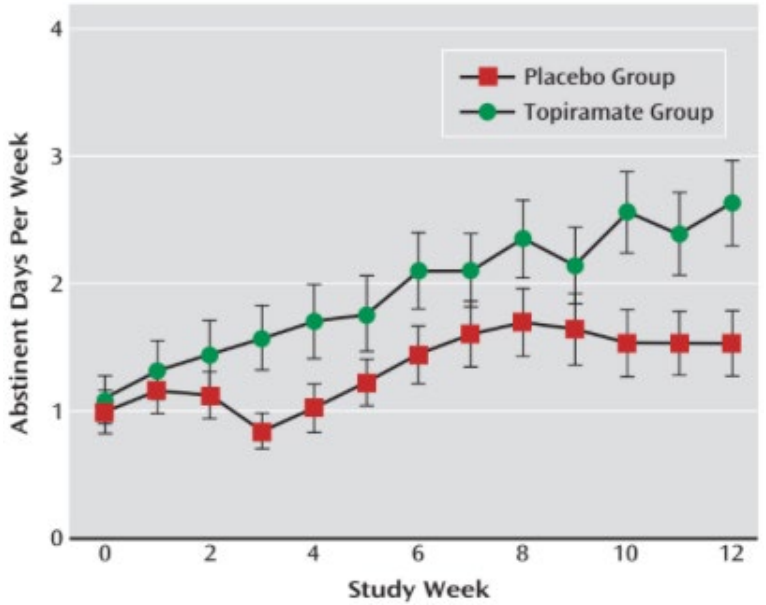
- Misuse Potential
  - Drug Abuse Warning Network Data:
    - ED visits involving non-medical use of gabapentin **INCREASED** 90% in the US since 2008
  - 1 in 10 overdose **DEATHS** between 2019 and 2020 gabapentin was ruled as a cause of death in reports from CDC Division of Overdose Prevention
  - In one study of patients OUD 22% of patients self-reported gabapentin misuse

Wilens et al, *Am J Addict*. 2015. Epub 2014/11/21
SAMHSA. Emergency Department Data. June 10, 2014
Kuehn BM. Gabapentin Increasingly Implicated in Overdose Deaths. *JAMA.* 2022;327(24):2387.

Topiramate

- Mechanism of Action:
  - Enhances GABA A (non-benzodiazepine site) activity
  - Glutamate receptor antagonist
- Dosing:
  - 25-50 mg/day
  - Titrate up by 25 mg per day week, to max dose 150mg BID
- Take Home:
  - Off-label use
  - Consider in patients intolerant of naltrexone or acamprosate
  - Patients with comorbid neuropathy, seizure disorder, CUD





Kanzler et al. *Am J Psychiatry*. 2014;171:445-452

Recommendations

- AUD has significant prevalence but *VASTLY* under-treated
  - Consider initiating therapy when you see patients with underlying AUDs
- Goals of therapy is usually abstinence OR reduction of heavy drinking
- Outside of gabapentin, all medications for AUD are not controlled substances and have no addiction potential
- Patient-centered, individualized care most effective

Thank You!

Shamim Nejad, MD, FASAM, FACLP

shamim_nejad@valleymed.org

shamim@uw.edu