Focus on Phenobarbital:
Applications for Alcohol and Sedative-Hypnotic Withdrawal

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Disclosure Information

- Dr. Jeremiah D. Fairbanks, DO – Allina Health
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- Dr. JoAn Laes, MD, FASAM – Hennepin County Medical Center
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- Dr. Alaina Steck, MD, FASAM – Emory University / Grady Memorial Hospital
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- Dr. Timothy Wiegand, MD, FACMT, FAACT, DFASAM – University of Rochester Medicine
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  - No disclosures

Learning Objectives

At the conclusion of this session, participants will be able to:

- Describe the pathophysiology of sedative hypnotic withdrawal, including alcohol, benzodiazepines, and other sedative-hypnotic agents such as gabapentin, pregabalin, phenibut, and GHB;
- Describe the pharmacology of phenobarbital; and,
- Implement treatment protocols using phenobarbital (either as the primary medication, as an adjunct, and other adjunctive agents if used as primary treatment) for the treatment of sedative-hypnotic and alcohol withdrawal in the acute care and ambulatory setting.

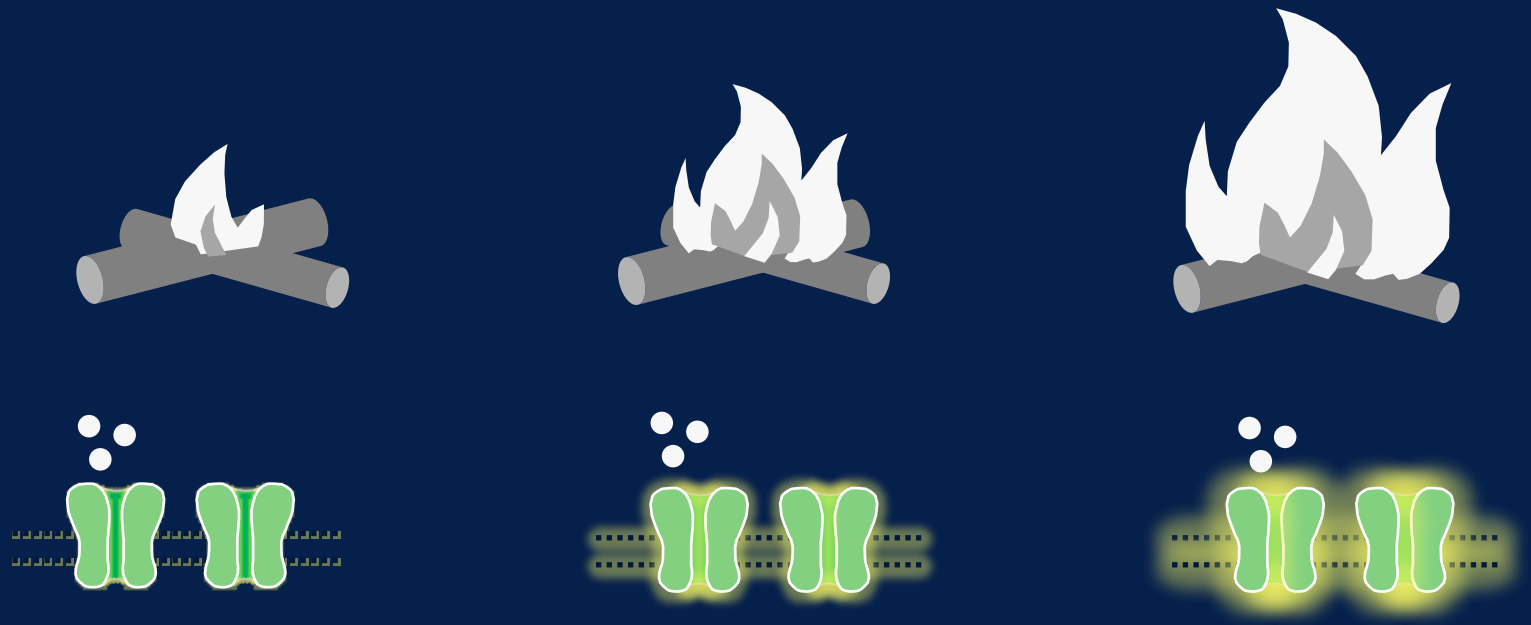
Case 1

52-year-old male with severe AUD

HR 146 bpm, BP 168/108, RR 24, SpO2 99% RA, Temp 99.0ºF

Time	Lorazepam dose (IV)	Total lorazepam	Diazepam equivalents*
0	2 mg	2 mg	10 mg
0:15	2 mg	4 mg	20 mg
0:40	4 mg	8 mg	40 mg
1:30	6 mg	14 mg	70 mg
2:00	4 mg bolus + 4 mg/hour gtt	18 mg	90 mg
16:00	4 mg/hour gtt	74 mg	370 mg

BDZ-Resistant Withdrawal

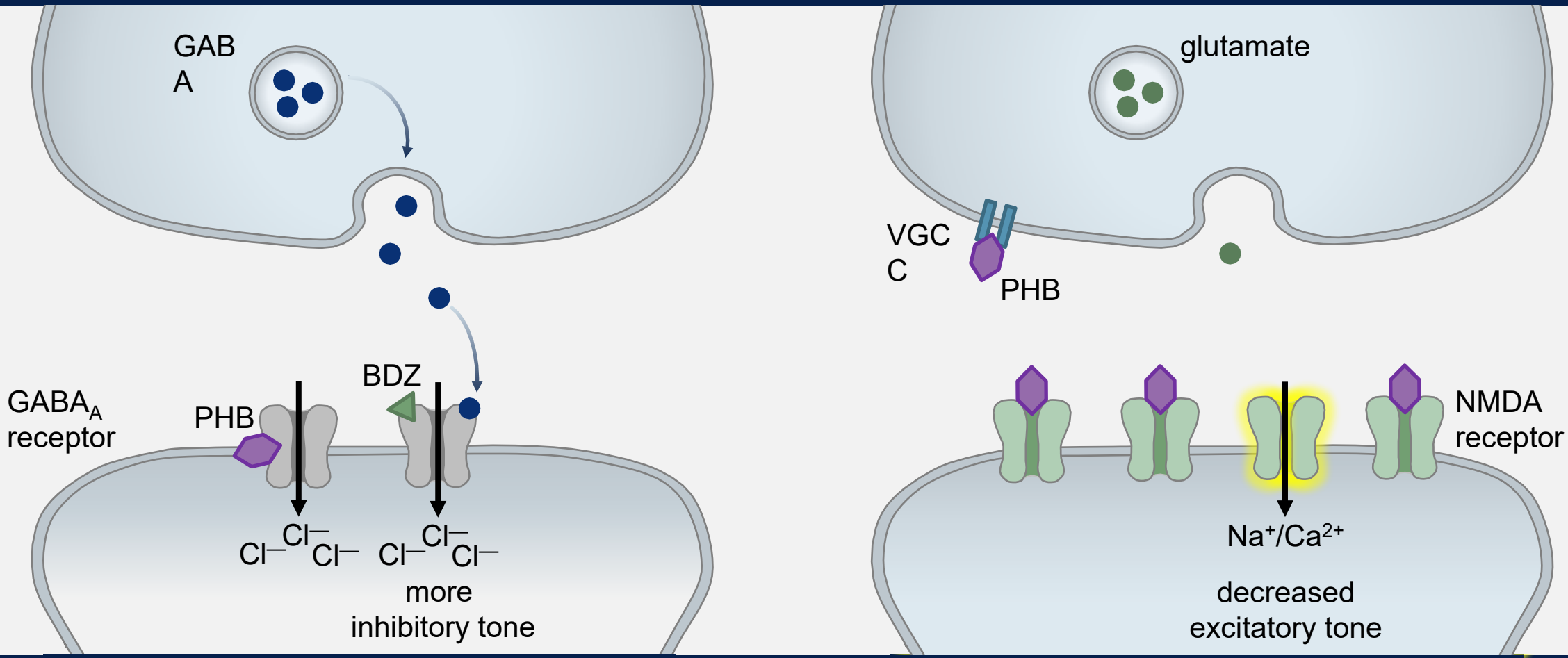


[1]Murphy JA, et al. (*Ann Pharmacother* 2021)

Panel Discussion

How do you define benzodiazepine-resistant withdrawal?

Pathophysiology & Rationale for PHB



[1]Murphy JA, et al. (*Ann Pharmacother* 2021); [2]Wolf C, et al. (*Open Access Emerg Med* 2020)

Pharmacology: PHB *v.* BDZ

Medication	Onset	Peak Effect	Duration	Half-life ($t_{1/2}$)
phenobarbital				
IV	5 min	≥15 min	10 – 12 hours	~ 80 hours
PO	60 min	6 – 8 hours		
lorazepam				
IV	5 – 10 min	15 – 30 min	3 – 6 hours	~ 14 hours
diazepam				
IV	<5 min	8 min	12 hours	10 – 48 hours* **metabolite: 100 hours*
PO	15 – 60 min	1 – 1.5 hours		
chlordiazepoxide				
PO	variable	2 – 4 hours	variable	24 – 48 hours* **metabolite: 100 hours*

Panel Discussion

What would be your next steps with this patient?

Case 1: PHB & Other Adjuncts

Safety:

- Protocols using adjunctive PHB vs protocols using other adjuncts (e.g., dexmedetomidine, haloperidol): no difference in rates of adverse events[1-3]

Efficacy:

- More effective when used in a protocolized manner *v*. at physician's discretion[1]

Benefits:

- BDZ-sparing[1,2]
- Reduction in rates of mechanical ventilation[1,2]
- Other comparisons (hospital LOS, ICU admission rate) difficult to compare between studies due to methodological differences

[1]Murphy JA, et al. (*Ann Pharmacother* 2021); [2]Hammond DA, et al. (*Hosp Pharm* 2017); [3]Nisavic M, et al. (*Psychosomatics* 2019)

Panel Discussion

If you encountered this patient early in his hospital course, would you have utilized a different medication strategy?

Case 1: PHB-Forward Strategies

ED-based studies:

- no difference in ICU admission, non-ICU LOS, complications, or need for intubation[1,2]

Surgical ICU population:[3]

- 10/31 patients required additional adjunctive therapy
- 3/31 (10%) intubated, 3/31 developed hypotension

Medical ICU population:

- 17/86 (20%) intubated[4]
- Reduced LOS and fewer adjunctive meds with PHB (4.3 days) vs BDZ (6.9 days) [p=0.004][5]

[1]Nelson AC, et al. (*Am J Emerg Med* 2019); [2]Sullivan SM, et al. (*Am J Emerg Med* 2019); [3]Ammar MA, et al. (*Ann Pharmacother* 2021); [4]Oks M, et al. (*J Int Care Med* 2020); [5]Tidwell WP, et al. *(Am J Crit Care* 2018*)*

Case 2 (Part A)

43-year-old patient with daily use of alcohol presents to the ED…

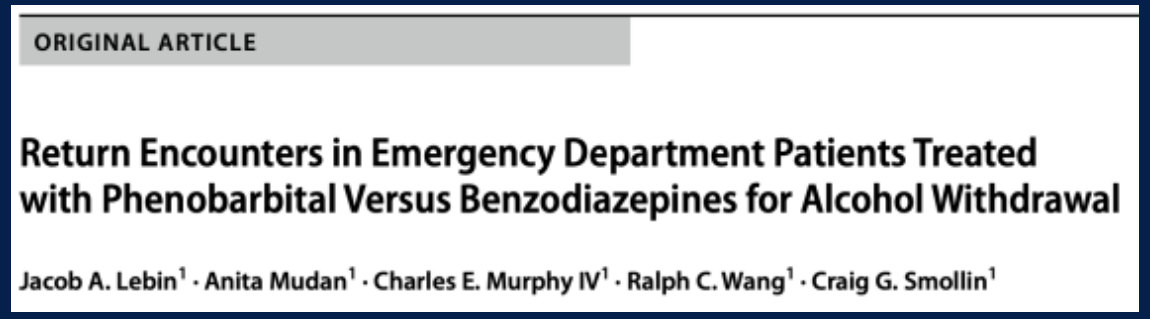
- Wants to decrease use, but no inpatient hospital or detoxification beds are available
- Past Medical History:
  - Prior episodes of alcohol withdrawal: seizures, delirium
- Current BAL: 0 mg/dL

Phenobarbital in the ED

Original Contribution

A prospective, randomized, trial of phenobarbital versus benzodiazepines for acute alcohol withdrawal☆

Gregory W. Hendey MD*, Robert A. Dery MD, Randy L. Barnes MD, Brandy Snowden MPH, CCRP, Philippe Mentler PharmD



ORIGINAL ARTICLE

Return Encounters in Emergency Department Patients Treated with Phenobarbital Versus Benzodiazepines for Alcohol Withdrawal

Jacob A. Lebin[1] · Anita Mudan[1] · Charles E. Murphy IV[1] · Ralph C. Wang[1] · Craig G. Smollin[1]

- IV PHB *v*. IV lorazepam + PO chlordiazepoxide
- 44 patients, mild-to-moderate AWS
- No difference in effectiveness or symptoms 48 hours after discharge

- Stratified according to ED management:
  - BDZ only
  - PHB only
  - Combination of both agents
- PHB group: less likely to return to ED within 3 days of index visit

[1]Hendey G, et al. (*Am J Emerg Med* 2011); [2]Lebin JA, et al. (*J Med Toxicol* 2022)

When poll is active, respond at **pollev.com/alainasteck822**

If the patient's symptoms are controlled in the ED after receiving phenobarbital, would you discharge this person from the ED?

Yes

No

I'm not sure / It depends

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Panel Discussion

Can patients be safely discharged from the ED if their withdrawal is controlled after receiving one to two doses of PHB?

- What doses would you use?
- What would be the home discharge medication regimen?
- What other information would guide your treatment?

Phenobarbital Options for Withdrawal

Mild

260 mg IV push or 100 mg PO

130 – 260 mg IV push or 100 mg PO
x 2 prn q60 min

Discharge

Moderate-Severe

10 mg/kg IV over 30 minutes

130 – 260 mg IV push or
100 – 200 mg PO
x 2 prn q60 min

3 day benzodiazepine taper of diazepam
or chlordiazepoxide

The ASAM Clinical Practice Guideline on Alcohol Withdrawal

- The following indicators should be present for discharge to an ambulatory alcohol withdrawal management setting from the ED:
  - Mild alcohol withdrawal (e.g., CIWA-Ar score <10)
  - Moderate alcohol withdrawal (e.g. CIWA-Ar score 10–18) with no other complicating factors
  - Not currently intoxicated (including alcohol or other drugs)
  - No history of complicated alcohol withdrawal (seizures, delirium)
  - No significant medical or psychiatric comorbidities that would complicate withdrawal management
  - Able to comply with ambulatory visits and therapy

Panel Discussion

What if the patient had no current symptoms of alcohol withdrawal?

- Would you give a prophylactic dose of a medication?
- Would you give a prophylactic dose of phenobarbital?

PAWSS:
Prediction of Alcohol Withdrawal Severity Scale

PART A: Threshold Criteria

1. Have you consumed any amount of alcohol w/i last 30 days OR have a (+) BAL on admission.?

If Yes, proceed…

PART B: Based on patient interview

2. Have you ever experienced previous alcohol withdrawal?
3. Have you ever experienced alcohol withdrawal seizures?
4. Have you ever experienced DTs?
5. Have you ever undergone alcohol rehabilitation Rx?
6. Have you ever experienced blackouts?
7. Have you combined alcohol with other "downers" like benzos or barbs in last 90 days?
8. Have you combined alcohol with any other substance of abuse in the last 90 days?

PART C: Based on Clinical Evidence

9. Was the patient's BAL on presentation > 200 mg/dL?
10. Is there evidence of ↑ autonomic activity (HR > 120, tremor, sweat, agitation, nausea)?

[1]Maldonado JR, et al. (*Alcohol Alcohol* 2015)

Case 2 (Part B)

The same 43-year-old patient with
history of alcohol withdrawal seizures and delirium
presents to an ambulatory setting instead of to the ED …

When poll is active, respond at **pollev.com/alainasteck822**

Can alcohol or sedative-hypnotic withdrawal be safely managed with phenobarbital in the outpatient setting?

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Panel Discussion

Can phenobarbital be used safely in the outpatient setting?

- Are there patient characteristics that favor this strategy?
- What dosing strategy would you use?
- Are there adjunct medications you would prescribe?

Ambulatory Phenobarbital Dosing

- ??

The ASAM Clinical Practice Guideline on Alcohol Withdrawal

- Patients at risk of 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
    - History of severe or complicated withdrawal
    - Risk for complications of significant medical, surgical, or psychiatric illness (particularly cardiovascular disease including coronary artery disease)
    - Displaying signs or symptoms of withdrawal concurrent with a positive blood alcohol content

The ASAM Clinical Practice Guideline on Alcohol Withdrawal

- Phenobarbital can be used as an alternative in Level 2-WM settings (Ambulatory Withdrawal Management with Extended Onsite Monitoring)
  - Particularly with contraindication for benzodiazepine
  - Narrow therapeutic window and extended half-life, recommend experienced clinicians

Phenobarbital Adjuncts

- For the patient not yet in acute withdrawal, or acute withdrawal is attenuated, but ongoing treatment is needed.

  - clonidine 0.1 mg PO q 6 hours PRN anxiety

    sometimes continued for 1 – 2 weeks after protocol:

    0.1mg PO q 8 hours PRN or qHS PRN

  - VPA 500 mg PO BID x 2 – 4 weeks

[1]Kawasaki SS, et al. (*J Subst Abuse Treat* 2012)

Case 3

25-year-old male

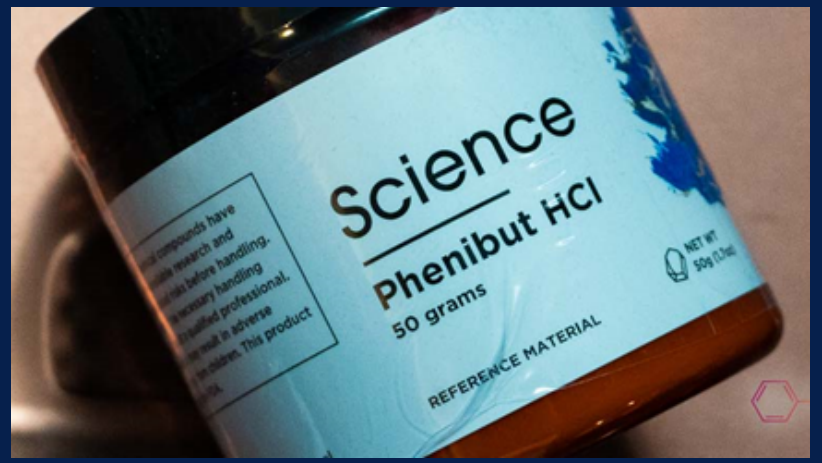
benzodiazepine use disorder, in sustained remission

- presents to clinic: severe anxiety, insomnia, muscle aches
  HR 95, BP 175/100
- seen in ED yesterday: workup unrevealing
- phenibut 4g TID (12g daily) for social anxiety x 2 years
  - stopped abruptly 2 days ago

Phenibut

(β-***phenyl***-γ-amino***but***yric acid)

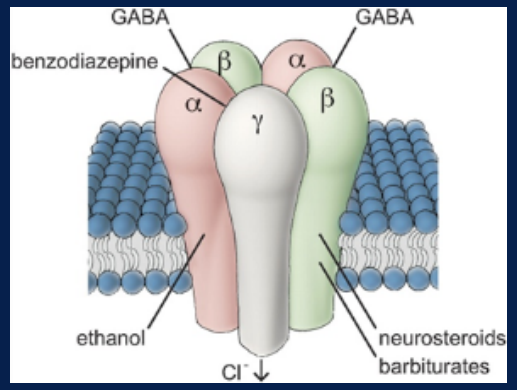
- Fenibut, phenybut, фенибут
- Developed in Soviet Union in the 1960s as an anxiolytic for participants in the space program
- U.S. and Europe: sold online as a supplement for anxiety and ”exercise recovery booster”
- Typically consumed orally, though IV, rectal, inhalation and insufflation use has been noted
- Purity of commercially available phenibut varies widely (40% – 98%)

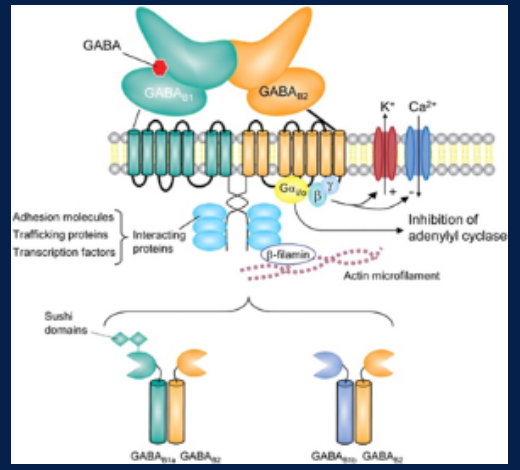


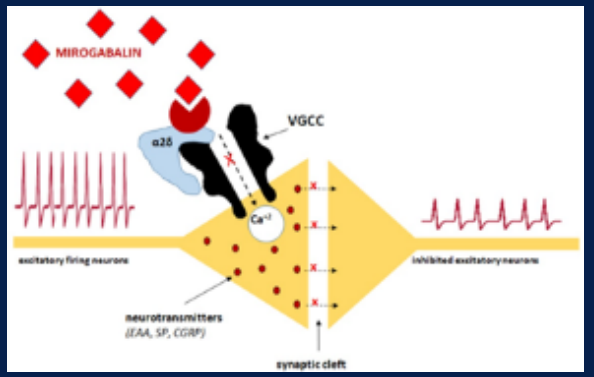
[1]Lapin I. (*CNS Drug Rev* 2001)

Mechanism of Action

- Primarily $GABA_B$ agonist (like baclofen)
- At very high doses can also be $GABA_A$ agonist
- Blockade of $\alpha_2\delta$ subunit of voltage dependent calcium channels (like gabapentinoids)
- In low doses, also increases concentration of dopamine, providing a stimulatory effect in addition to anxiolysis







[1]Lapin I (*CNS Drug Rev* 2001); [2]Benarroch EE (*Neurology* 2012)

Withdrawal Symptoms

Severe withdrawal can last up to 2 weeks:

- Insomnia
- Rebound anxiety
- Anger/irritability
- Muscle tension
- Paranoia
- Nausea
- Visual/Auditory Hallucinations

[1]Lapin I. (*CNS Drug Rev* 2001)

Panel Discussion

25-year-old male

Hx benzodiazepine use disorder, now in acute phenibut withdrawal.

- Given lack of data on treatment options, what are other pharmacological interventions would make sense based on mechanism of action?

PHB for Phenibut Withdrawal

- PHB: $GABA_A$ receptor agonist with little to no $GABA_B$ / α2δ properties
- precedent (but limited data) of managing phenibut withdrawal with other $GABA_A$ agonists[1-5]
  - inpatient benzodiazepine tapers with/without continuation of benzodiazepines and with/without the use of other pharmacotherapy (antipsychotics, diphenhydramine, melatonin, gabapentin)[2]
- baclofen ($GABA_B$ agonist) withdrawal management[3] with
  - clonazepam[3] ($GABA_A$ agonist)
  - diazepam[4] ($GABA_A$ agonist)

[1]Hogberg L, et al. (*J Subst Use* 2013); [2]Hardman MI, et al. (*Bos J Basic Med Sci* 2019); [3]Roopa S, et al. (*Prim Care Companion CNS Disord* 2021); [4]Esposito CM, et al. (*Front Psychiatry* 2021); [5]Mash JE and Leo RJ (*Prim Care Companion CNS Disord* 2020)

Phenobarbital for Phenibut Withdrawal

- One case report of an outpatient phenobarbital taper
  - Patient taking 14 g/day and using over 4 months
  - Patient was already on buprenorphine and gabapentin for comorbidities
  - Titrated to 64.8 mg phenobarbital 4x daily to minimize withdrawal symptoms and then successfully tapered over 9 days at 25 – 50% reduction every 2 – 3 days.
- Is phenobarbital a reasonable consideration for phenibut withdrawal management?
  - Limited data and lack of gold standard
  - I would argue yes

[1]Brunner E and Levy R. (*J Addict Med* 2017)

Alternative / Augmenting Agents

- Phenibut itself: one case report of self taper after only 10 days use at 1 g/day
- $GABA_B$ agonist: baclofen
  - Case report: cross-tapering 8 g phenibut to baclofen (10mg of baclofen : 1 gram phenibut) over 9 weeks, followed by a 12-week baclofen taper
  - One other report: starting on much lower dose of baclofen and tapering over shorter period of time though phenibut dose was 100-300 mg “every few days”
- α2δ ligands: gabapentin / pregabalin
  - No case reports for monotherapy, can consider for augmentation
- $GABA_A$ agonists: BDZ
  - No case reports in outpatient setting though few successful inpatient tapers

[1]Samokhvalov AV, et al. (*BMJ Case Rep* 2013); [2]Ahuja T, et al. (*Case Rep Psychiatry* 2018);
[3]Magsalin RMM and Khan AY (*J Clin Psychopharmacol* 2010)

Final Takeaways

- Phenobarbital acts on multiple molecular targets to alleviate alcohol and sedative-hypnotic withdrawal
  - Role as an adjunctive therapy and monotherapy
  - Consideration for inpatient, ED, and ambulatory care settings
  - Multiple studies demonstrate comparable safety profile to benzodiazepines

- Expanding access to and use of designer benzodiazepines, gabapentinoids, and $GABA_B$ agonists (e.g., phenibut) may result in more patients seeking care for withdrawal from these agents
  - Phenobarbital has a role in these cases as well

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