Novel Benzodiazepines and Sedative-Hypnotics: Down but Not Out

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Disclosure Information (Required)

- JoAn Laes, MD FASAM FACMT
  - No Disclosures
- Timothy Wiegand, MD FACMT, FAACT, DFASAM
  - No Disclosures
- Jeremiah Fairbanks, DO
  - No Disclosures

Learning Objectives

1. Discuss the current market of “novel” benzodiazepines and sedative-hypnotics such as phenibut and gamma-hydroxybutyrate analogues, including availability, use patterns, pharmacology, and methods of detection
2. Explain the pathophysiology and clinical presentation of withdrawal from novel sedative-hypnotics and whether this differs from traditional benzodiazepine withdrawal
3. Discuss the management of use disorders and withdrawal syndromes of novel sedative-hypnotics using GABA agonists and non-GABA agonists in a variety of medical settings

Novel Benzodiazepines

Novel Benzodiazepines and Sedative-Hypnotics

Benzodiazepines

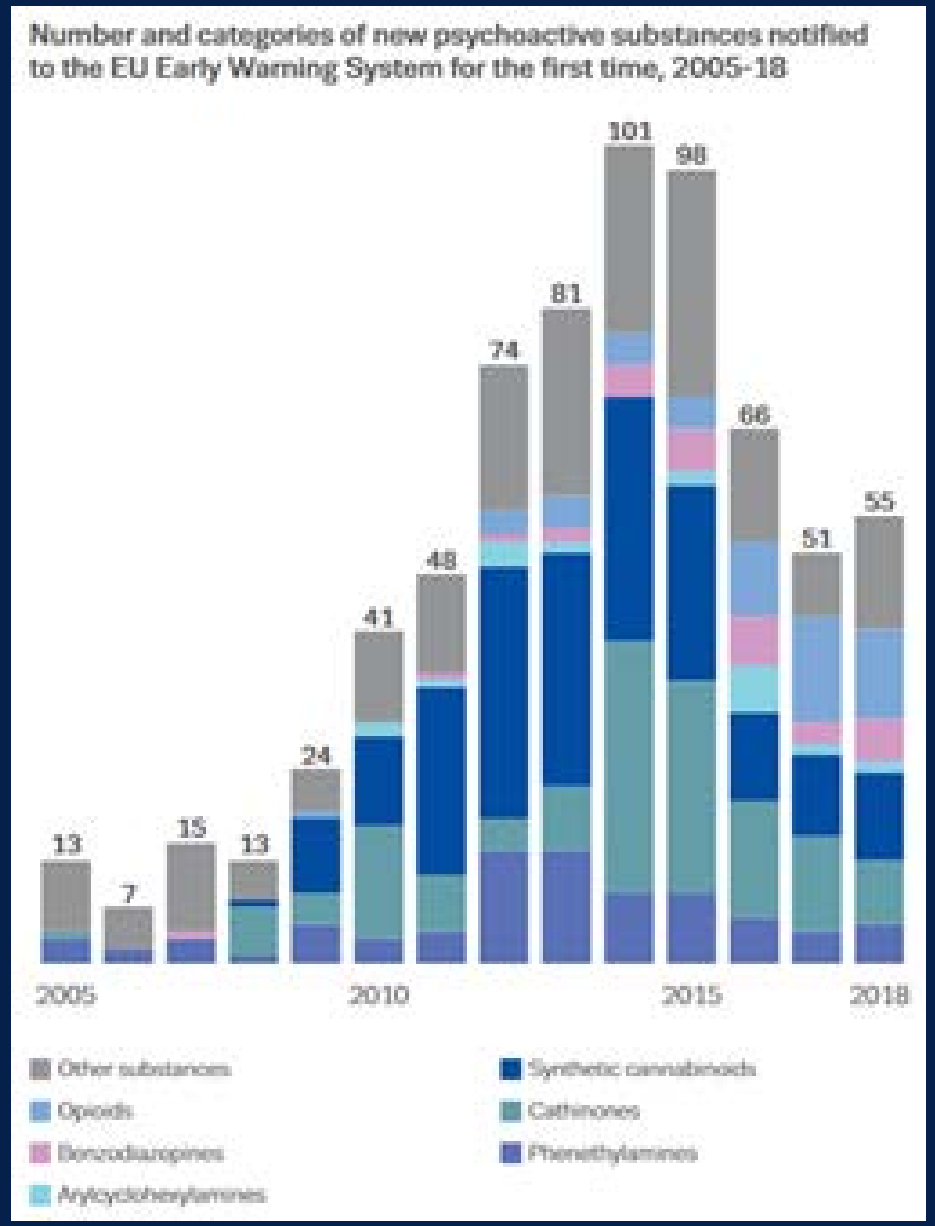
- Etizolam
- Flubromazolam
- Clobazam
- Meclonazepam
- Flubromazepam
- Deschloroetizolam
- Nifoxipam
- Pyrazolam
- Clonazolam
- Phenazepam
- Ketazolam

Other

- Gamma-aminobutyric acid (GABA) analogues
  - Phenibut
- Gamma Hydroxybutyrate (GHB) analogues
  - Gamma-butyrolactone (GBL)
  - 1,4-Butanediol
  - Gamma-hydroxyvalerate (GHV)
  - Gamma-valerolactone (GVL)

Zawilska JB, Wojcieszak J. An Expanding world of new psychoactive substances –designer benzodiazepines. Neurotoxicology 73; (2019): 8-16.

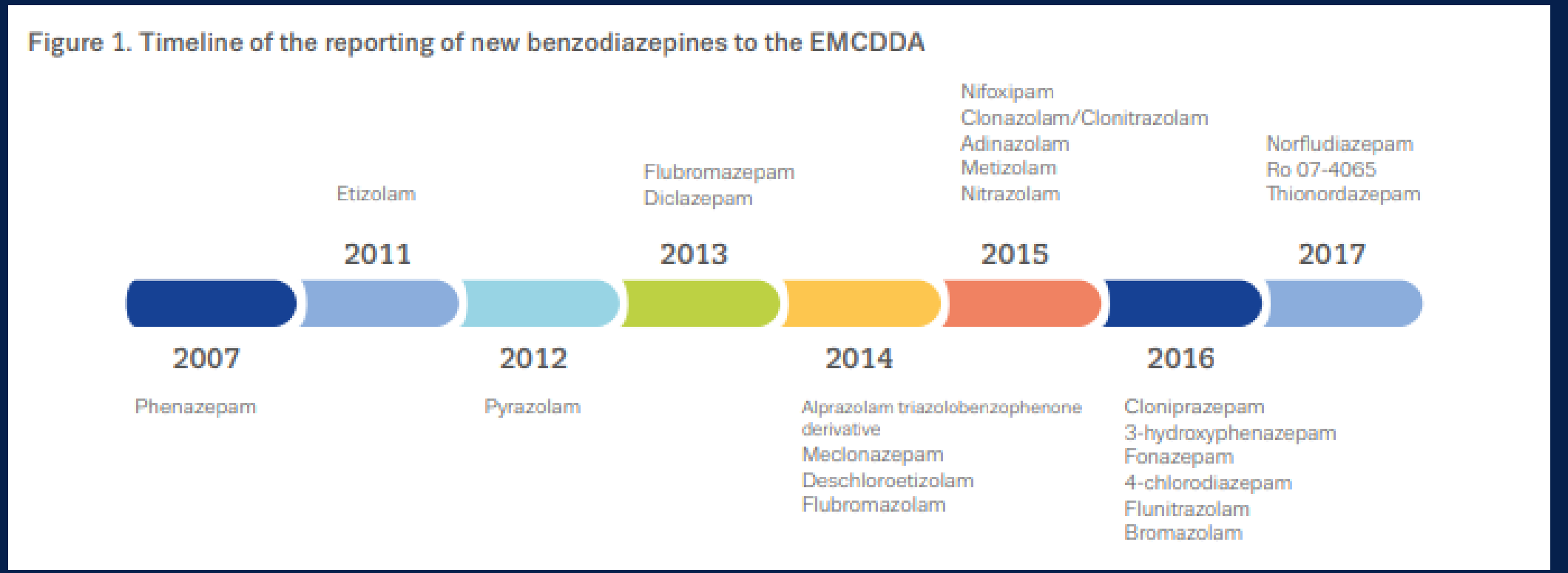
Trends in New Psychoactive Substances



- European Monitoring Centre for Drugs and Drug Addiction (2019), European Drug Report 2019: Trends and Developments, Publications Office of the European Union, Luxembourg.

https://www.unodc.org/LSS/Announcement/Details/af9c6b26-5715-4043-86e6-f6d7a2acad50

European Monitoring Centre on Drugs and Drug Addiction



https://www.emcdda.europa.eu/system/files/publications/2733/Misuse%20of%20benzos_POD2015.pdf

National Poison Data US

- 2014—2017: **330% increase**
  - Single agent exposures: adinazolam, clonazolam, cloniprazepam, diclazepam, etizolam, flubromazepam, flubromazolam, meclonazepam, nifoxipam, norflurazepam, and pyrazolam.
- 234 agents reported
  - 1: etizolam (n=162)
  - 2: clonazolam (n=50)

Carpenter, Joseph E., et al. "Designer benzodiazepines: a report of exposures recorded in the National Poison Data System, 2014–2017." *Clinical toxicology* 57.4 (2019): 282-286.

Distribution

- 2016 Research and Development (RAND) corporation report
  - Number of online vendors of illegal drugs on the darknet
    - USA 1st
    - UK 2nd (but more transactions?)
- Drug composition
  - "Alprazolam": melatonin, fentanyl, flubromazolam
  - "Etizolam" : alprazolam, flubromazepam, diphenylprolinol

Manchester KR, Lomas EC, Waters L, Dempsey FC, Maskell PD. The emergence of new psychoactive substance (NPS) benzodiazepines: A review. Drug Test Anal. 2018 Jan;10(1):37-53. doi: 10.1002/dta.2211. Epub 2017 Jul 31. Erratum in: Drug Test Anal. 2018 Feb;10 (2):392-393. PMID: 28471096.

NPS Benzodiazepine detection during emergency care in Sweden 2012-2016 (STRIDA project)

- 2012-2016
- Intoxicated NPS accessing emergency healthcare in Sweden
  - Intoxicated patients with admitted or suspected intake of NPS, or of unknown drugs of abuse
- NPS BZD : 4%-->20% July 2015
  - 217 with analytical confirmation of 1913 cases
  - 81% male, age 15-66, mean 28 years
  - 29%: other depressants (i.e., opioids, ethanol, cannabis), 11%: stimulants (i.e., phenethylamines, cathinones), and 50%: mixture of drugs

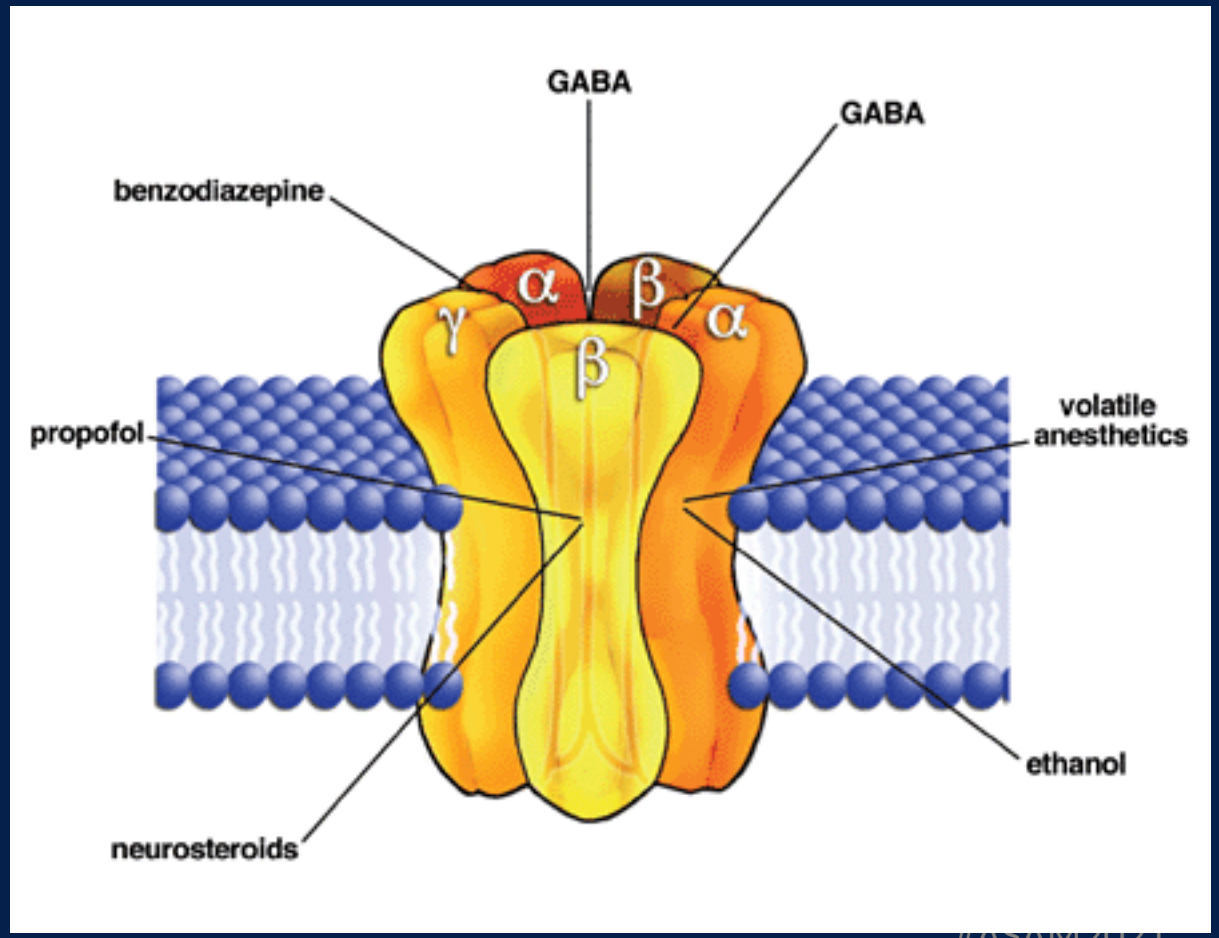
Backberg M, Bergstrand MP, Beck O, Helander A. Occurrence and time course of NPS benzodiazepines in Sweden –results from intoxication cases in the STRIDA project. Clinical Toxicology 57(3): 203-212, 2019.

GABA-A receptor

Benzodiazepines

- Positive allosteric modulator
- Increased conduction of chloride ions: decrease neuronal activity
- Therapeutic Index (TI) > barbiturates
  - TI not > GABA activity itself
- Different BZD binding sites
  - BZ1 (alpha-1)
    - Z-drugs specifically bind only BZ1*
  - BZ2 (alpha-2)
  - BZ3 (alpha-3)

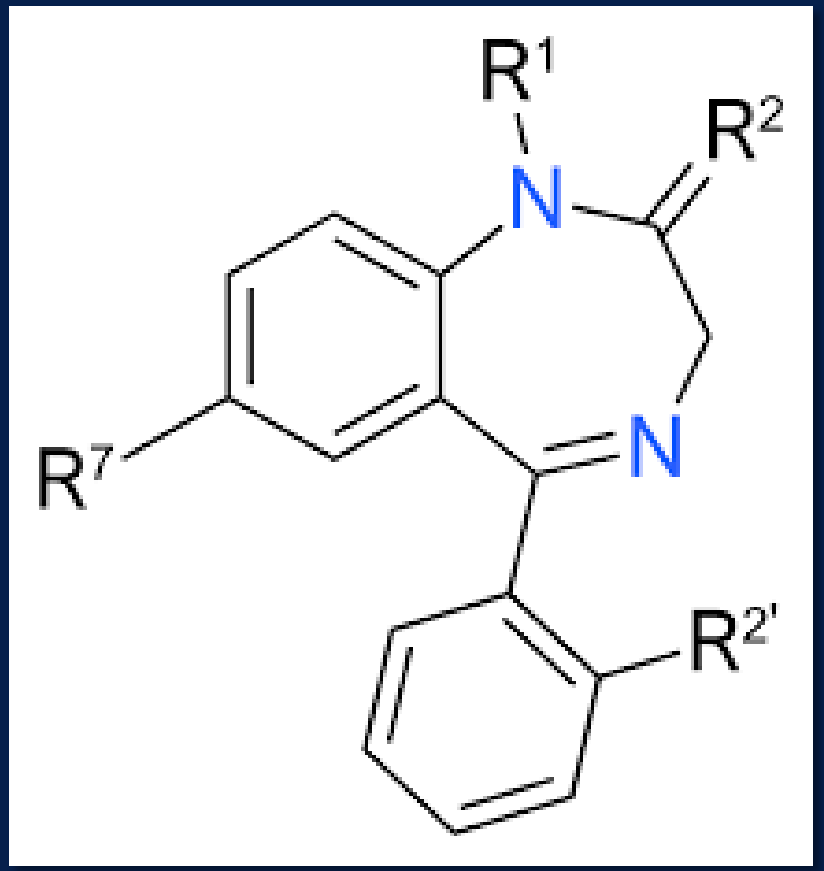
Chloride Channel/GABA-A receptor



Wikipedia

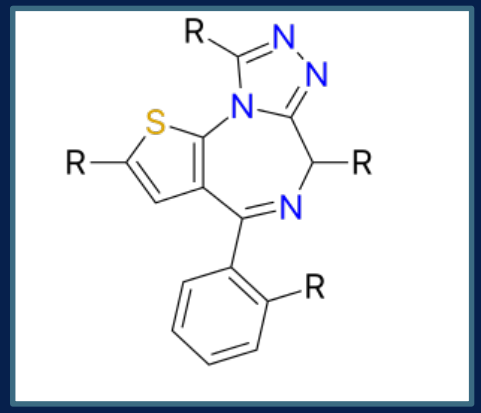
Benzodiazepine

- Fusion of a benzene ring and a diazepine ring

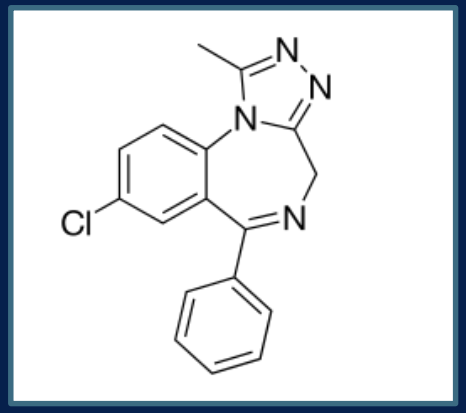


Benzodiazepines

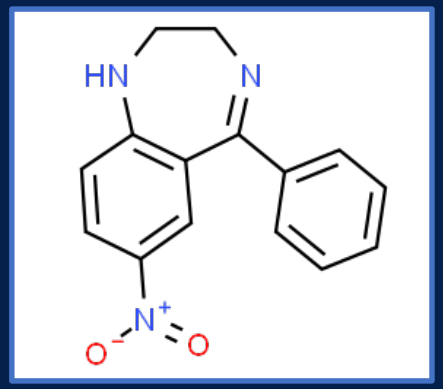
1,4 benzodiazepine:
Diazepam
Chlordiazepoxide
Lorazepam
Phenazepam



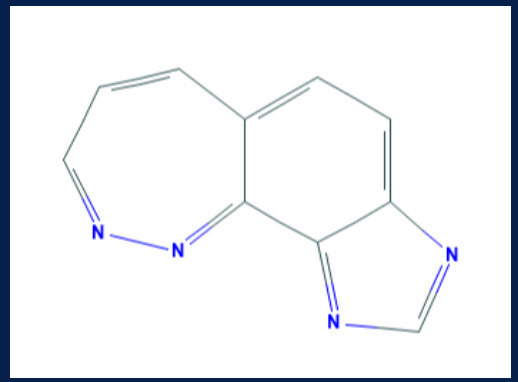
Thienotriazolobenzodiazepine:
Etizolam



Triazolobenzodiazepine:
Flubromazolam
Clonazolam
Pyrazolam



7-nitrobenzodiazepine
Clonazepam
Meclonazepam



Imidazobenzodiazepines:
Midazolam

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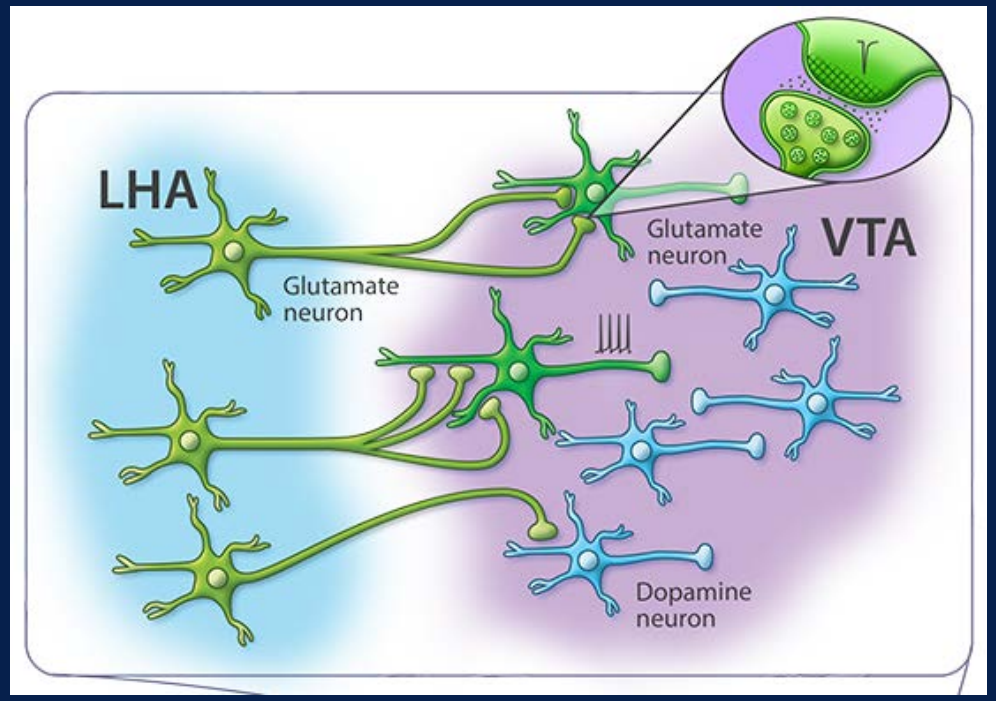
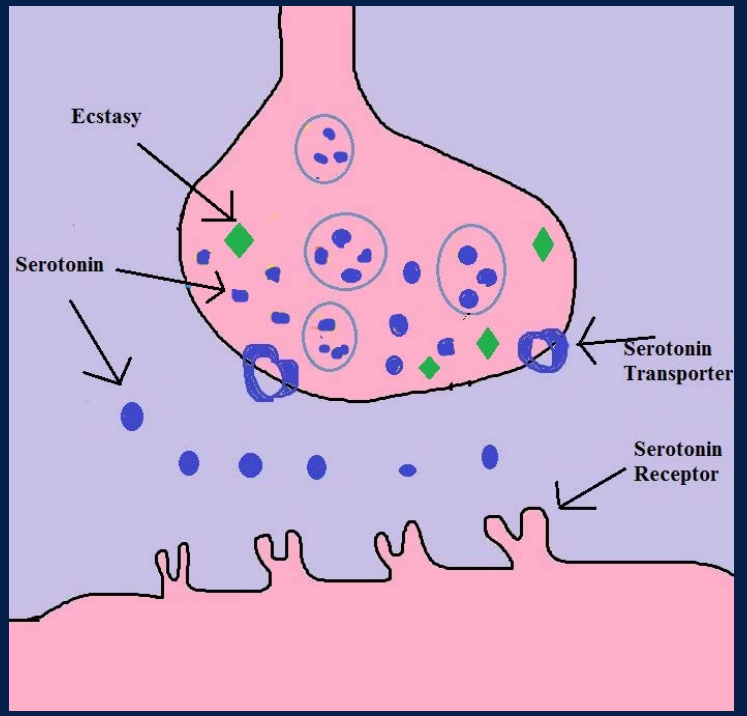
Other Pharmacology

https://irp.drugabuse.gov/hot-off-the-press-november-2020/



Glutamic acid decarboxylase and glutamate receptor changes during tolerance and dependence to benzodiazepines



Clonazepam-induced up-regulation of serotonin1 and serotonin2 binding sites in rat frontal cortex

1.) Emanuela Izzo, James Auta, Francesco Impagnatiello, Christine Pesold, Alessandro Guidotti, Erminio Costa. Proceedings of the National Academy of Sciences Mar 2001, 98 (6) 3483-3488.
2.) Wagner HR, Reches A, Yablonskava E, Fahn S. Clonazepam-induced up-regulation of serotonin1 and serotonin2 binding sites in rat frontal cortex. Adv Neurol. 1986; 43:645-51.

Benzodiazepine Pharmacokinetics

- Metabolism
  - Half life, Metabolites half lives
    - Short acting: etizolam, adinazolam
    - Long acting: diclazepam, phenazepam, flubromazepam
  - Liver
    - Phase 1 oxidation CYP enzymes (CYP3A4)
      - Hydroxylation
      - Reduction
    - Phase 2 uridine 5′-diphospho-glucuronosyltransferase (UGT) enzymes
      - Glucuronide conjugation
  - Elimination urine, mainly glucuronidated metabolites
- Bioavailability
- Plasma protein binding
- Volume of distribution
- Increased toxicity
  - Hydrazone fragments, primary amines, saturated heterocyclic rings
  - Potency: Triazolo>1,4 benzodiazepines
  - Functional groups R position: receptor affinity

Manchester KR, Lomas ED, Waters L, Dempsey FC, Maskell PD. The emergency of new psychoactive substances (NPS) benzodiazepines: A review. Drug Test Anal. 2018 Jan; 10(1): 37-53.

Clinical Presentation Benzodiazepines

- Clinical presentation: CNS depression, tachycardia (BPM 100; eight patients), dilated pupils (seven patients), and slurred speech (six patients).
- All patients recovered and all but four were discharged within 24 h.
- Flumazenil, a selective BZD receptor antagonist used as antidote, was administered to seven patients (doses 0.1–1.0mg) and all reported improved alertness

Backberg et al. *Occurrence and time course of NPS benzodiazepines in Sweden – results from intoxication cases in the STRIDA project.* Clinical Toxicology 57(3): 203 – 212, 2019.

Clinical Presentation NPS Benzodiazepines

- In cases where death occurred (or NPS BZD detected post mortem)*
  - Multiple classes of drugs implicated
    - Phenazepam (and other NPS-BZD) data indicate opioids commonly detected along with alcohol and stimulants.
- Long-acting flubromazolam users: unpleasant night dreams, sleeping paralysis, and somnambulistic states that persisted for several days.
- Phenazepam intoxication may last several days

1.) Zawilska JB, Wojhcieszak J. An expanding world of new psychoactive substances-designer benzodiazepines. Neurotoxicology. 2019 Jul;p 73:8-16.

2.) Anderson M and Kjellgren A. The slippery slope of flubromazolam: Experiences of a novel psychoactive benzodiazepine as discussed on a Swedish online forum. Nordic Studies on Alcohol and Drugs. 2017; 34(3): 217-229.

GHB Analogues

GHB (γ-Hydroxybutyrate)

- Research started in 1960's by Dr. Henri Laborit as GABA analogue that was able to be ingested orally and cross the blood brain barrier
- Dietary supplement in 1970s-1990's
  - Burn fat and build muscle; stimulate Growth Hormone release
  - Increased sex drive and libido
- Date Rape
- Schedule I as of 2000
- Endogenous at low levels (0.5-2 mg/L) with involvement of GHB and GABA receptors
- Mechanism of Action
  - High affinity for GHB receptor stimulating release of dopamine and glutamate
  - Low affinity for $GABA_B$ receptor
  - GHB metabolizes to GABA depending on GHB concentration
- Sodium salts of GHB
  - Xyrem®: Narcolepsy-associated cataplexy; schedule III in US
  - Alcover®: Alcohol detoxification/cravings in Italy

Busardò F, Jones A. GHB pharmacology and toxicology: acute intoxication, concentrations in blood and urine in forensic cases and treatment of the withdrawal syndrome. *Curr Neuropharmacol*. 2015;13(1):47-70

GHB/Analogues Effect

- Biphasic: Euphoric at low doses (liquid ecstasy) and sedative at high doses
- Goal intoxication is euphoria, sedation, hypnosis, aphrodisiac, sensuality
- Dose of GHB
  - Euphoria achieved around 1-2.5 g
    - About 80-100 mg/L plasma concentration
  - Life threatening respiratory depression at doses as low as 7 g
    - As low as 300-500 mg/L plasma concentration
  - 1mL liquid typically about 1.65 g*
- With oral ingestion rapid absorption with average peak plasma concentration 20-40 min after ingestion though dose dependent and depending on fasting state
  - Higher doses and non-fasting state prolong peak concentration
  - Bioavailability 25-40% orally

Busardò F, Jones A. GHB pharmacology and toxicology: acute intoxication, concentrations in blood and urine in forensic cases and treatment of the withdrawal syndrome. *Curr Neuropharmacol*. 2015;13(1):47-70

GHB/Analogues Pharmacology

- GHB
  - Significant variability between subjects due to differences in bioavailability, absorption rate, drug metabolizing enzyme activities, etc.
  - 1st order kinetics at low plasma concentration though 0 order at high concentration due to hepatic enzyme saturation
  - Half life 30-50 min when 1st order kinetics apply
- Analogue pharmacology often depends on other factors
  - Butanediol: Alcohol Co-ingestion
  - GBL: Induction of lactonases

Busardò F, Jones A. GHB pharmacology and toxicology: acute intoxication, concentrations in blood and urine in forensic cases and treatment of the withdrawal syndrome. *Curr Neuropharmacol*. 2015;13(1):47-70

GHB Analogues

- BD (1,4-Butanediol) and GBL (γ-Butyrolactone)
- GHB prodrugs
  - GBL – (peripheral lactonases) → GHB
  - BD ---- (alcohol dehydrogenase) → GHB
- No known independent effects
- Near 100% in vivo conversion to GHB
- Available worldwide as cleaning products and as solvents.
- Colorless, odorless though slightly bitter taste
- Almost always ingested orally as a liquid though powder/capsules are sold
  - Rarely IV, nasal insufflation or rectal use

Liakoni E, et al. Butanediol Conversion to Gamma-Hydroxybutyrate Markedly Reduced by the Alcohol Dehydrogenase Blocker Fomepizole. *Clin Pharmacol Ther*. 2019;105(5):1196-1203.

Legal Status of GHB Analogues

- GHB = Schedule 1 since 2000
  - High potential for abuse, no medical use and no safe amount of ingestion
- GBL = List 1
  - Chemicals that are used to manufacture controlled substances and are important to the manufacture of the substances (e.g. pseudoephedrine)
- 1,4-Butanediol = no schedule or list
- Under Federal Analogue Act of 1986
  - Schedule I or II analogues used/sold for human consumption are treated as scheduled substance
  - US Vs Washam (2002), US Vs Roberts (2004), US Vs Fisher (2002), US Vs Turcotte (2005)
  - Cases based on language in FAA, not questioning if drugs are analogues

21 U.S. Code 841- Prohibited acts A. *LII / Legal Information Institute*. Retrieved 02-02-2021.

Trends in Use

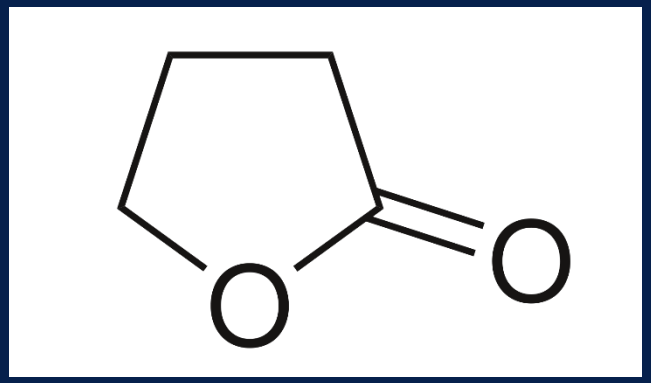
- Very limited data for GHB as well as analogues
  - GBL and BD rapid conversion to GHB
  - GHB window of detection only 3-10 hours
- Highest period of use was 1994-2000 in US
- Along with GHB, analogues have played a role in chem sex and electronic music scene as well as in bodybuilding
- Study in NYC EDM dance clubs estimated use of GHB increase from 1.0% to 4.6% among that population between 2016 and 2019
- A study in NYC from 2018 found men who have sex with men were nearly 12 times more likely to use GHB and women who have sex with women 7 times more likely within the last year

Richardson S. An old, dangerous drug has made a comeback with new users. *NBC News.* August 2020.

GBL (γ-Butyrolactone)

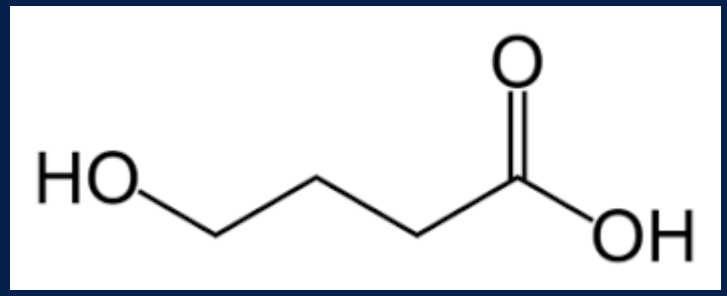
- Developed as a solvent, paint stripper, cleaner and as an intermediary for other compounds (NMP, 2-Pyrolidone, etc)
- Harder to find given List 1 status like pseudoephedrine
- More lipophilic than GHB so orally absorbed more quickly than GHB with higher bioavailability
- Metabolizes to GHB via lactonase activity of paraoxonase enzymes
- ½ life less than 1 minute
- Previously sold as a supplement with brand names Renewtrient, Revivarant or Revivarant G, Blue Nitro or Blue Nitro Vitality, GH Revitalizer, Gamma G, and Remforce
- Lactonase enzymes are induced with repeated dosing so onset of GBL effects may be slower on first several doses

Gamma-butyrolactone (GBL) Pre-Review Report Agenda Item 5.4 Expert Committee on Drug Dependence Thirty-fifth Meeting Hammamet, Tunisia, 4-8 June 2012



γ-butyrolactone

Lactonase

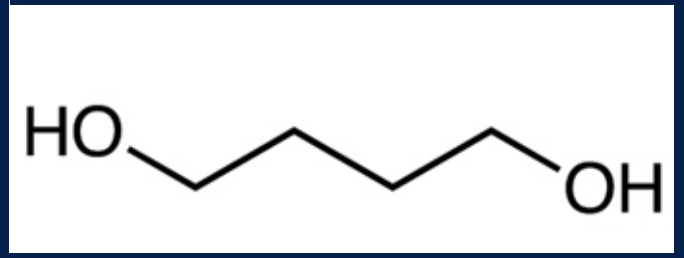


γ-hydroxybutyrate

BD (1,4-Butanediol, Bute, BDO)

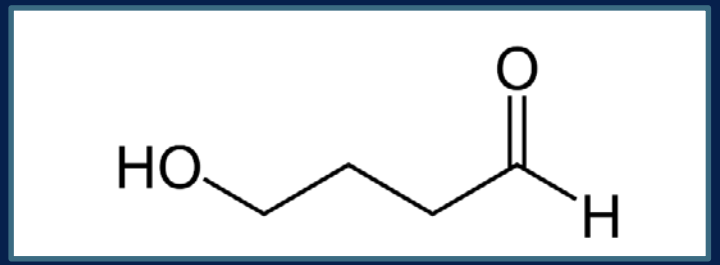
- Sold as cleaning product and solvent and is used as an intermediate to other compounds
  - Has been found on Amazon, Ebay, Walmart, etc
- Converted to GHB once absorbed by alcohol dehydrogenase and aldehyde dehydrogenase
- Prolonged intoxication when used with alcohol
  - Competition with alcohol dehydrogenase
- Following IV administration of BD, peak GHB levels can be measured within 2 min
- Measurable GHB within 5 min of oral ingestion with very similar pharmacokinetics to GHB

Irwin R. NTP Summary Report on the Metabolism, Disposition and Toxicity of 1,4-Butanediol. Cas No 110-63-4. NIH Publication 96-3932. May 1996



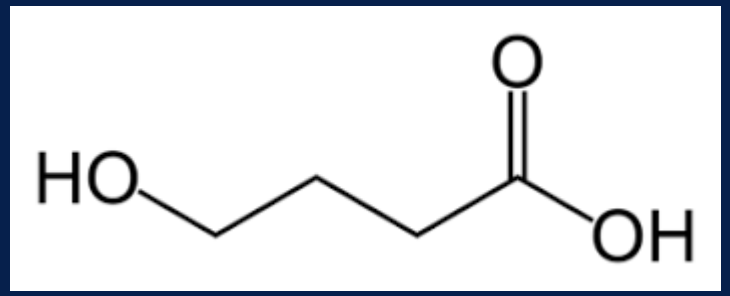
1,4-Butanediol

Alcohol Dehydrogenase



γ-hydroxybutyraldehyde

Aldehyde Dehydrogenase



γ-hydroxybutyrate

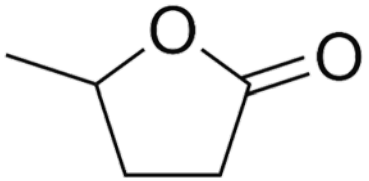
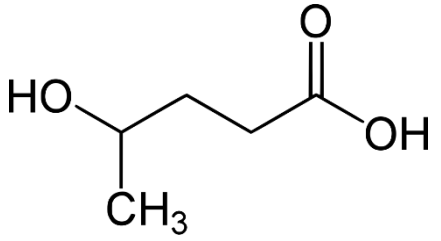
Irwin R. NTP Summary Report on the Metabolism, Disposition and Toxicity of 1,4-Butanediol. Cas No 110-63-4. NIH Publication 96-3932. May 1996

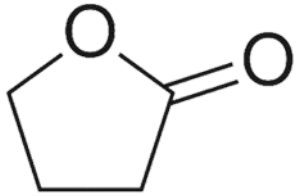
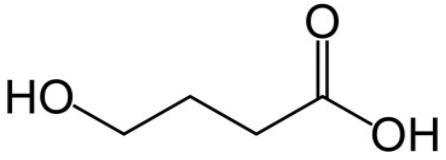
GHV and GVL(γ-Hydroxyvaleric acid; 4-methyl-GHB)

- Methylated GHB and GBL
- Not well studied
- GVL (γ-valerolactone) prodrug to GHV (γ-Hydroxyvaleric acid) using lactonase
- Approximately 10 times less potent than GHB
- GHB-like effects, such as sedation, catalepsy and ataxia
- Not produced endogenously or converted to GHB

Carter L, Chen W, Wu H, et al. Comparison of the behavioral effects of gamma-hydroxybutyric acid (GHB) and it's 4-mthyl-substituded analog, gamma-hydroxyvaleric acid (GHV). *Grug and Alcohol Dependence.* 78(1):91-9

GHV/GHB and GVL/GBL structures

GVL  Lactonase → GHV 

GBL  Lactonase → GHB 

Carter L, Chen W, Wu H, et al. Comparison of the behavioral effects of gamma-hydroxybutyric acid (GHB) and it's 4-mthyl-substituded analog, gamma-hydroxyvaleric acid (GHV). *Grug and Alcohol Dependence*. 78(1):91-9; Wikipedia

Phenibut

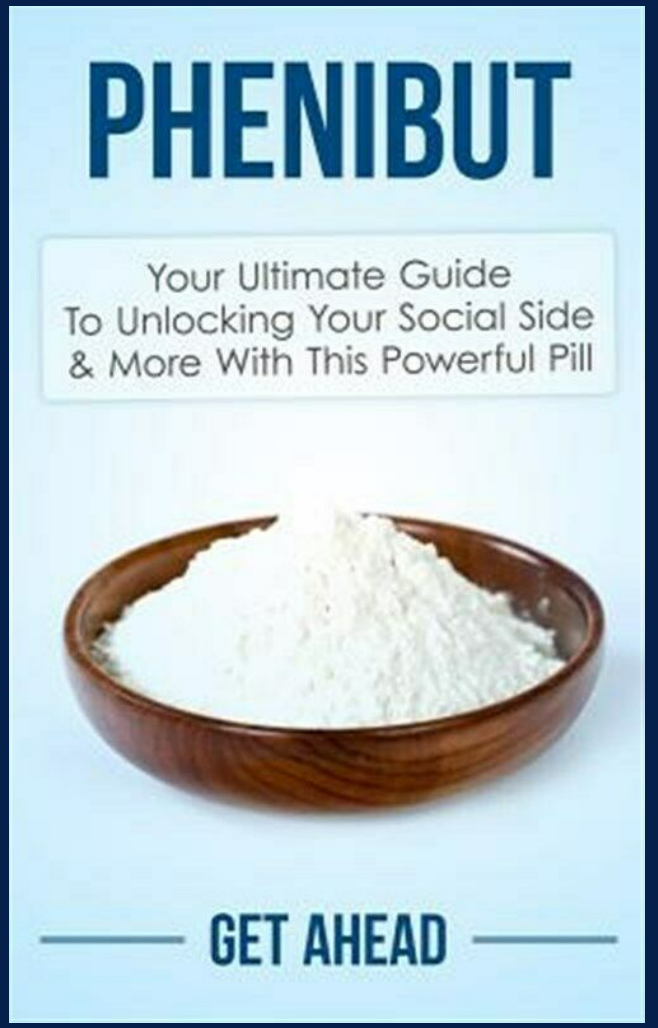
Phenibut (fenibut, phenybut, фенибут, *β-**phenyl**-γ-amino**but**yric acid)*

- Developed in Soviet Union in the 1960s for anxiety and insomnia and is still used in Russia, Ukraine, Belarus, Kazakhstan and Latvia
- Currently used to treat other conditions as well including and notably alcohol use disorder and alcohol withdrawal
  - Asthenia, depression, alcohol use disorder, alcohol withdrawal, PTSD, stuttering, tics, vestibular disorders, Meniere's disease, dizziness, motion sickness, "smart drug", exercise recovery booster
- Sold as supplement in US and Europe
- Controlled Substance in Australia
- Ban on substance in Hungary, Lithuania and Italy
- Typically consumed orally though IV use has been noted
- Brand name: Anvenifen, Fenibut, Bifren and Noofen

Owen DR, Wood DM, Archer JR, Dargan PI. Phenibut (4-amino-3-phenyl-butyric acid): Availability, prevalence of use, desired effects and acute toxicity. *Drug and Alcohol Review*. 2016;35(5):591–6

Phenibut Effect

- Recommended dose 250 mg BID/TID to 750 mg BID
  - Not FDA regulated
  - Should not exceed 1 g/dose or 2 g/day
- **Calming effect**
  - No depressive effects
- **Increased focus**
  - No stimulant effects otherwise



Lapin I (2001). Phenibut (beta-phenyl-GABA): A tranquilizer and nootropic drug. *CNS Drug Reviews*. 2001;7(4):471–81

Phenibut Availability

- 250 and 500 mg tablets
- Powder
- 10 mg/mL solution
- Very accessible

#ASAM2021

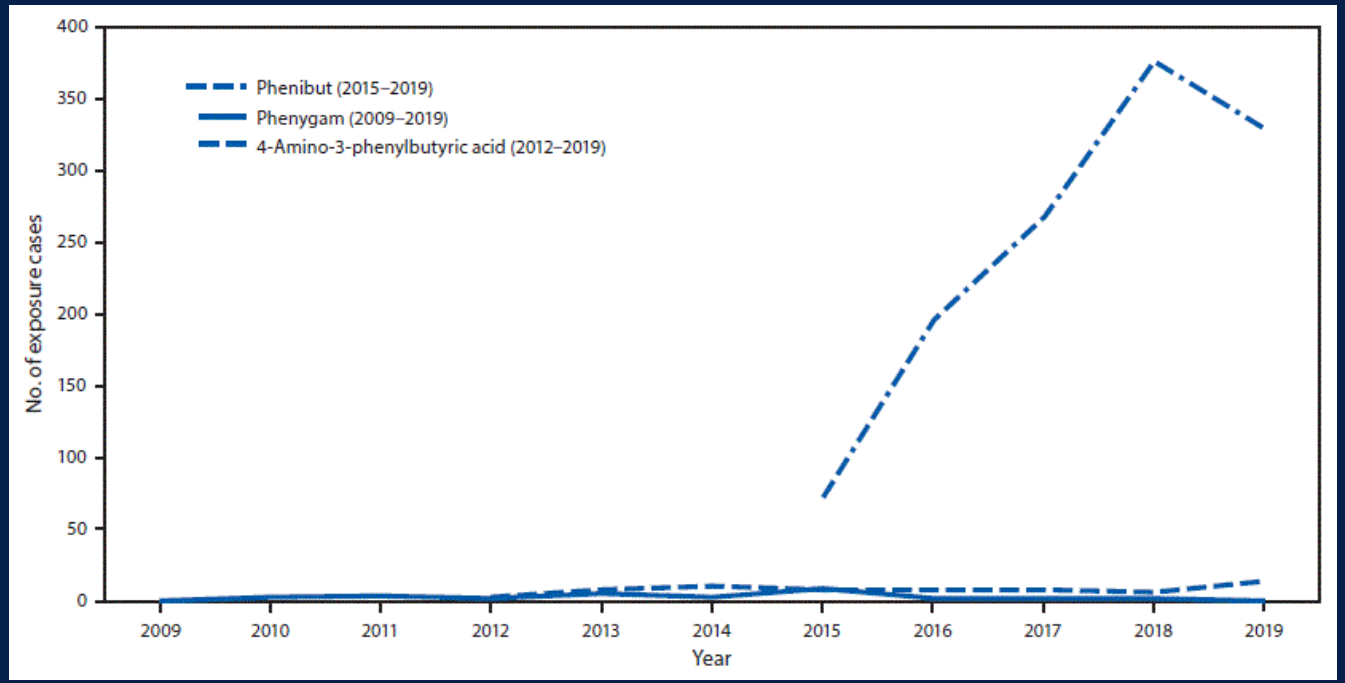
Phenibut CDC Recent Use Patterns

- September 2020
- Data analysis from 2009-2019
- Exposure to phenibut through U.S. poison centers
- Caller demographics
  - Total of 1320 calls
  - All 50 states represented
  - 58.4% ages 18-34
  - 75.5% men
  - 65.1% tabs, 24.8% powder
  - 93% ingestion, 2.8% inhalation
  - 40.2% polysubstance

Graves JM, Dilley J, Kubsad S, Liebelt E. Notes from the Field: Phenibut Exposures Reported to Poison Centers- United States, 2009-2019. *Morbidity and Mortality Weekly Report*. 2020;69(35):1227–1228

CDC Recent Use Patterns

- 6.2% reported coma
- 12.6% reported life-threatening/life altering symptoms
  - 10.2% in those with phenibut as only substance, including at least 1 death



Graves JM, Dilley J, Kubsad S, Liebelt E. Notes from the Field: Phenibut Exposures Reported to Poison Centers- United States, 2009-2019. *Morbidity and Mortality Weekly Report*. 2020;69(35):1227–1228

Phenibut Pharmacology

- $GABA_B$ agonist
- At very high doses can also be $GABA_A$ agonist
- Also increases concentration of dopamine in low doses providing a stimulatory effect in addition to anxiolysis
- Blockade of $\alpha_2\delta$ subunit of voltage dependent calcium channels
  - Major difference in neuroreceptor mechanism of action compared to baclofen

Zvejniece L, Vavers E, Svalbe B, Veinberg G, Rizhanova K, Liepins V, et al. R-phenibut binds to the α2-δ subunit of voltage-dependent calcium channels and exerts gabapentin-like anti-nociceptive effects. *Pharmacology, Biochemistry, and Behavior*. 2015;137:23–9

Phenibut Pharmacology

GABA and analogues at biological targets		
COMPOUND	$GABA_B$	$GABA_A$
GABA	0.08	0.12
GHB	>100	>100
GABOB	1.10	1.38
Phenibut	9.6	>100
4-F-phenibut	1.70	>100
Baclofen	0.13	>100
(R)-Baclofen	0.13	>100
(S)-Baclofen	74.0	>100
IC_{50} (50% of receptor inhibitory concentration)		

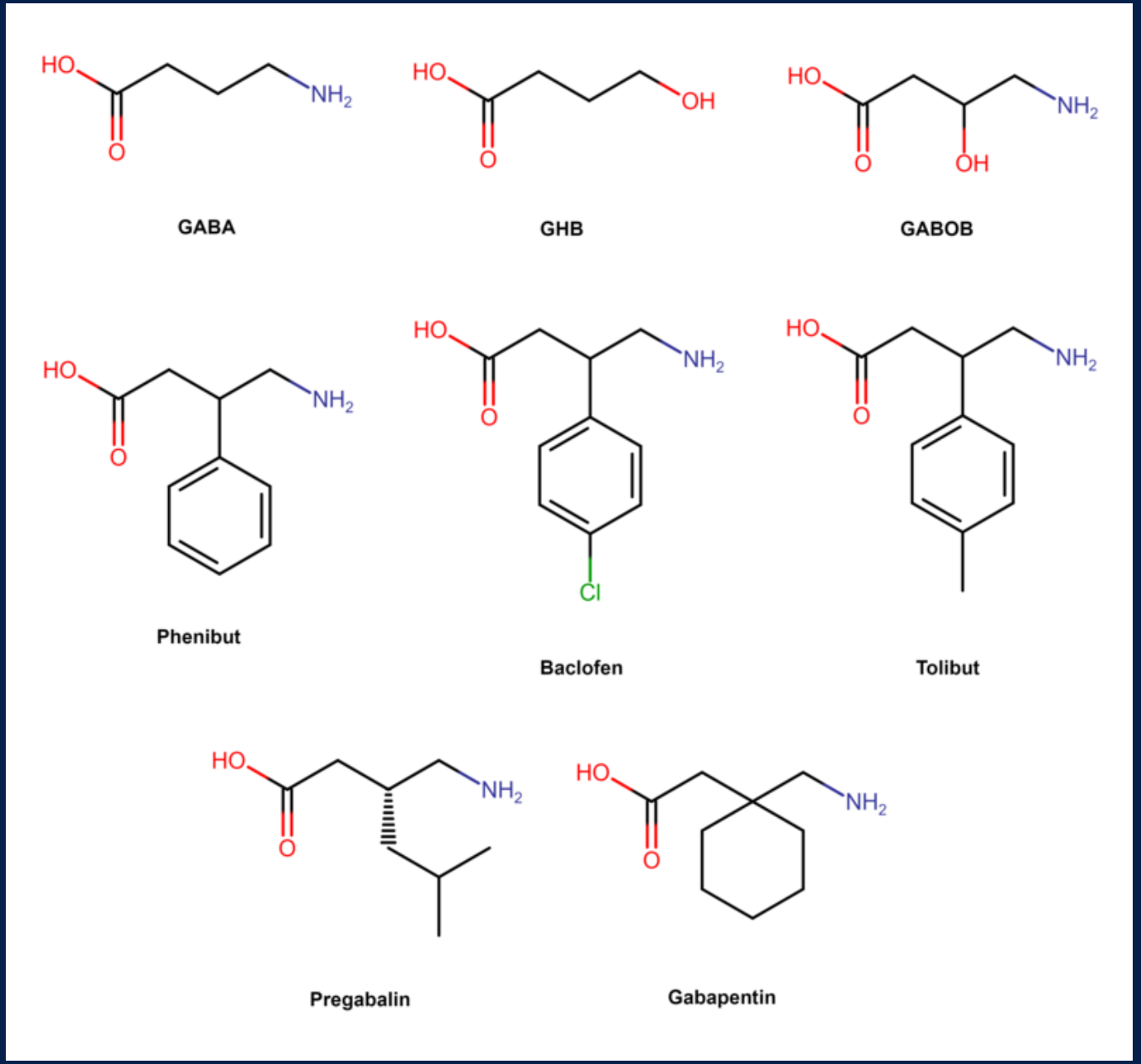
Phenibut and analogues at biological targets		
COMPOUND	$\alpha_2\delta$	$GABA_B$
(R)-Phenibut	23	92
(S)-Phenibut	39	>1,000
Baclofen	156	6
Gabapentin	0.05	>1,000
K_i valutes (inhibition constant)		

Zvejniece L, Vavers E, Svalbe B, Veinberg G, Rizhanova K, Liepins V, et al. R-phenibut binds to the α2-δ subunit of voltage-dependent calcium channels and exerts gabapentin-like anti-nociceptive effects. *Pharmacology, Biochemistry, and Behavior*. 2015;137:23–9

Bowery NG, Hill DR, Hudson AL. Characteristics of GABAB receptor binding sites on rat whole brain synaptic membrane. *British Journal of Pharmacology*. 1983;78(1):191–206.

GABA analogues

- All structurally similar to GABA
  - Pro-drugs BD and GBL not shown here but also considered in group
- Differences?
  - Binding site
    - $GABA_B$,
    - $\alpha_2\delta$ subunit of voltage dependent Ca+ channels
    - BZD binding site*
- Potency
- Other pharmacologic and clinical characteristics.



Wikipedia

Phenibut Pharmacology

- Half life approximately 5.3 hours
- Excreted by kidneys
- In animal models, bioavailability was approximately 64% oral/IV administration
- Metabolites are not thought to be active
- Onset of action 2-4 hours orally (20-30 min rectally) with peak being 4-6 hours orally
  - Typically used orally
  - 1st time users may take too much
  - Nasal insufflation is really painful

Lapin I (2001). Phenibut (beta-phenyl-GABA): A tranquilizer and nootropic drug. *CNS Drug Reviews*. 2001;7(4):471–81

Thank You

Looking forward to the live interactive case discussion during the interactive portion at the Annual Scientific Meeting!

Novel Benzodiazepines and Sedative-Hypnotics: Down but Not Out

- Part II: Live & Interactive!

- JoAn Laes, MD FASAM FACMT
- Timothy Wiegand, MD FACMT, FAACT, DFASAM
- Jeremiah Fairbanks, DO

Disclosure Information (Required)

- JoAn Laes, MD FASAM FACMT
  - No Disclosures
- Timothy Wiegand, MD FACMT, FAACT, DFASAM
  - No Disclosures
- Jeremiah Fairbanks, DO
  - No Disclosures

Learning Objectives

1. Discuss the current market of “novel” benzodiazepines and sedative-hypnotics such as phenibut and gamma-hydroxybutyrate analogues, including availability, use patterns, pharmacology, and methods of detection
2. Explain the pathophysiology and clinical presentation of withdrawal from novel sedative-hypnotics and whether this differs from traditional benzodiazepine withdrawal
3. Discuss the management of use disorders and withdrawal syndromes of novel sedative-hypnotics using GABA agonists and non-GABA agonists in a variety of medical settings

Case 1

- 29 year old male presenting for withdrawal symptoms and management of an addiction to a nutritional supplement
- Past Medical History
  - Methamphetamine Use Disorder in sustained remission
  - Alcohol use disorder in sustained remission
  - Childhood attention deficit disorder
  - Generalized Anxiety Disorder
  - Panic Disorder
- Significant family history of substance use (alcohol) with parents on both sides with mood and anxiety problems as well
- Had been prescribed benzodiazepines for anxiety for many years
  - He was eventually able to successfully taper off approximately 2 years prior when he also quit drinking alcohol.

Brief Psychiatric and Substance Use History

- Anxiety has been a large part of his life since as long as he can remember with first panic attack in high school
- Substance use started as a teenager through mid 20s including ecstasy, other hallucinogenic drugs, marijuana, tobacco, methamphetamine and alcohol.
  - Methamphetamine use from 23-26 years old
  - Alcohol use through 27 years old
- History of approximately 25 inpatient/outpatient treatment programs
- Currently living in sober housing for 1.5 years.
- Increased anxiety with onset of COVID pandemic for 3 months

Recent History

- Friend recommended he try phenibut which friend obtained from a nutrition store
- Didn’t consider that it could be addictive given it being sold in a nutrition store
- Gradually increased dose and bought a scale to weigh out daily dose.
- He realized he was taking 6-7 grams daily divided TID which was much higher than he wanted to be on
  - Recommended absolute daily max of 2 g divided
- Did some research online and found out it could be addictive
- Also developed several dental carries and some epigastric pain due to acidity of powder
- Tried to taper off on own via rapid self taper based off relatively easy self taper off benzodiazepines several years ago

Taper Results

- Severe adverse reaction to rapid taper which ended in ED evaluation x 2 and referral to addiction medicine clinic
- 1st visit due to severe anxiety not being able to taper lower than 5-6 g phenibut daily:
  - EKG normal
  - Referral to addiction medicine
  - “continue efforts toward sobriety”
  - Did provide gabapentin 300 mg BID prescriptions as well as citalopram 20 mg and mirtazapine 15 mg q HS
- 2nd visit due to panic attack woke him from sleep at 5:00 AM
  - Checked blood pressure, 180s systolic with 5/10 substernal chest pain
  - In ED, EKG and CXR normal
  - BP 120/100 mmHg

On Presentation to the Clinic

- Had been able to taper himself down by 100 mg/day and on initial presentation was taking 1.7g phenibut TID totaling about 5.05 g per day
- Has 80 g at home though will throw this away if alternative taper available
- Met 8 criteria for DSM diagnosis of substance use disorder
- Denies current depression though experiences significant anxiety
- Seeing therapist
- Urine toxicology negative for other substances

Audience Response

- **Question:** *Which of the following treatment recommendations (only medication related) would you consider?*

- A.) Treatment with long-acting benzodiazepines slowly tapered after initial control of symptoms.
- B.) Use of phenobarbital detoxification protocol (similar to use for benzodiazepine dependence and withdrawal).
- C.) Assist in determining appropriate taper schedule with the patient's phenibut.
- D.) Stop the phenibut and transition to gabapentin for a slow taper after stabilizing symptoms.
- E.) Something other than above.

Phenibut Interactive Discussion

- 1.) Should management of this patient be done in an inpatient setting or would you feel comfortable managing as an outpatient?
- 2.) What are some potential treatment options for this patient?
- 3.) If you were to choose to transition to an alternative medication, what would it be and what would your dosing/schedule be?
- 4.) How frequently are you seeing phenibut in your clinical practice?

Treatment Considerations

- Detox
  - Hospital vs home detox
- Gradual taper of phenibut; 10% every 2-4 weeks
- Transition and taper
  - Baclofen
  - Benzodiazepine
  - Gabapentin
  - Phenobarbital
  - Valproic acid (adjunctively)

Medical Evidence Best Practice

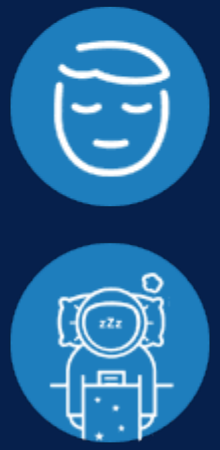
- 2 outpatient case reports
- 2013 Case report from Boston Medical Journal
  - 9 weeks transition from Phenibut to Baclofen
  - 8 g/day phenibut plus 18 g/day kratom to 60 mg/day baclofen
  - Taper off baclofen over 5 weeks
  - Recommended 10 mg baclofen for 1 g phenibut cross taper
- 2017 Case report from Journal of Addiction Medicine
  - 14 g/day phenibut to 64.8 mg QID phenobarbital
  - Taper off phenobarbital over 12 weeks

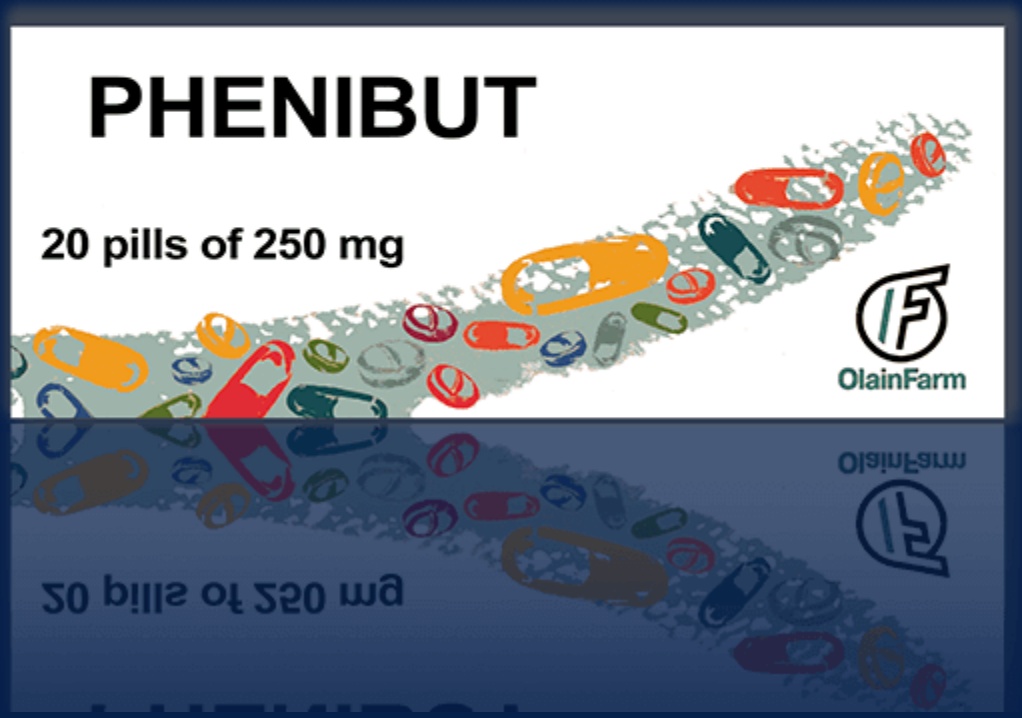
Samokhvalov A, Paton-Gay C, Balchand K, Rehm J. Phenibut Dependence. *BMJ Case Reports.* 2013;BCR2012008381.

Brunner E, Levy R. Case Report of Physiologic Phenibut Dependence Treated With a Phenobarbital Taper in a Patient Being Treated With Buprenorphine. *Journal of Addiction Medicine.* 2017;11(3):239-240

Phenibut Overdose

- Drowsiness/unconsciousness
- Hypothermia
- Nausea/Vomiting
- Eosinophilia
- Hypotension
- Renal impairment
- Hepatic Steatosis
- Tonic Colonic Seizure
- Death





Owen DR, Wood DM, Archer JR, Dargan PI. Phenibut (4-amino-3-phenyl-butyric acid): Availability, prevalence of use, desired effects and acute toxicity. *Drug and Alcohol Review*. 2016;35(5):591–6

Phenibut Withdrawal Symptoms

- Can last up to 2 weeks
- Insomnia
- Rebound anxiety
- Anger/irritability
- Muscle tension
- Paranoia
- Nausea
- Visual/Auditory Hallucinations

Owen DR, Wood DM, Archer JR, Dargan PI. Phenibut (4-amino-3-phenyl-butyric acid): Availability, prevalence of use, desired effects and acute toxicity. *Drug and Alcohol Review*. 2016;35(5):591–6

Case Approach

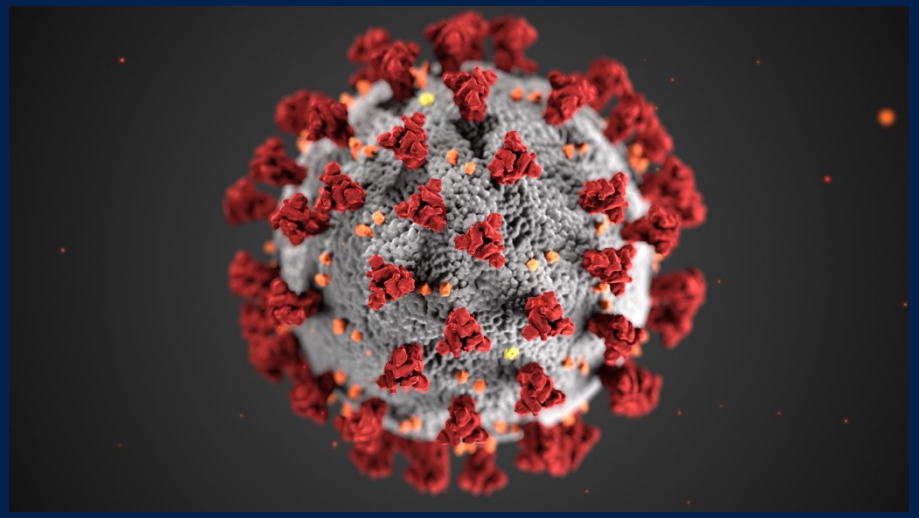
- Planned to model after previously mentioned BMJ case report
- Given most recent use was 5.05 g per day, an approximate 10 mg baclofen to 1 g phenibut was used with likely 50 mg baclofen daily expecting to be required
- Dose finding in week 1 with much more rapid cross taper
- 10 mg baclofen BID for 2 days, 20 mg baclofen BID for 2 days, 25 mg baclofen BID
- Gabapentin as adjunctive treatment
- Weekly psychotherapy already in place
- Sober housing already in place
- Begin SSRI

Follow Up

- Cross taper was successful
- Ended up on TID dosing given previous TID phenibut, 1st week at 15mg/15mg/20mg
- Now approximately 3.5 months into treatment being seen every other week
- Significant progress, now at 10mg/10mg/10mg with gabapentin adjunctive
- Progress slows with more stress and initiation of SSRI medications though continues to meet therapeutic goals, stay motivated and remains engaged in treatment
- Goal is continued progress toward taper, ideally reducing by 2.5 mg baclofen daily every other week

COVID

- High stress
  - 10/2020 poll from APA demonstrated 62% of Americans feeling more anxious than they did the year prior
- New work environment
  - Difficulty concentrating?
  - Extra time to research
  - Working on a computer screen
  - Little oversight
- Alcohol/cannabis home delivery booming



Case 2

- 27 year-old M
- HPI:
  - Opioid and sedative use disorder
  - 9 months in outpatient treatment program with mix of counseling and buprenorphine/naloxone.
- 9 months prior while in a “28 day inpatient program”
- transitioned from heroin/fentanyl to buprenorphine
  - "detoxified” from 2-4 mg alprazolam and/or 2-4 mg clonazepam daily with phenobarbital.
- Found sleeping at work and when woken by boss is ataxic and slurring speech.
  - Prior job loss due to intoxication with sedatives/opioids –this job rehired him after 6 months sobriety (3 months prior to this episode).
- Tells his parents and boss, “I wasn’t using I was just tired!”

Case 2

The parents communicate with his counselor and he is brought in for a urine drug test –which initially tests positive for benzodiazepines but the confirmation is negative.

He repeatedly denies use.

- This is about 4 months ‘pre-COVID-19’.

BENZODIAZEPINES W/CONF	See Below	50	ng/mL	2019-11-09 17:00	F
Confirmation testing was performed. See confirmation test results.					

BENZODIAZEPINE LCM CON

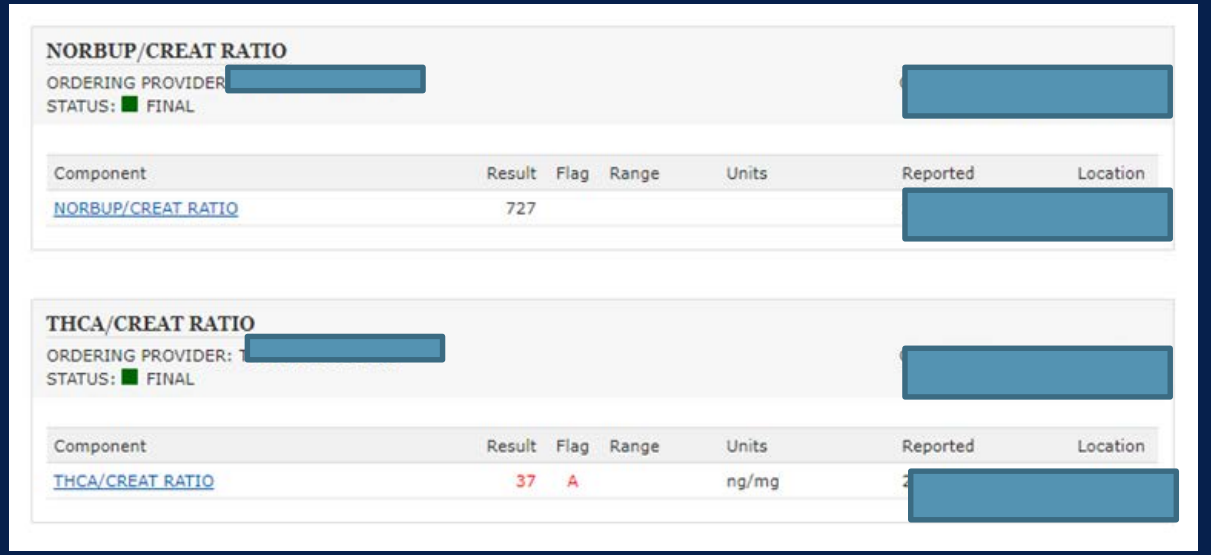
ORDERING PROVIDER: TIMOTHY WIEGAND
STATUS: FINAL

COLLECTED: 2019-11-06 17:45
RECEIVED: 2019-11-07 16:01

Component	Result	Flag	Range	Units	Reported	Location
--NORDIAZEPAM	Negative		50	ng/mL	2019-11-09 17:00	F
--OXAZEPAM	Negative		50	ng/mL	2019-11-09 17:00	F
--LORAZEPAM	Negative		50	ng/mL	2019-11-09 17:00	F
--TEMAZEPAM	Negative		50	ng/mL	2019-11-09 17:00	F
--HYDROXYALPROAZOLAM	Negative		50	ng/mL	2019-11-09 17:00	F
--NITRAZEPAM	Negative		50	ng/mL	2019-11-09 17:00	F
--7-AMINOCLONAZEPAM	Negative		50	ng/mL	2019-11-09 17:00	F
--FLUNITRAZEPAM	Negative		50	ng/mL	2019-11-09 17:00	F
--TRIAZOLAM	Negative		50	ng/mL	2019-11-09 17:00	F
--FLURAZEPAM	Negative		50	ng/mL	2019-11-09 17:00	F
--MIDAZOLAM	Negative		50	ng/mL	2019-11-09 17:00	F
--ESTAZOLAM	Negative		50	ng/mL	2019-11-09 17:00	F

Case 2

- The patient has good buprenorphine metabolite levels (norbup-cr 727 ng/mg Cr).
- The only other confirmed positive is THC at 37 ng/mg Cr).
- “From CBD tabs” started taking for insomnia.



NORBUP/CREAT RATIO

ORDERING PROVIDER: [redacted]

STATUS: FINAL

Component	Result	Flag	Range	Units	Reported	Location
NORBUP/CREAT RATIO	727				[redacted]	

THCA/CREAT RATIO

ORDERING PROVIDER: [redacted]

STATUS: FINAL

Component	Result	Flag	Range	Units	Reported	Location
THCA/CREAT RATIO	37	A		ng/mg	[redacted]	

Case 2

- The patient is confronted about “designer benzodiazepines” a
  - Some of the ‘Xanax’ he’d gotten in the past appeared to be ‘pressed’ and not really pharmaceutical tablets.
- For a week he is reported to be “acting normal” but then mother finds him slumped over at the side of his bed
  - After making sure he was breathing she took a photo of him. She sends it to his counselor.
  - 5-6 hours later he wakes up but is groggy and slurring speech.
  - He is irritable and denies use.
  - Provides another UDS the following day: same as the previous (good buprenorphine metabolites, preliminary positive BZD but confirmatory negative).

Discussion Question

- Question: How frequently is this coming up in your clinical practice?

Case 2

- The patient's mother installed a 'tracking device' on his car since the episodes
  - Making one stop prior to his episodes of 'intoxication'.
- Meds
  - sertraline, Valproic acid (500 mg PO BID), clonidine 0.1 mg PO BID PRN anxiety, buprenorphine/naloxone 8/2 mg SL BID
- The patient has a few more "groggy" episodes, very disinhibited and "fell down the stairs," at a family event, later falling asleep at the table during the family dinner, photographs showing him unresponsive
  - The patient blames it on his "meds not use!"
- Later admits he'd been getting some, "Pressed Xanax" from a guy but no longer has access to them.
  - "not really 'Xanax' (alprazolam) but something the guy had been ordering over the Internet and "pressing into the bars".
  - He mentions he is aware that there is quite a bit of this going around and it feels, "not quite like the alprazolam but close not as euphoric but 'stronger' if that makes sense."

Case 2

- Patient's parents report a month of him doing quite well; he's keeping appointments and attending group and "normal" at home. During a call with his provider (phone) his speech is thick and slurred.
- He is brought in for a UDS –denies taking any benzodiazepines (including synthetic/designer).

- BZD preliminary negative but the expanded panel shows…?

Case 2 Discussion Questions

- **Question:** What are your thoughts regarding this incident?
- **Question:** How do you interpret the toxicology results (BZD preliminary (+) & confirmatory (-)?
- Question: What types of substances have been found in counterfeit alprazolam/Xanax bars?

Laboratory Detection Benzodiazepines

Immunoassays

- May be incidentally detected by commercial immunoassays targeting the standard set of benzodiazepines due close structural resemblance
  - Clonazolam, deschloroetizolam, diclazepam, estazolam, etizolam, flubromazepam, flubromazolam, flutazolam, 3-hydroxyphenazepam, meclonazepam nifoxipam phenazepam, and pyrazolam
  - Lowest detectability: flutazolam
- Note cut-off levels

Confirmatory

- LC-TOF-MS*
  - Molecular formula
- LC-MS/MS
- UHPLC-MS/MS

Pettersson Bergstrand M, Helander A, Beck O. Development and application of a multi-component LC–MS/MS method for determination of designer benzodiazepines in urine. J Chromatogr B Analyt Technol Biomed Life Sci. 2016;1035:104–110.

Laboratory Detection Benzodiazepines

- Pyrazolam
  - No metabolites, excreted in urine up to 6 days
- Diclazepam
  - Low concentrations 4 days
  - Metabolites: delorazepam 6 days urine; lorazepam 19 days urine
- Flubromazolam
  - Metabolites 28 day urine
- Phenazepam and cinazepam
  - Both have metabolite 3-hydroxyphenazepam

Question

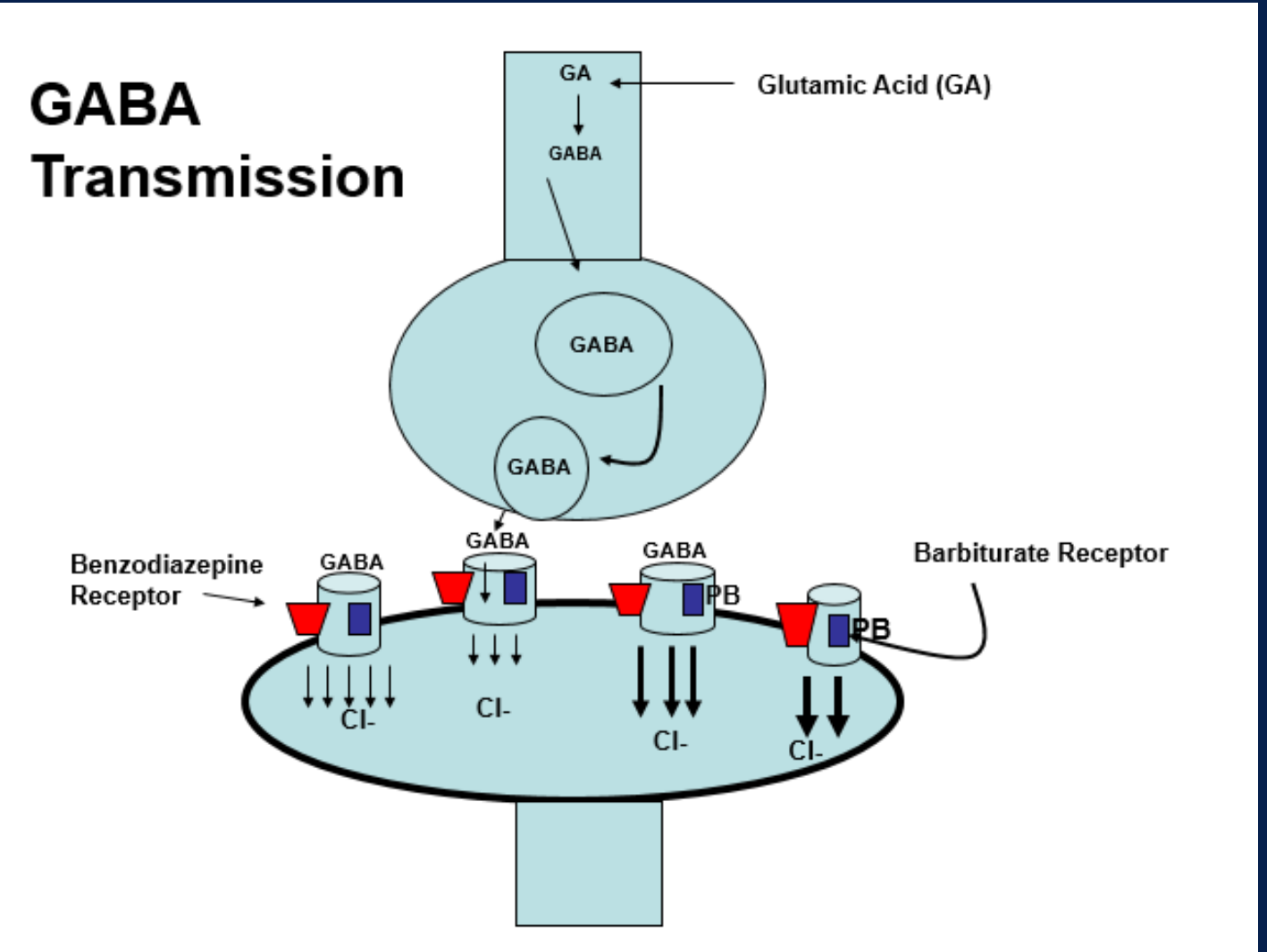
- **Which of the following is correct regarding the medication listed and its site of action?**
- A.) Phenobarbital exerts a primary effect at the alpha-2-delta (α2δ) subunit of the calcium channel.
- B.) Benzodiazepines are allosteric modulators of the GABA receptor and bind at different BZD receptors which vary in density depending on which part of the CNS the receptor is in.
- C.) Propofol binds at the $GABA_B$ receptor in addition to high affinity for the BZD1 receptor
- D.) Valproic acid preferentially binds the BZD1 receptor
- E.) Pregabalin and gabapentin are selective $GABA_B$ agonists

Case 2 Discussion Questions

- **Question:** What types of treatments are available for sedative/benzodiazepine use disorder?
- **Question:** Does management of novel/synthetic benzodiazepine withdrawal differ from that of standard benzodiazepine withdrawal?

Withdrawal Management

Benzodiazepine vs. phenobarbital vs gabapentinoid vs other? +/- adjunctive



Phenobarbital Protocol

- 130 mg PO or IV of phenobarbital test dose
  - Day 1: 130 mg PO q 4 hours x 6
  - Day 2: 130 mg PO q 6 hours x 4
  - Day 3: 130 mg PO q 8 hours x 3
- Hold for sedation if holding x 2 d/c (or if initial dose causes sedation).
- This protocol for the patient not yet in acute withdrawal or acute withdrawal attenuated but ongoing treatment needed.
  - Clonidine 0.1 mg PO q 6 hours PRN anxiety (continued sometimes 1-2 weeks after protocol PO q 8 hours PRN or at HS PRN).
  - VPA 500 mg PO BID x 2-4 weeks adjunctively

Kawasaki SS, Jacapraro JS, Rastegar DA. Safety and Effectiveness of a fixed-dose phenobarbital protocol for inpatient benzodiazepine detoxification. Journal of Substance Abuse Treatment 43 (2012); 331-334.

Phenobarbital Protocol

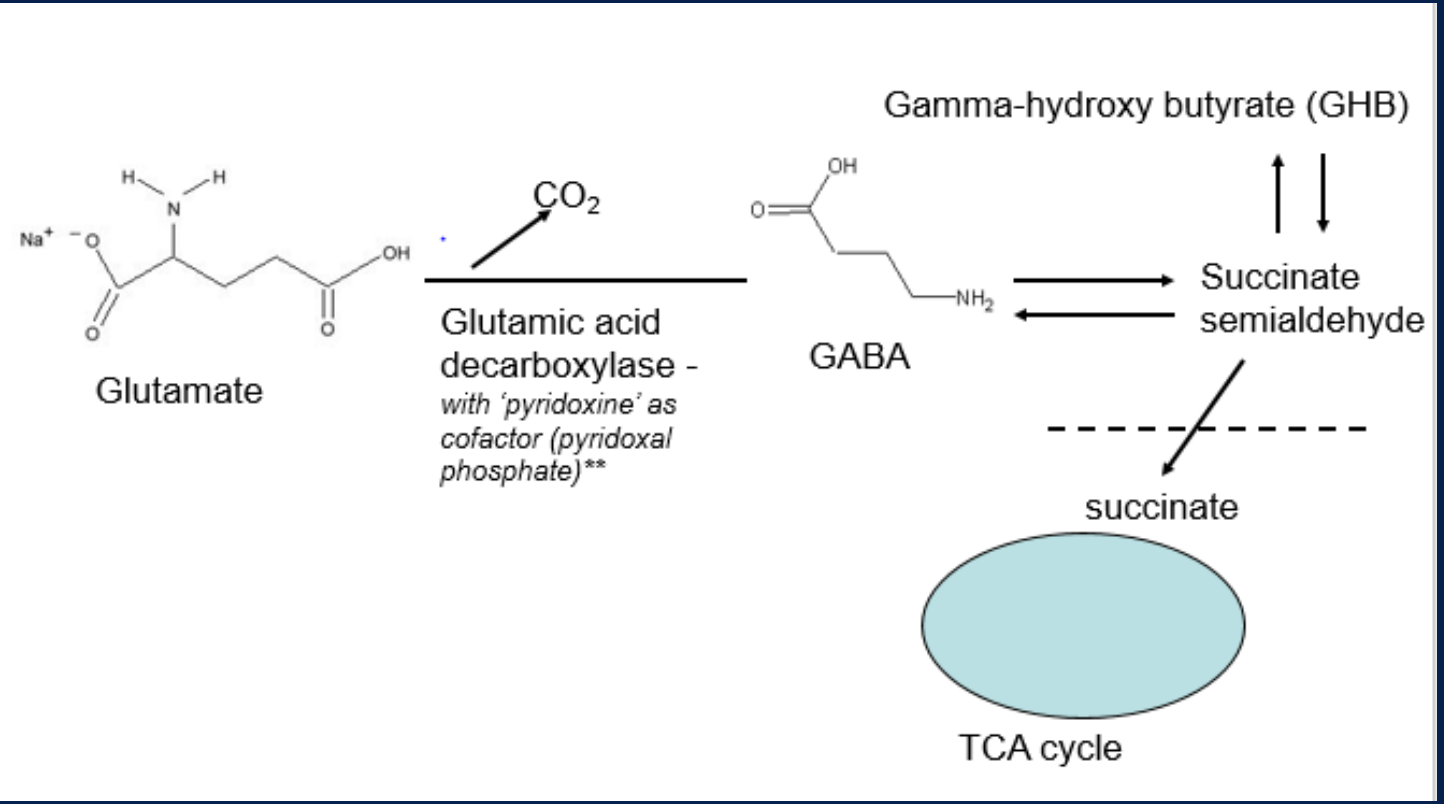
- Based on protocol from Johns Hopkins (Kawasaki et al).
  - 200 mg PO x 1
  - 100 mg PO q 4 hours x 5
  - 60 mg PO q 4 hours x 4
  - 60 mg PO q 8 hours x 3

  - 310 patients studied
    - No seizures
    - 3 (1.0%) delirium
    - 53 (17.1%) left AMA
    - 22 (7.1% ED visit within 30 days
    - 19 (6.1% readmitted to medical or psychiatry service 30 days only N=3 for recurrent BZD w/d.

Kawasaki SS, Jacapraro JS, Rastegar DA. Safety and Effectiveness of a fixed-dose phenobarbital protocol for inpatient benzodiazepine detoxification. Journal of Substance Abuse Treatment 43 (2012); 331-334.

Sedative Dependence & Withdrawal

- Protracted withdrawal with ‘neuropsychiatric’ symptoms:
- Appropriate medications for mood/anxiety + CBT/support.
- Consider sub-acute withdrawal: VPA 500 mg PO BID x 2-4 weeks.
- *Adjunctive*



Case 3

- 23 year-old M with extensive history of substance use
  - Stimulants and “club drugs” along with alcohol.
- Brought to the Emergency Department after a “bystander” called from an alley behind a local club with electronic music/dance until early AM hours.
- Deeply obtunded (RR 10) not responding to sternal rub.
- HR 60’s bpm, BP 110/70 mmHg. Sats 94% with oxygen.
- Some evidence of having vomited on clothes.
- “Partying with friends and may have overdone it” (bystander).

Case 3

- Noted to be stumbling, ataxic “jerking around” on dance floor.
- “Was drinking, had used cocaine earlier and then took GBL.”
- The patient is maintaining oxygen saturation but remains mildly bradypneic.
- Due to inability to get the patient to react to pain he is intubated in the ED.

Case 3

- 4 hours later the hospitalist is examining the patient in the ED (intubated, not requiring any sedation) he abruptly sits up and pulls out his ET tube.
  - Rapid change obtunded to awake and “ready to go”
    - “I need this thing out (Foley) so I can get back to my friends!”

Discussion Questions

- What is the differential for this intoxication syndrome
- What is the typical intoxication syndrome of GHB analogues?

GHB/Analogues Overdose

- Nausea/Vomiting
- Confusion
- Agitation
- Coma (G-ing out)
- Fluctuating level of consciousness (rapid changes)
- Seizure (and myoclonic activity)
- Respiratory depression/Hypoxia
  - Higher risk with other sedatives concomitantly or alcohol co-ingested
- Cardiac Arrest
- Death

Busardò F, Jones A. GHB pharmacology and toxicology: acute intoxication, concentrations in blood and urine in forensic cases and treatment of the withdrawal syndrome. *Curr Neuropharmacol*. 2015;13(1):47-70

Case 3

- Laboratory
  - EtOH level returns back at 120 mg/dL
  - UDS positive for cocaine, methamphetamine and THC.

Discussion Questions

- Can GHB analogues be identified on drug testing?

Laboratory Detection GHB Anlogues

- GHB is detectable in urine but rapid testing required as levels fall to those detectable simply as endogenous GHB within 2-8 hours (though varies by analogue and other factors e.g. BD consumed with alcohol).
  - If no alcohol would not expect detection of BD or GBL unless samples taken from blood quickly after ingestion or during administration in controlled setting.
- Testing of products available at various forensic laboratories.

Discussion Questions

- Can this patient be allowed to leave the emergency department?
- What are the treatment for use disorder options?

Case 4

- A 27 year-old M is brought to the ED after MVC
  - “May have fallen asleep.”
- Initial vital signs
  - HR 80’s bpm, BP 140/74 mmHg, RR 18, Sat 96% RA
- In the ED the patient had scalp laceration sutured (takes approximately 90 minutes)
  - becoming tangential and making odd comments

Case 4

- Admission labs with mild leukocytosis, slight elevation of Cr (1.4) and an EtOH of 60 mg/dL.
- About 15 minutes after the suture completion
- Given a 1 mg dose of lorazepam “for agitation and tachycardia.”
  - Continues acting bizarre and a dose of flumazenil (0.5 mg IV) is administered due to ? of paradoxical reaction to the BZD
  - Generalized tonic-clonic seizure about 2 min after flumazenil
  - Given additional lorazepam and the seizures stop.

Case 4

- Continued delirium
- History
  - “Drinks occasionally,” he has had “staring episodes he was supposed to get checked out for.
  - Denies recent substance use but prior to their relationship was active in the bodybuilding and EDM scene using “lots of things.”
  - No h/o hallucinations or psychosis.

Case 4

- Treated with several doses of haloperidol
- Ongoing tachycardia, hypertension, confusion, agitation, diaphoresis
- Next 3 days
  - Different doses of diazepam, lorazepam and primarily neuroleptics (large doses of haloperidol).
- Hospital day 4
  - Hypotension, tremors, pulling and picking
  - Anion gap with rising lactate and Cr

Case 4

- Partner able to obtain history of GBL and BD use for past several months

Discussion Questions

- How does withdrawal present for GHB analogues?
- How would you manage withdrawal from these substances?

GHB/Analogues Withdrawal

- Symptoms wax and wane and can last up to 15 days if complications
- Typically requires at least 10 g/day with average daily dosing of 32-67.2 g/day for dependency
- Autonomic instability less likely than other direct GABA agonists
- Prolonged GABA receptor sensitization leading to decreased effect of endogenous GABA and upregulation of dopamine and NMDA
- Symptoms
  - Tremor
  - Diaphoresis
  - Anxiety/Agitation/Insomnia
  - Confusion
  - Severe: delirium/hallucinosis/seizure
- GBL/BD: Similar to GHB w/d as the clinical effects are due to GHB

Busardò F, Jones A. GHB pharmacology and toxicology: acute intoxication, concentrations in blood and urine in forensic cases and treatment of the withdrawal syndrome. *Curr Neuropharmacol*. 2015;13(1):47-70

Case 4

- The patient is intubated and placed on propofol (60 mcg/kg/min) with midazolam titrated to between 6-10 mg/hour to keep calm.
- Two initial doses of phenobarbital 260 mg IV are administered and midazolam titrated down to 2 mg/hour.
  - Following days: combination of load 5-mg/kg and intermittent doses of 130-260 mg IV total > 20 mg/kg PB) facilitate weans of midazolam and propofol.
- Dexmedetomidine HD 8 prior to extubation
- Transitioned to clonidine from dexmedetomidine and quetiapine at night
  - He has some persistent delirium but no autonomic hyperactivity.

Final Takeaways/Summary

- Novel benzodiazepines have a number of compounds but generally present and are managed similarly to "traditional" benzodiazepines
- GHB and Analogues have a similar clinical syndrome characterized by abrupt changes in mental status
- Phenobarbital, baclofen, benzodiazepines among other GABA agonist and adjunctive non-GABA agonist medications such as alpha 2 agonists can be used for withdrawal syndromes from novel benzodiazepines and other GABA related sedative hypnotics

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