Management of Benzodiazepine Withdrawal in the Outpatient and Non-Hospital Settings

Robert Cole Pueringer, MD (presenting)
JoAn Laes, MD (presenting)
Soumya Pandalai (presenting)
Timothy Wiegand, MD (presenting)
Emily Brunner, MD (non-presenting)

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Disclosure Information (Required)

- Robert Cole Pueringer, MD (presenter)
  - No Disclosures
- Timothy J. Wiegand, MD, FACMT, FAACT, DFASAM (presenter)
  - No Disclosures
- JoAn Laes, MD (presenter)
  - No Disclosures
- Soumya L. Pandalai, MD, MD DFASAM (presenter)
  - No Disclosures
- Emily Brunner, MD, DFASAM (non-presenting)
  - No Disclosures

Learning Objectives

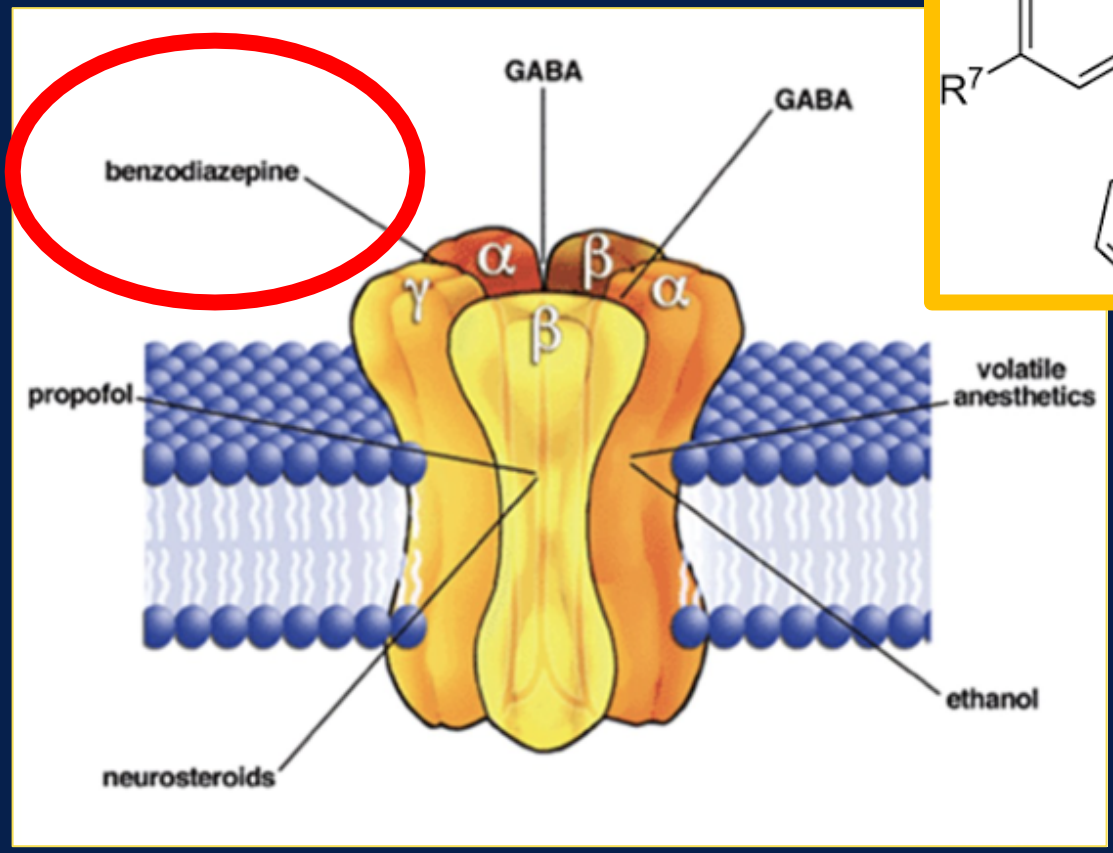
- Compare and contrast the use of GABAergic and non-GABAergic agents for the treatment of benzodiazepine withdrawal in outpatient and nonhospital-based settings.
- Describe the evaluation of patient clinical characteristics to determine appropriateness for outpatient benzodiazepine withdrawal management.
- Understand the risks and benefits of various withdrawal regimens for management of benzodiazepine withdrawal.

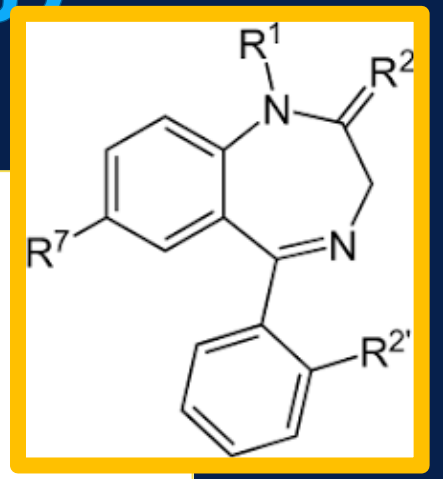
Pathophysiology of BZD dependence and withdrawal

Robert Cole Pueringer, MD

Benzodiazepine (BZD) Pharmacology

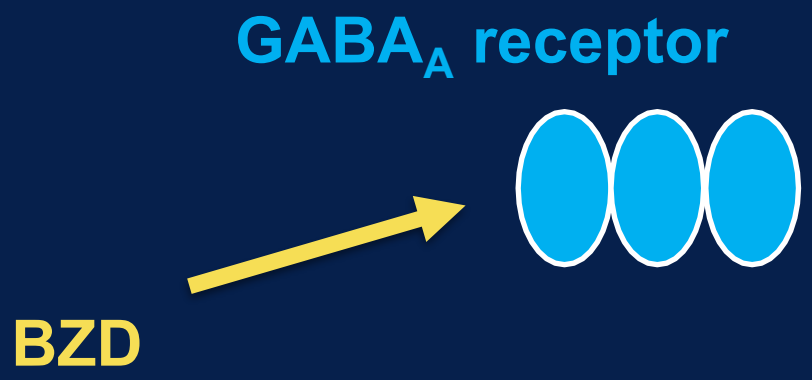
- Fusion of…
  - Benzene + diazepine rings
- Agonist at $GABA_A$ R
- Potentiates GABA
- Different BZD binding site
  - BZ1 (α1)
    - **Z-drugs bind here!**
  - BZ2 (α2)
  - BZ3 (α3)
- BZDs bind at α-γ interface
  - Augment GABA binding
  - ↑ frequency of channel opening
  - Require presence of GABA





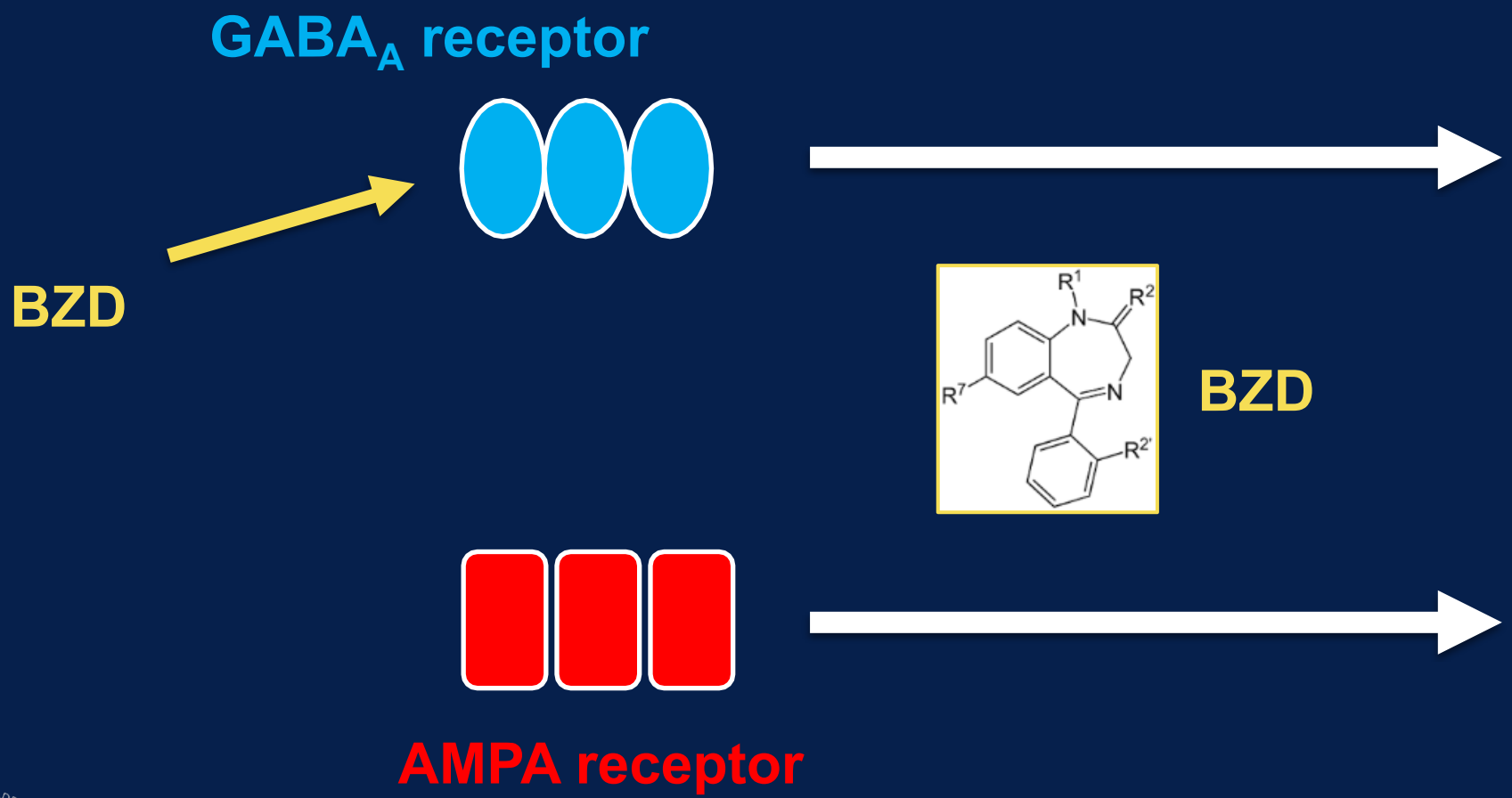
(Brent et al, 2017)

Pathophysiology of BZD withdrawal syndrome (BWS)



AMPA receptor

Pathophysiology of BWS

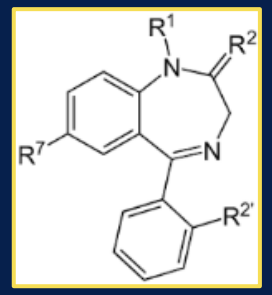


Pathophysiology of BWS

Neuroexcitation

$GABA_A$ receptor

BZD



BZD

AMPA receptor

Chronic BZD exposure → $GABA_A$ R downregulation and sensitivity reduced + AMPA R upregulation

BWS symptoms

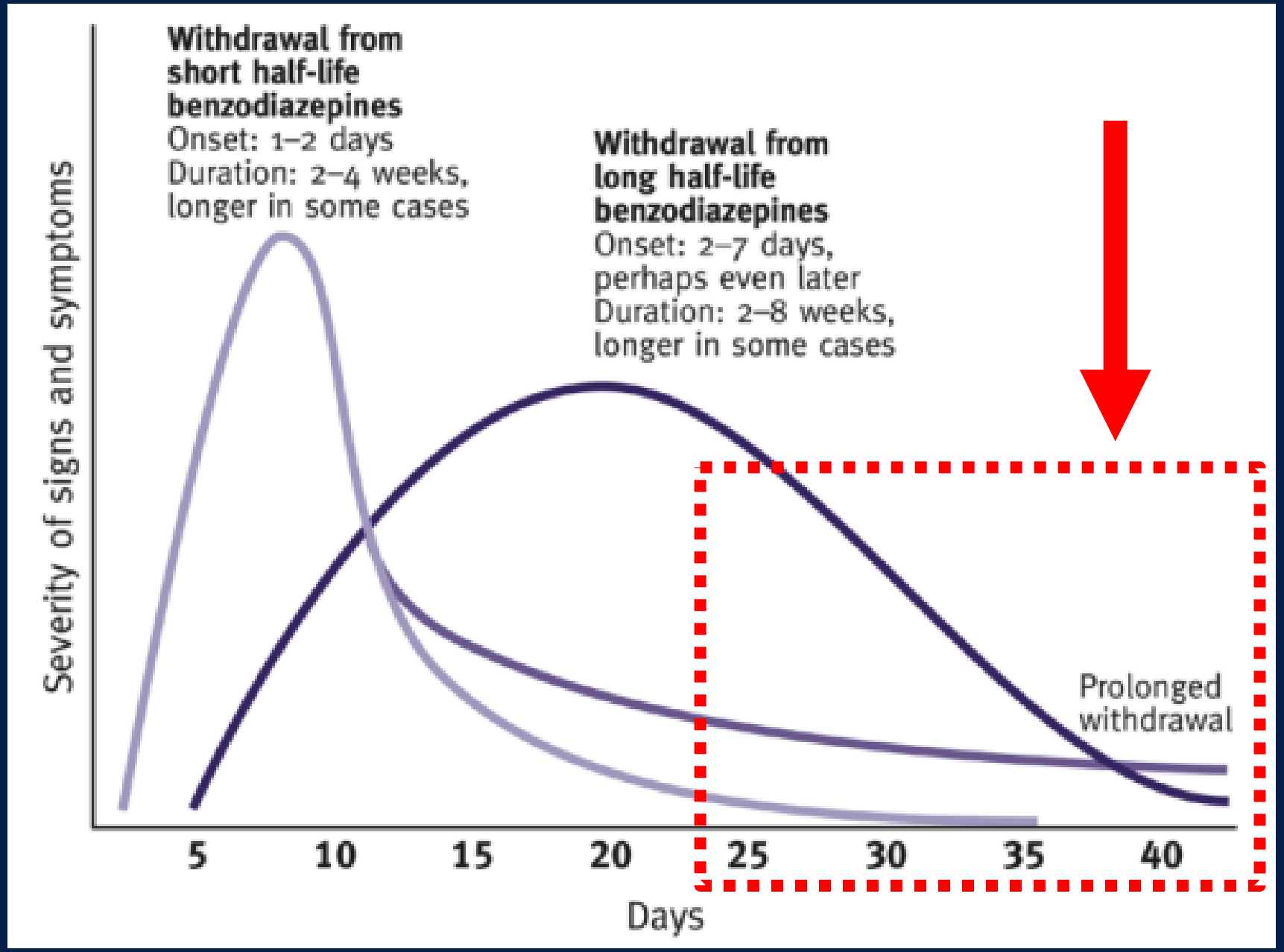
- Anxiety, irritability, insomnia
- Hallucinations (preserved sensorium)
- Diaphoresis
- Headaches, myalgias
- Nausea/vomiting
- Tremors
- Tachycardia, hypertension, hyperthermia

- **Complicated (life-threatening) BWS**
  - **Seizures (4-5%)**
  - **Psychosis (2-7%)**
  - **Agitation (50-100%)**

How does BWS differ from alcohol withdrawal syndrome (AWS)?

BWS → neuropsychiatric symptoms predominate

AWS → more autonomic/hemodynamic manifestations



(Lader et al, 2016)

Kindling effect

- BWS severity ↑ after repeated withdrawal episodes
- History of severe BWS (or alcohol withdrawal syndrome)…
  - Likely to experience this again
  - May need more aggressive treatment
  - Likely related to upregulation of AMPA receptors

(Becker et al, 1998)

Prolonged BZD taper vs acute BWS management

- Evidence-based gold standard = BZD taper over months
  - The Joint Clinical Practice Guideline on Benzodiazepine Tapering: Considerations When Benzodiazepine Risks Outweigh Benefits

- What if the patient is unwilling to be hospitalized or receive care in a medical-managed unit?

- What if underlying neuropsychiatric disease or psychosocial barriers limit the ability to start or continue a BZD taper safely?

The Joint Clinical Practice Guideline on Considerations when Benzodiazepine Risks Outweigh Benefits. American Society of Addiction Medicine. 2025.

Pharmacology and toxicology of BZD, including novel designer BZD

JoAn Laes, MD

Generic drug (trade name)	Estimated equivalency (mg)	Half-life parent compound (hr)	Estimated duration (hr)[a]
Onset: 2–3 h			
Halazepam (Paxipam)	20	14–15	Long[b]
Oxazepam (Serax)	20	3–25	Intermediate
Prazepam (Centrax)	20	Prodrug	Long[b]
Temazepam (Restoril)	15	5–20	Intermediate
Zolpidem (Ambien)	10	1.4–4.5	Short
Onset: 1–2 h			
Alprazolam (Xanax)	0.75	6.3–26.9	Intermediate
Chlordiazepoxide (Librium*)	25	5–48	Long[b]
Clonazepam (Klonopin)	2	18–50	Long[b]
Estazolam (ProSom)	2	10–34.6	Intermediate
Flurazepam (Dalmane)	15	Prodrug	Long[b]
Lorazepam (Ativan)	1	10–20	Intermediate
Quazepam (Doral)	15	25–53	Long[b]
Triazolam (Halcion)	0.375	1.5–5.5	Short
Onset: <1 h			
Clorazepate (Tranxene)	15	Prodrug	Long[b]
Diazepam (Valium)	10	20–80	Long[b]
Midazolam (Versed)	0.035	1.5–12	Intermediate
Flunitrazepam (Rohypnol)	1	10–30	Intermediate

[a]Arbitrarily based on mean half-life of parent compound: half-life <4 h = short; half-life ≤24 h = intermediate; half-life >24 h = long duration

[b]Due to presence of active metabolite with a long half-life

(Brent et al, 2017)

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*

Graves, N. M. (1993). Pharmacokinetics and interactions of antiepileptic drugs. *American Journal of Hospital Pharmacy*, *50*(12_Suppl), S23-S29.

Novel BZD and Sedative-Hypnotics

Benzodiazepines

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

Other

- GABA analogues
  - Phenibut
- GHB analogues
  - GBL
  - 1,4-butanediol
  - GHV
  - GVL

(Zawiska et al, 2019)

Selected Novel Designer BZD Pharmacokinetics

Medication	Onset	Peak Effect	Duration	Half-life ($t_{1/2}$)
Flubromazolam				
PO	20-45 min	Multiple serum peaks	3-6 hours	Prolonged activity in case reports
Clonazolam				
PO	20-60 min	? min	2-8 hours	3.6 hours
Deschloroetizolam				
PO	? fast	?	?	? short
Meclonazepam				
PO	?	?	?	80 hours

(Edinoff et al, 2022)

Composition of Benzodiazepines, Canada 2024

Expected Composition	Detected Composition	Number of Pills/Tablets
Alprazolam (Xanax)	Flualprazolam	4
	Bromazolam	3
	Alprazolam (Xanax)	2
	Unknown	1
Clonazepam (Klonopin)	Benzodiazepine (unknown type)	1
	Clonazepam (Klonopin)	1
Diazepam (Valium)	Diazepam (Valium)	1
Etizolam	Alprazolam (Xanax)	1
	Bromazolam	1
	Etizolam	1
Flualprazolam	Flualprazolam	1

https://substance.uvic.ca/blog/april-2024-monthly-report/

Myths about BZD misuse and dependence, and the evidence for prolonged tapers

Soumya L. Pandalai, MD, MD DFASAM

Dangerous Myths about BZDs Debubnked

MYTHS

- Patients who misuse BZDs are at high risk for abuse or frank SUD
- Patients who are Rx'ed BZDs tend to escalate their doses
- Dependence = SUD

REALITY

- NSDUH suggests just 1.5% of BZD users develop SUD
- Tolerance may develop to sedating effects but not for anxiolytic effects
- Dependence is a physiological phenomenon resulting in a withdrawal syndrome and SUD is a chronic illness

APA Task Force on Benzo Dependency, 1990

National Survey on Drug Use and Health

Addressing Taper-Related Anxiety #1

- N=104 chronic users of BZD hypnotics (avg = 13.5 years)
  - Double-blind taper (i.e., placebo pills during taper) over 2 months
  - Comparison group of N=34 who preferred to continue BZD treatment

OUTCOMES:

- Those that STOPPED had IMPROVED performance on cognitive function compared to continuers
- Those that CONTINUED had WORSE anxiety, irritability and lack of energy
- Those that withdrew vs. continuers DID NOT DIFFER in sleep or BZD withdrawal symptoms

Curran et al, Psychoanal 2003

Maust, D ASAM BZD Tapering 2025

Addressing Taper-Related Anxiety #2

- 532 chronic users, 3 arms
  - Usual Care
  - Structured Intervention with Follow-Up Visits
  - Structured Intervention with Written Instructions

A) Info on BZD dependence, abstinence and WDS
B) Risks of long-term use including memory, cognition, falls and accidents
C) Reassurance about reducing medications
D) Self-help pamphlet to improve sleep quality if BZD use was for insomnia

Vicens et. Al, BJP 2014

Addressing Taper- Related Anxiety #2

- OUTCOMES at 12 months:
  - USUAL CARE: 15% discontinued
  - INTERVENTION ARMS: 45% discontinued
  - "NO INCREASE in Hospital Anxiety and Depression Scale scores, sleep dissatisfaction or alcohol consumption compared to baseline, with ALL groups IMPROVING slightly in these parameters over time"

Vicens et al, BJP 2014

SURVEY says…

- ‘Benzos ruined my life. I have been benzo-free for two years and still in protracted withdrawal’.
- ‘I went full blown psychosis and had seizures’.

Some reported outright misrepresentation of benzodiazepine risks

While nearly all respondents (>98%) were prescribed benzodiazepines at some point, their relationship to the medical establishment often soured as they experienced problems with adverse effects or when they reported wanting to stop taking the benzodiazepines.

- ‘The doctor who prescribed the benzo said it was “medically impossible” to overdose or become addicted to benzos. That is plainly false’.

Many reported suicidal thoughts and actions

While many respondents described despair, anguish, and hopelessness, some described specifically suicidal intentions.

- ‘I tried to commit suicide by stabbing myself in the heart. Knife was too big to fit between my ribs. So, I stabbed myself three times. I felt nothing’.
- ‘I attempted suicide three times after my last dose of benzos and Ambien® [zolpidem]. I have never been suicidal before benzo use’.

Health care professionals did not treat them well

There was a great deal of criticism about clinicians, and little praise for doctors or caregivers. A few said that their physicians ‘abandoned’ them as they struggled to discontinue benzodiazepines.

- ‘I’m treated like I did something wrong for taking the prescription as prescribed and never told what it was and when I looked at medical information years ago, she [my doctor] told me not to because I was making up symptoms by reading medical information’.

Life consequence	*n* = 1207
Significantly affected marriage, other relationships	56.8%
Suicidal thoughts or attempted suicide	54.4%
Lost a job, fired, became unable to work	46.8%
Experienced significant increase in medical costs	40.9%
Loss of wages or lower wages in reduced job capacity	32.6%
Lost savings or retirement funds	26.7%
Violent thoughts or actual violence against others	23.5%
Lost a home	12.6%
Lost a business (if business owner)	8.4%
Lost child custody	2.6%
None of these apply	18.6%

Note that not all respondents answered this question and respondents could give more than one answer.

There were adverse consequences in their personal and professional lives because of benzodiazepine use, tapering, and withdrawal

The adverse effects of benzodiazepines exceeded physical symptoms and sometimes involved negative events in the respondents’ personal, social, psychological, and professional lives.

- ‘Lost my successful PR company’.
- ‘These drugs … have robbed my child of his mum’.
- ‘I lost my corporate job after 20 years with the same employer due to low-dose benzodiazepines. This drug destroyed my entire health, personality, and quality of life’.

(Reid et al, 2022)

Table 3. Respondents were asked how severely benzodiazepine discontinuation symptoms affected their professional and private lives.

Domain	Not at all	Mild problem	Moderate problem	Severe problem	Quite severe problem	Enormous problem
Work life	16.2%	4.5%	9.9%	9.9%	9.4%	49.1%
Fun, recreation, hobbies	10.3%	5.9%	9.4%	12.3%	13.3%	48.0%
Social interaction, friendships	12.8%	7.5%	11.2%	11.4%	14.5%	41.7%
Ability to take care of home, others	13.7%	7.8%	13.6%	12.3%	13.3%	38.4%
Relationship with spouse, family	14.3%	8.4%	14.7%	11.2%	12.8%	37.7%
Ability to drive or walk	22.8%	13.8%	15.2%	9.1%	9.0%	29.2%

Note that not all respondents answered this question ($n = 1207$).

(Reid et al, 2022)

Clinical Indications for Tapering

	INDICATIONS	TAPER METHOD
SHORTER TAPER	• Patients who have been on low doses of benzodiazepines for a relatively short time (less than a year)[7] • Medication adverse effects indicate risks are greater than benefit • Comorbidities increase risk of complication	• Gradually reduce total dose by 50% over the first 4 weeks (e.g., 10-15% decrease weekly) • Maintain on that dose (50% original dose) 1-2 months, *then* • Reduce dose by 25% every 2 weeks
LONGER TAPER	• Patients on high doses of benzodiazepines or those who have been taking the medication consistently for many years[7,11] • Function is not improved with benzodiazepine use • Tolerance has developed with long-term prescription • Comorbidities increase risk of complication	No faster than 10% every 2- 4 weeks

A slower or longer taper schedule is recommended in most cases. A gradual taper of benzodiazepines can prevent adverse events from severe withdrawal (e.g., seizures) and effectively aid in benzodiazepine discontinuation. *See pages 8 and 9 for example tapers.*

When to consider tapering vs withdrawal management?

TAPER PROTOCOL 1

Shorter example taper for a Veteran taking lorazepam 2 mg twice daily[1-4,13]

Milestone suggestions	Month	Week(s)	Dose of lorazepam	
			Morning	Night
Week 2: 25% of initial dose	1	1	1.5 mg	2 mg
		2	1.5 mg	1.5 mg
Week 4: 50% of initial dose		3	1 mg	1.5 mg
		4	1 mg	1 mg
Weeks 5-8: Hold dose for one to two months	2	5-8	1 mg	1 mg
Week 9 – Discontinuation: Decrease dose by 25% every two weeks	3	9-10	0.5 mg	1 mg
		11-12	0.5 mg	0.5 mg
	4	13-14	0.25 mg	0.5 mg
		15-16	0.25 mg	0.25 mg
	5	17-18	0 mg	0.25 mg

For a taper calculator and other resources, go to https://dvagov.sharepoint.com/sites/vhaacademicdetailing

Veterans HA, DOD, VADoD Guideline for Management of SUD, Version 4.0, 2021

TAPER PROTOCOL 2

Longer taper with conversion from alprazolam to diazepam[*,7]

	Morning	Midday	Night	Daily diazepam equiv.
Starting dose	alprazolam 2 mg	alprazolam 2 mg	alprazolam 2 mg	120 mg
Stage 1 (one week)	alprazolam 2 mg	alprazolam 2 mg	alprazolam 1.5 mg diazepam 10 mg	120 mg
Stage 2 (one week)	alprazolam 2 mg	alprazolam 2 mg	alprazolam 1 mg diazepam 20 mg	120 mg
Stage 3 (one week)	alprazolam 1.5 mg diazepam 10 mg	alprazolam 2 mg	alprazolam 1 mg diazepam 20 mg	120 mg
Stage 4 (one week)	alprazolam 1 mg diazepam 20 mg	alprazolam 2 mg	alprazolam 1 mg diazepam 20 mg	120 mg
Stage 5 (1-2 weeks)	alprazolam 1 mg diazepam 20 mg	alprazolam 1 mg diazepam 10 mg	alprazolam 1 mg diazepam 20 mg	110 mg
Stage 6 (1-2 weeks)	alprazolam 1 mg diazepam 20 mg	alprazolam 1 mg diazepam 10 mg	alprazolam 0.5 mg diazepam 20 mg	100 mg

Ashton CH, Benzodiazepines. How they work and how to withdraw. NewCastle University. https://www.benzo.org/uk/manual. Published 2002. Accessed March 22, 2021.

TAPER PROTOCOL 2 (cont'd)

Longer taper with conversion from alprazolam to diazepam[*,7] *(continued)*

	Morning	Midday	Night	Daily diazepam equiv.
Stage 7 (1-2 weeks)	alprazolam 1 mg diazepam 20 mg	alprazolam 1 mg diazepam 10 mg	Stop alprazolam diazepam 20 mg	90 mg
Stage 8 (1-2 weeks)	alprazolam 0.5 mg diazepam 20 mg	alprazolam 1 mg diazepam 10 mg	diazepam 20 mg	80 mg
Stage 9 (1-2 weeks)	alprazolam 0.5 mg diazepam 20 mg	alprazolam 0.5 mg diazepam 10 mg	diazepam 20 mg	70 mg
Stage 10 (1-2 weeks)	alprazolam 0.5 mg diazepam 20 mg	Stop alprazolam diazepam 10 mg	diazepam 20 mg	60 mg
Stage 11 (1-2 weeks)	Stop alprazolam diazepam 20 mg	diazepam 10 mg	diazepam 20 mg	50 mg
Stage 12 (1-2 weeks)	diazepam 25 mg	Stop midday; move 5 mg to morning and night	diazepam 25 mg	50 mg

Continue reducing dose by 10% every 2-4 weeks, adjusting taper speed based on patient response.

*Rapid taper with alprazolam or abrupt switching is not recommended due to risk of seizures. Clearly document cross taper in medical record.

Medications used to treat BZD dependence and withdrawal

Soumya L. Pandalai, MD, MD DFASAM

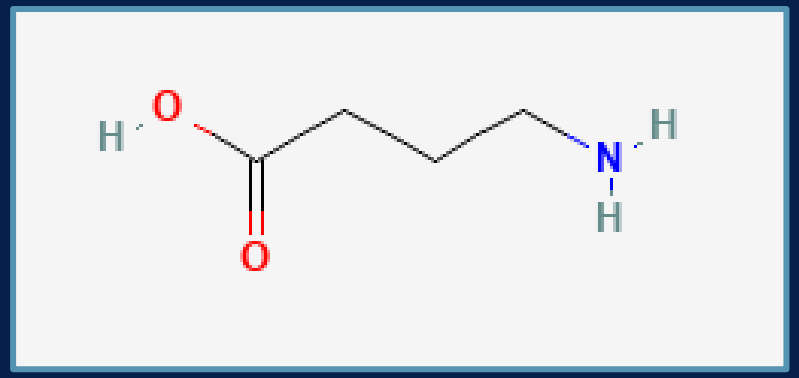
Pharmacotherapies for BWS

- GABAergic medications ($GABA_A$)
  - Benzodiazepines
  - Phenobarbital (PHB)
  - Propofol
  - Carbamazepine (CBZ)
  - Valproic acid (VPA)
  - Topiramate
  - Gabapentinoids (indirectly)
    - ❑ AEDs → multiple/other MOAs
- Sympatholytics (α_2, imidazole) agonists
  - Dexmedetomidine
  - Clonidine
- Ketamine (NMDA antagonist)
- $GABA_B$ agonists
  - Baclofen
  - GHB
- Antipsychotics (DA, 5HT antagonism)
  - Haloperidol/droperidol
  - Risperidone
  - Olanzapine
  - Quetiapine

Benzodiazepines	Barbiturates
Mechanism of Action	
$GABA_A$ receptors	$GABA_A$ receptors
↑ ***Frequency*** of chloride-channel opening - Require the ***presence*** of GABA	↑ ***Duration*** of chloride-channel opening *Do ***NOT*** need the presence of GABA
Biologic Effect	
CNS depression Anxiolysis Anterograde amnesia CYP-450 enzyme induction (PHB) [only with chronic use)	

Benzodiazepines resistance exists…

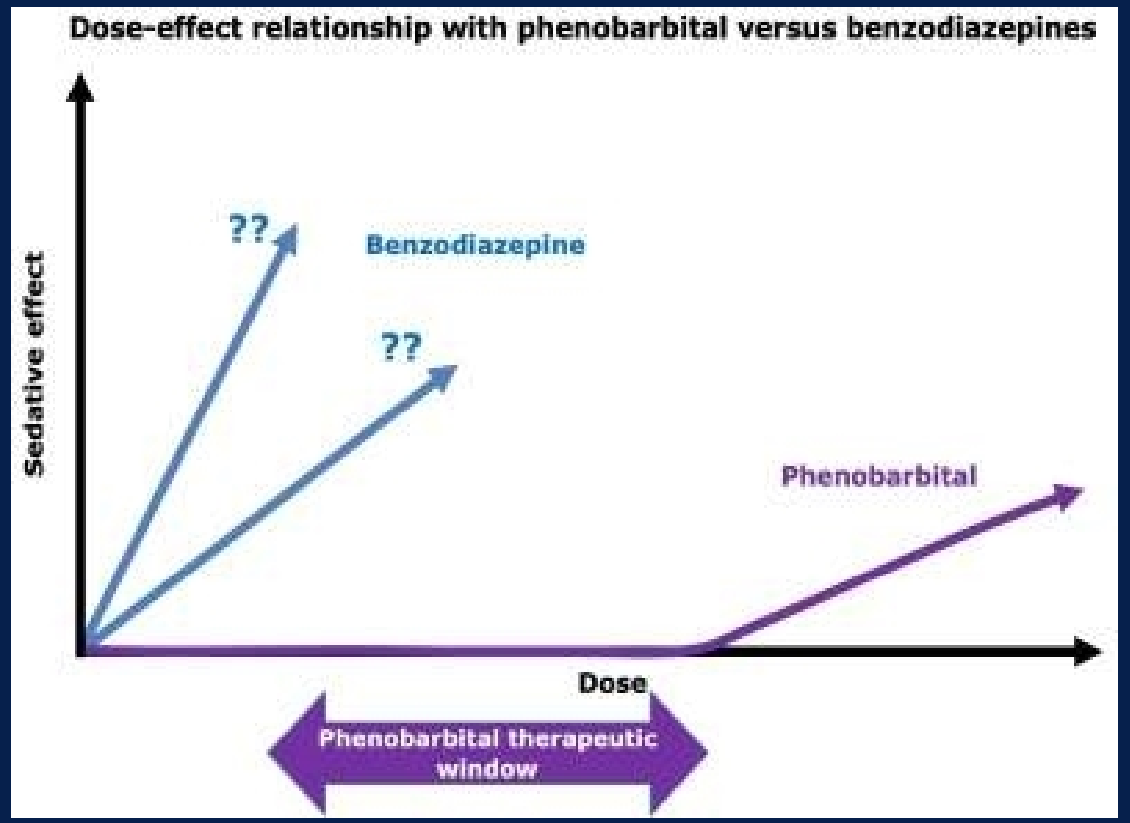
- Requiring >50mg diazepam in 1 hour or >200mg in 3 hours
- Proposed mechanism
  - BZD ceiling effect
  - GABA needed
  - ↓ function of GABA-A R
  - Upregulation of AMPA-R
- *Association with kindling*
- Treatment options
  - Barbiturates
  - Propofol
  - Ketamine?



(Langlois et al, 2020; Umar et al, 2023; Shah et al,2022)

Why phenobarbital over benzodiazepines?

- Favorable pharmacodynamics
  - Also $GABA_A$ agonist (slightly different MOA)
  - Does NOT require presence of GABA
- Clinical
  - Less delirium or paradoxical agitation
  - No evidence of PHB-resistant withdrawal
  - Less sedation at moderate doses
  - Better seizure prevention
  - Formulations: PO, IV, and IM
- Larger therapeutic index
  - Severe toxicity/sedation
    - >50mg/kg
    - BWS dosing → Usually <10-20mg/kg



(Umar et al, 2023; Farkas et al, 2023; Malone et al, 2023)

Determining appropriateness for outpatient BZD withdrawal management

Timothy J. Wiegand, MD, FACMT, FAACT, DFASAM

Questions to consider…

- A patient with chronic BZD use presents to the clinic...
  - Where do we send?
    - Medically managed withdrawal treatment (or Emergency Department)?
    - Outpatient management?

- Who will develop complicated BWS?
  - Complicated withdrawal:
    - Seizures, psychosis, severe agitation

Who is at risk for developing severe withdrawal?

- Failing an outpatient or prior taper
- Severe withdrawal symptoms
  - History or concern for severe withdrawal
  - Persistent uncontrolled signs/symptoms
- Complicated medical/psychiatric comorbidities
  - Seizure disorder, use of medications that lower seizure threshold
  - Cardiopulmonary disease, acute illness/infection
- High risk for significant harm related to ongoing BZD use
  - Overdose, falls, possible self-harm
- Poor nutritional status
- Increased age (>65)

- ***There is no accepted evidence-based risk assessment tool to aid in placement for BWS management***
- ***Recommendations are based on conclusions reached from alcohol withdrawal research and expert opinion***

Considerations for outpatient BWS management

- **Absence of severe BWS risks**
  - Severe symptoms currently
    - *Or in the past year*
  - Long-term intake of large BZD doses
  - Poorly controlled chronic medical conditions
  - Pregnancy
  - Acute illness
- **Social factors**
  - Support network
    - Someone to directly observe the patient
  - Cognitive impairment or TBI
  - Level of cooperation and reliability

CIWA-Ar

- Nausea and vomiting
- Tremor
- Paroxysmal sweats
- Anxiety
- Agitation
- Tactile disturbances
- Auditory disturbances
- Visual disturbances
- Headache
- Orientation / Sensorium

- Scoring:
  - 10 Categories; each scored 0-7, orientation (0-4); max 67

- AWS Severity
- **Mild < 15**
- **Moderate 16 to 20**
- **Severe > 20**

(Sullivan et al, 1989)

CIWA-B

Clinical Institute Withdrawal Assessment Scale - Benzodiazepines

Name:

Objective physiological assessment

For each of the following items, please circle the number which best describes the severity of each symptom or sign.

1	Observe behaviour for restlessness and agitation	0 None, normal activity	1	2 Restless	3	4 Paces back and forth, unable to sit still
2	Ask patient to extend arms with fingers apart, observe tremor	0 No tremor	1 Not visible, can be felt in fingers	2 Visible but mild	3 Moderate, with arms extended	4 Severe, with arms not extended
3	Observe for sweating, feel palms	0 No sweating visible	1 Barely perceptible sweating, palms moist	2 Palms and forehead moist, reports armpit sweating	3 Beads of sweat on forehead	4 Severe drenching sweats

Patient self-report

For each of the following items, please circle the number which best describes how you feel.

4	Do you feel irritable?	0 Not at all	1	2	3	4 Very much so
5	Do you feel fatigued (tired)?	0 Not at all	1	2	3	4 Unable to function due to fatigue
6	Do you feel tense?	0 Not at all	1	2	3	4 Very much so
7	Do you have difficulties concentrating?	0 No difficulty	1	2	3	4 Unable to concentrate
8	Do you have any loss of appetite?	0 No loss	1	2	3	4 No appetite, unable to eat
9	Have you any numbness or burning in your face, hands or feet?	0 No numbness	1	2	3	4 Intense burning or numbness
10	Do you feel your heart racing (palpitations)?	0 No disturbance	1	2	3	4 Constant racing
11	Does your head feel full or achy?	0 Not at all	1	2	3	4 Severe headache
12	Do you feel muscle aches or stiffness?	0 Not at all	1	2	3	4 Severe stiffness or pain
13	Do you feel anxious, nervous or jittery?	0 Not at all	1	2	3	4 Very much so
14	Do you feel upset?	0 Not at all	1	2	3	4 Very much so
15	How restful was your sleep last night?	0 Very restful	1	2	3	4 Not at all
16	Do you feel weak?	0 Not at all	1	2	3	4 Very much so
17	Do you think you had enough sleep last night?	0 Yes, very much so	1	2	3	4 Not at all
18	Do you have any visual disturbances? (sensitivity to light, blurred vision)	0 Not at all	1	2	3	4 Very sensitivity to light, blurred vision
19	Are you fearful?	0 Not at all	1	2	3	4 Very much so
20	Have you been worrying about possible misfortunes lately?	0 Not at all	1	2	3	4 Very much so

21	How many hours of sleep do you think you had last night?	
22	How many minutes do you think it took you to fall asleep last night?	

Total CIWA-B Score:	

Interpretation of scores: Sum of items 1-20

1–20 = mild withdrawal
21–40 = moderate withdrawal
41–60 = severe withdrawal
61–80 = very severe withdrawal

(Busto et al, 1989)

Benzodiazepine Withdrawal Symptom Questionnaire

Each moderate score is given a rating of 1 and each severe score a rating of 2. The maximum score possible is 40, unless of course additional symptoms are included.

Note also whether the symptoms occurred when the tablets were reduced or stopped, or if the symptoms occurred when the tablets were the same.

	No	Yes - moderate	Yes - severe
Feeling unreal	0	1	2
Very sensitive to noise	0	1	2
Very sensitive to light	0	1	2
Very sensitive to smell	0	1	2
Very sensitive to touch	0	1	2
Peculiar taste in mouth	0	1	2
Pains in muscles	0	1	2
Muscle twitching	0	1	2
Shaking or trembling	0	1	2
Pins and needles	0	1	2
Dizziness	0	1	2
Feeling faint	0	1	2
Feeling sick	0	1	2
Feeling depressed	0	1	2
Sore eyes	0	1	2
Feeling of things moving when they are still	0	1	2
Seeing or hearing things that are not really there (hallucinations)	0	1	2
Unable to control your movements	0	1	2
Loss of memory	0	1	2
Loss of appetite	0	1	2

(Tyler et al, 1990)

Several outpatient BZD withdrawal management regimens

Dr Wiegand's 3-day outpatient PHB protocol

- The night before…
  - Stop BZD
  - Start VPA 500mg BID for 2-4 weeks (and reassess)

- PHB
  - Day 1 = 130mg PO q4H x6
  - Day 2 = 130mg PO q6H x4
  - Day 3 = 130mg PO q8H x3

- Check-in (in person or virtual): day 2 and day 3

Dr Wiegand's 3-day outpatient PHB protocol

- Tips
  - Rx for one day at a time if concerned about overuse
  - For persistent insomnia/nighttime anxiety, give 130mg PHB tabs qHS PRN x2 on days 4 and 5
  - Ideally, a significant other should be in charge of holding/giving PHB
  - If any signs of sedation or intoxication (slurred speech, ataxia, lethargy) are present, hold the dose and reassess if held x2 PHB
  - If doing outpatient Day 1, bring in for observation dose one and then hang around or return a few hours later for 2nd dose (may not be exactly 4 hours later but close

Dr Wiegand's 1-month non-BZD Outpatient Protocol

- Start gabapentin taper the morning after last BZD use
- Days:
  - 1-5 = Gabapentin 800mg TID + qHS PRN for anxiety/insomnia
  - 5-10 = Gabapentin 600mg TID
  - 11-15 = Gabapentin 600mg BID
  - 16-20 = Gabapentin 300mg TID
  - 21-25 = Gabapentin 300mg BID
  - 26-30 = Gabapentin 300mg qHS
- Start VPA 500mg PO BID for 2-4 weeks (and reassess)
- Clonidine 0.1 mg PO TID PRN anxiety
- Melatonin qHS

Dr Laes' outpatient protocols

- Clonazepam taper over 2-3 weeks
  - 0.75mg x 5-7 days
  - 0.5mg x 5-7 days
  - 0.25mg x 5-7 days, then discontinue

- 3-day PHB taper
  - Day 1: 32.4mg tablet PO q8H x3 doses
  - Day 2: 32.4mg tablet PO q12H x2 doses
  - Day 3: 32.4mg tablet PO x1 dose

Dr. Brunner's 5-day PHB protocol

- DAY 1
  - 64.8mg initial dose, then 32.4mg q4H
  - Assess CIWA q6H; If CIWA is >15, add 32.4mg… max dose 330mg.
  - For a history of seizures: Carbamazepine 200mg TID until discharge
- DAY 2
  - 32.4mg q4H
  - Assess CIWA q6H; If CIWA is >15, add 30mg… max dose 300mg
- DAY 3
  - 32.4mg q6H
  - Assess CIWA q6H; If CIWA is >15, add 30mg… max dose 240mg
- DAY 4
  - 32.4mg q8H
  - Assess CIWA q8H; If CIWA is >15, add 30mg… max dose 180mg
- DAY 5
  - 32.4mg q12H
  - Assess CIWA q8H; If CIWA is >15, add 30mg… max dose 150mg
- DAY 6+
  - Assess CIWA q8h. If CIWA is >15 give 32.4mg
  - Discharge when dose <60mg within 24 hours

Dr Pueringer's outpatient non-BZD BWS protocol

- **Start morning after stopping BZD**
- **Phenobarbital** (PHB):
  - Days 1 to 2: 65-130mg BID
  - Days 3 to 4: 32-65mg BID
  - … or 5-10mg/kg IVPB or one-time 260mg
- **VPA** 500mg BID, for 4-6 weeks
  - Followed by taper over 1-2 weeks
  - Can continue for mood stabilization PRN
- **Gabapentin** 400-800mg TID + PRN qHS insomnia/restlessness for 1-2 weeks
  - Followed by taper over 1-2 weeks
  - Hold or decrease the dose for sedation/sleepiness
- **Combinations**:
  - VPA + PHB
  - VPA + gabapentin
  - Severe cases → PHB + VPA + gabapentin

Dr Pueringer's outpatient non-BZD BWS protocol

- Decrease PHB or gabapentin if oversedation occurs
- Ideally, frequent virtual or in-person check-ins
  - Daily to 2x weekly
- If BZD tolerance and use in diazepam equivalents are ***known***, adjust the starting total daily PHB dose to equal this and then taper accordingly over several days.
- This can be started in the hospital

Dr Unger's 6-day outpatient PHB protocol

- Days 1 and 2: 64.8 mg three times daily
- Days 3 and 4: 64.8 mg twice daily
- Days 5 and 6: 64.8 mg at bedtime

- To be used only in patient's with relatively low-dose BZD dependence

Cases

Case 1

- 41yo with OUD on buprenorphine 24 mg/day, chronic BZD use
- Uses 2-3 tabs of “street Xanax”
  - Bromazolam tabs pressed to look like Xanax bars
- When access to BZD is disrupted, he has days of uncomfortable “withdrawal”, but eventually says, “it feels great, I have myself back”
- No gabapentin, minimal EtOH use (socially)
- Questions:
  - How would you manage this patient?

Case 2

- 38yo with daily alcohol use and daily methamphetamine use presents to the ED for “help”
- Uses 3mg of prescription alprazolam 3-4x daily
- 3-5 drinks daily, smokes methamphetamine 1-2x daily
- Last use of all substances 36H prior

- Currently:
  - Somnolent and apathetic; intermittent periods of confusion/agitation/restlessness
  - Hallucinations/delusions; diffuse perspirations
  - Vital signs: SBP 150s, HR 100bpm
  - Urine drug immunoassay +BZD, +amphetamines (BAC of 0)

- Failed previous BZD taper, poor follow-up in the past year, refuses to be admitted

- Questions:
  - How would you manage this patient?
  - What setting? What clinic resources are needed?
  - What pharmacotherapy and/or regimen would you choose?

Case 3

- 72yo with AUD and cognitive impairment
- On clonazepam 1mg BID for decades (anxiety); zolpidem 10mg qHS (insomnia), pregabalin 75mg BID (pain)
- Multiple recent falls
- Drinks 2 glasses of wine per night
- She lives by herself but has home healthcare and family in the area; medications in a pill box; refuses admission

- Currently:
  - Pleasant and slightly forgetful; fearful and hesitant to have sedatives stopped
  - Vital signs: SBP 110s, HR 70bpm
  - Urine drug immunoassay +BZD

- Questions:
  - What would you do first?
  - Can this be managed in an outpatient setting? If so, what clinic resources are needed?
  - What pharmacotherapy and/or regimen would you choose?

Case 4

- 25yo with daily injection fentanyl use presents to the ED via EMS
- Used “Xanax” bars obtained off the street for 1+ year and any prescription BZD she can get
- Last use of fentanyl and BZDs was ~18H prior
- History of severe BZD withdrawal

- Currently:
  - Anxiety/irritability, agitation, restlessness, rhinorrhea/lacrimation, mydriasis, myalgias, piloerection (COWS > 25)
  - Hallucinations/delusions
  - Vital signs: SBP 150s, HR 110bpm
  - Urine drug immunoassay is unrevealing

- Refuses inpatient/non-hospital admission; history of several self-directed discharges; unhoused

- Questions:
  - What would you do first?
  - Can this be managed in an outpatient setting? If so, what clinic resources are needed?
  - What pharmacotherapy and/or regimen would you choose?

Final Takeaways/Summary

- BWS exists on a spectrum of central neuroexcitation
- GABAergic medications address/treat the underlying physiology/cause of BWS and are the primary treatment
- BWS management principles have a strong evidence base; specifics do not and vary among institutions
- There are several safe/effective regimens to manage outpatient BZD withdrawal if a prolonged BZD taper is not safe/feasible

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