An Overview of the Management of Benzodiazepine Use Disorder

Logan Adams, MD

ASAM 55th Annual Conference
Friday April 5, 2024
10:30AM – 11:45AM

Disclosure Information

An Overview of Management of Benzodiazepine Withdrawal and Benzodiazepine Use Disorder

April 5, 2024 10:30AM – 11:45AM

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- No Disclosures

Learning Objectives

1. Describe the epidemiology of benzodiazepine use and use disorder

2. Distinguish the signs and symptoms of benzodiazepine withdrawal

3. Summarize protocols for management of benzodiazepine withdrawal

4. Discuss the chronic management of benzodiazepine use disorder

Patient Case: Part I

Ben is a 40 year old cis-gender white male with a history of anxiety, severe benzodiazepine use disorder with chart history of withdrawal seizure, severe opioid use disorder, stimulant use (methamphetamine and cocaine), and untreated HCV

History of Present Illness

- 1 week of fatigue, cough, and congestion
- CXR consistent with multifocal pneumonia
- On RA, not needing supplemental O2
- Given 1L lactated ringers, IV ceftriaxone , Azithromycin
- Review of systems:
  - **skin crawling**
  - **cold sweats**
  - **Restlessness**
  - **Yawning**
  - **abdominal cramping**
- Found to be in withdrawal from both benzodiazepines (BZD) and opioids
- Admitted for treatment of pneumonia and withdrawal management

Substance use history

Benzodiazepines:

- First use: while incarcerated for 7 years
  - started on alprazolam, on stable dose for anxiety
  - First exposure to BZD
  - Released, unable to find prescriber, starting using non-rx
- ~10 mg of pressed alprazolam or clonazepam daily (100 diazepam equivalents)
- Last use ~36h prior to presentation

Substance use history

- Opioids: using IV fentanyl daily, up to 6g/day, last use 36h PTA
- Stimulants:
  - IV and IH methamphetamine several times per week “when available”
  - Last use 36h prior to presentation
  - Denies recent cocaine use, last use 9mo ago IN
- Smokes 5-10 cigarettes daily
- Denies EtOH

Substance use history

Complications of use

- Benzodiazepines: withdrawal seizure 6 years ago
- Overdoses: 3 prior in the past 2 years
- Infectious: multiple SSTIs, HCV

Other history

Social history

- Mostly unsheltered for last 7 years
- Occasionally doubles up with his brother
- Has a partner and a 5 year old who he is separated from
- Occasional contact with parents though relationship is strained

Medications

- No prescribed medications; largely unengaged with outpatient care

Diagnosis and Epidemiology

Objective 1

Describe the epidemiology of benzodiazepine use and use disorder

General Principles

Spectrum of use

- Use
- "Misuse"[1]
  - Any other use than how it is prescribed
- Benzodiazepine use disorder
  - DSM 5 Diagnosis meeting diagnostic criteria

Definitions

- Sedative Hypnotic Use Disorder
  - Definition includes BZD, barbiturates, z-drugs, and carbamates
  - NSDUH – 77% of misuse in this class was BZD[2]
- **Therapeutic dose** vs **High dose**
  - Literature typically describes in therapeutic range only
  - High dose:> 3-5x upper limit of generally prescribed range

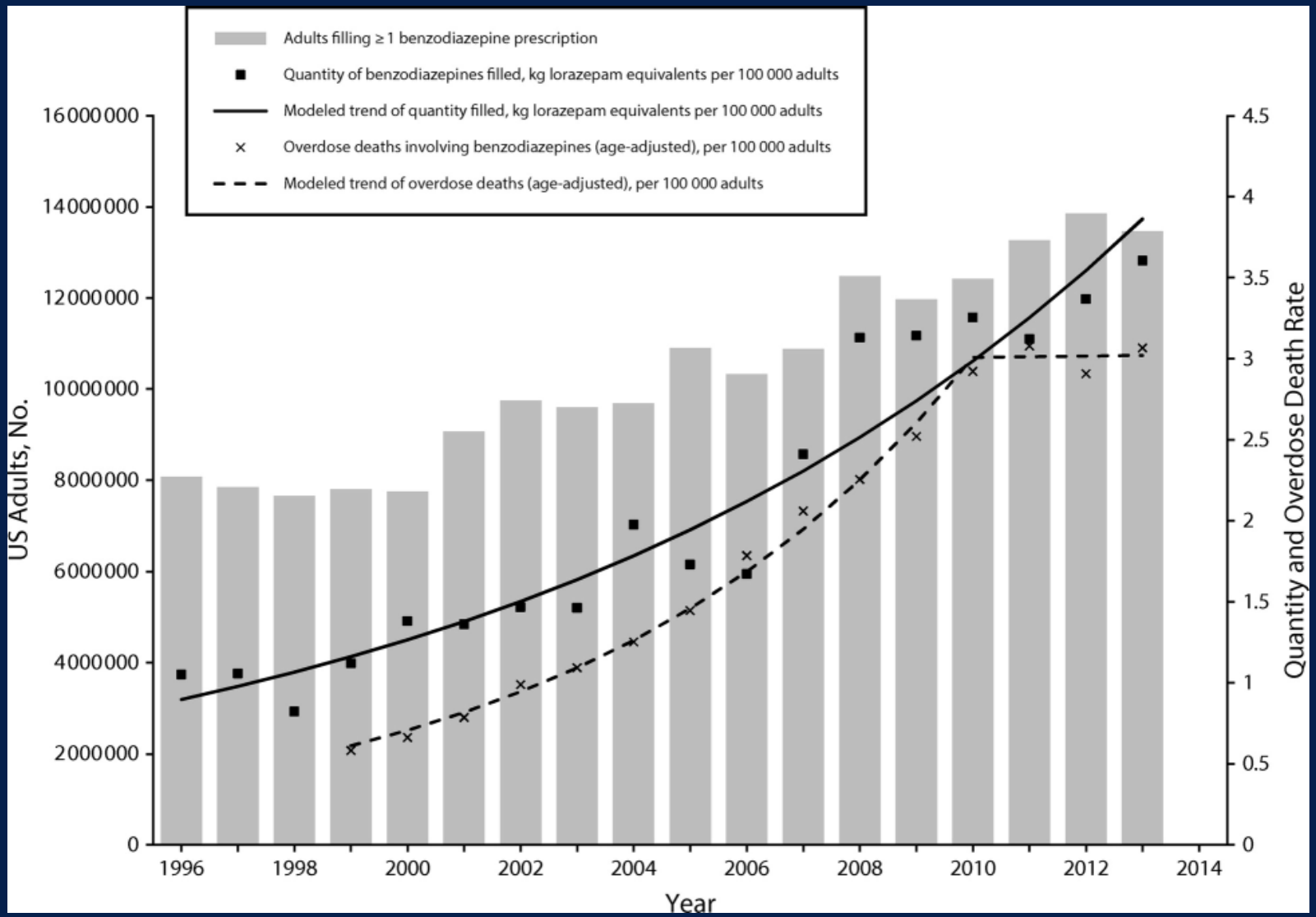
Blanco et al. *J Clin Psychiatry.* 2018

SAMSHA. National Survey on Drug Use and Health. 2022

Epidemiology: Prescribing

- Benzodiazepine prescribing from 1996 – 2013:
  - increased 67% in number of prescriptions
  - dose equivalents prescribed increased by 3 fold

Adults filling BZD prescription, quantity, and overdose deaths

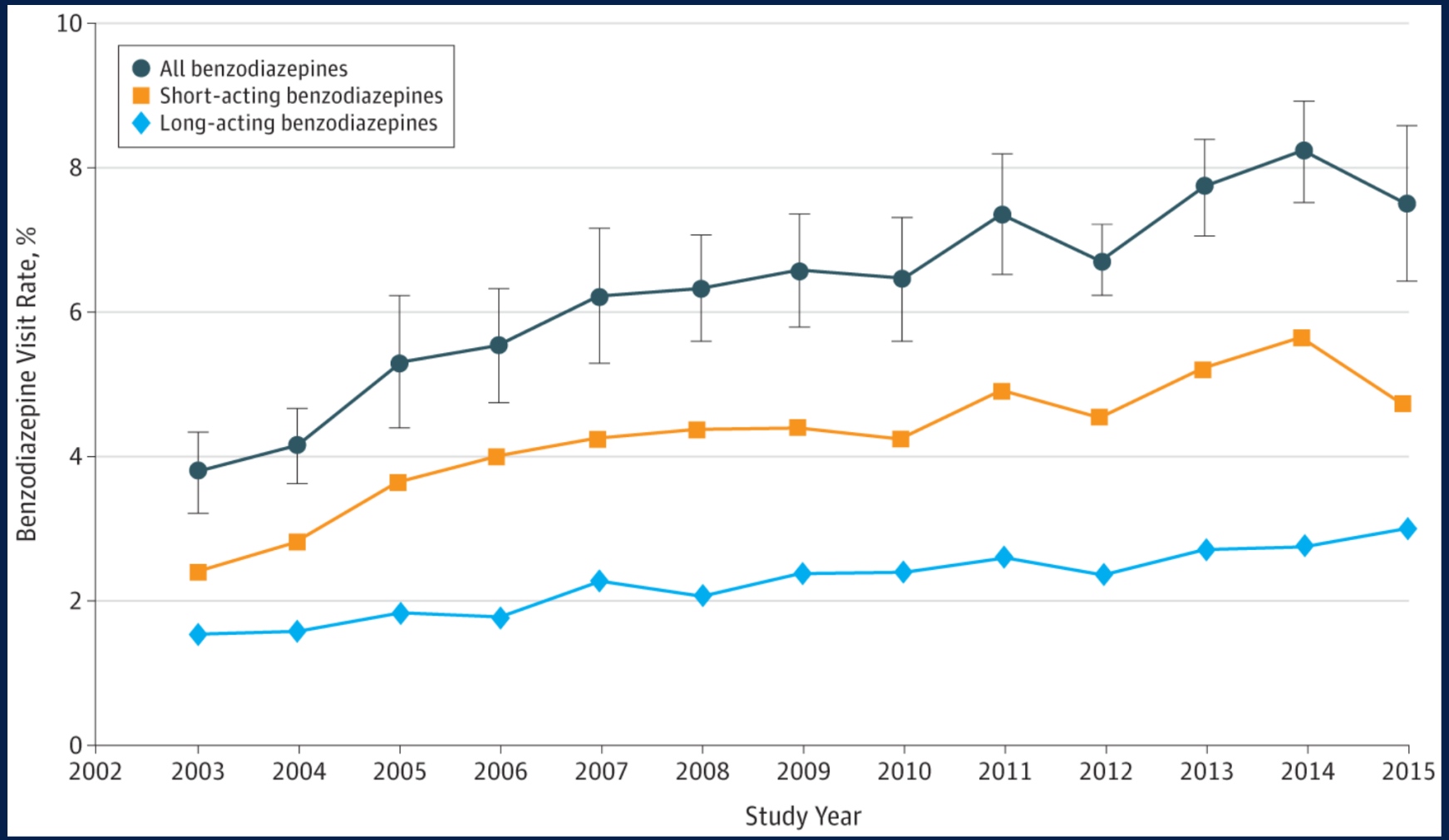


Bachhuber et al. *Am J Public Health*. 2016

Epidemiology: Prescribing

- Outpatient visits where BZD are prescribed doubled from 2003 to 2015

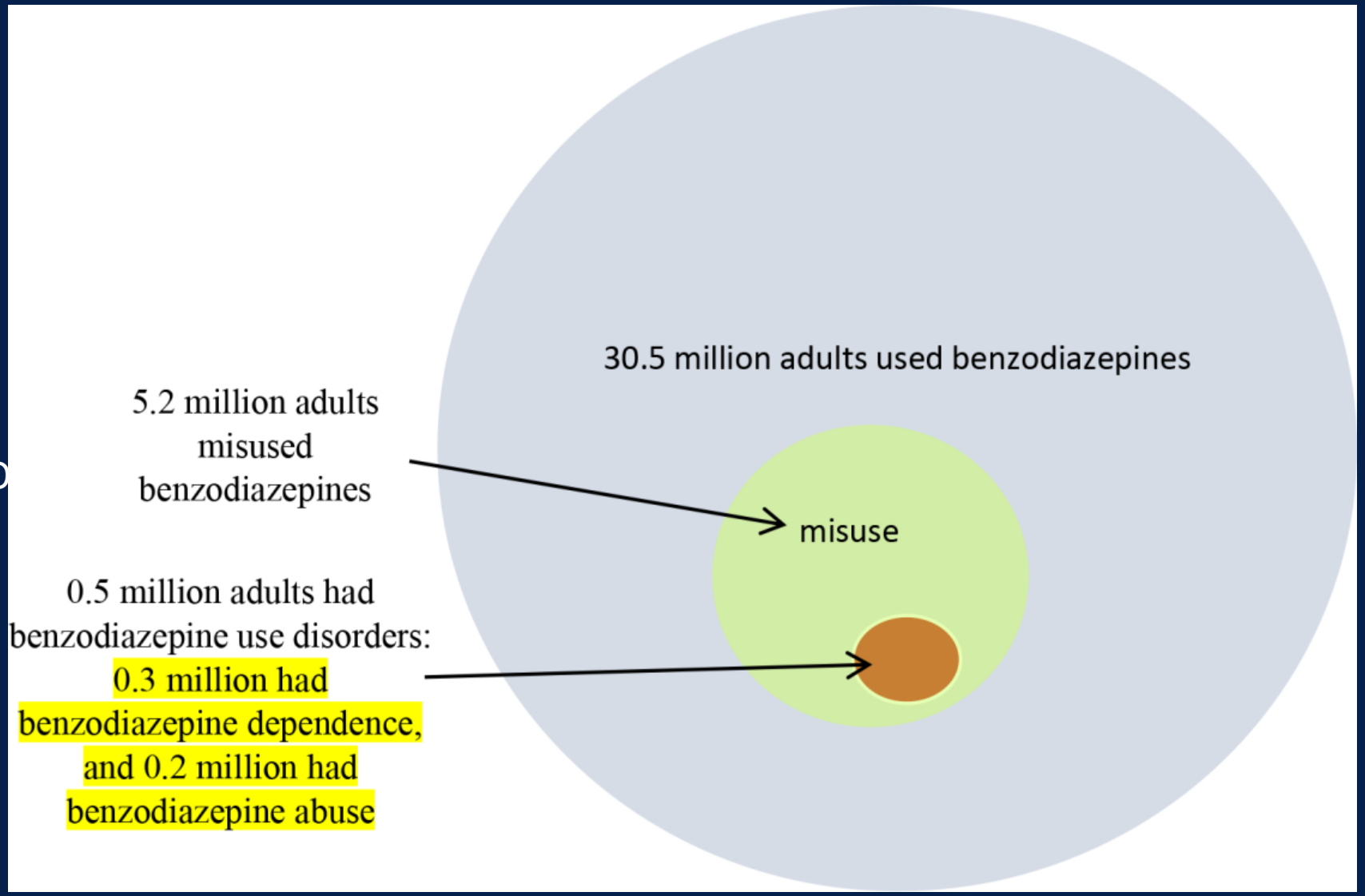
Benzodiazepine visits in the US from 2003 to 2015



Argarwal et al. *JAMA Netw Open*. 2019

17% of those prescribed BZD

1.6 %



Annual averages, 2015–2016 (all circles below are approximately proportionally sized by area)

Blanco et al. *J Clin Psychiatry.* 2018

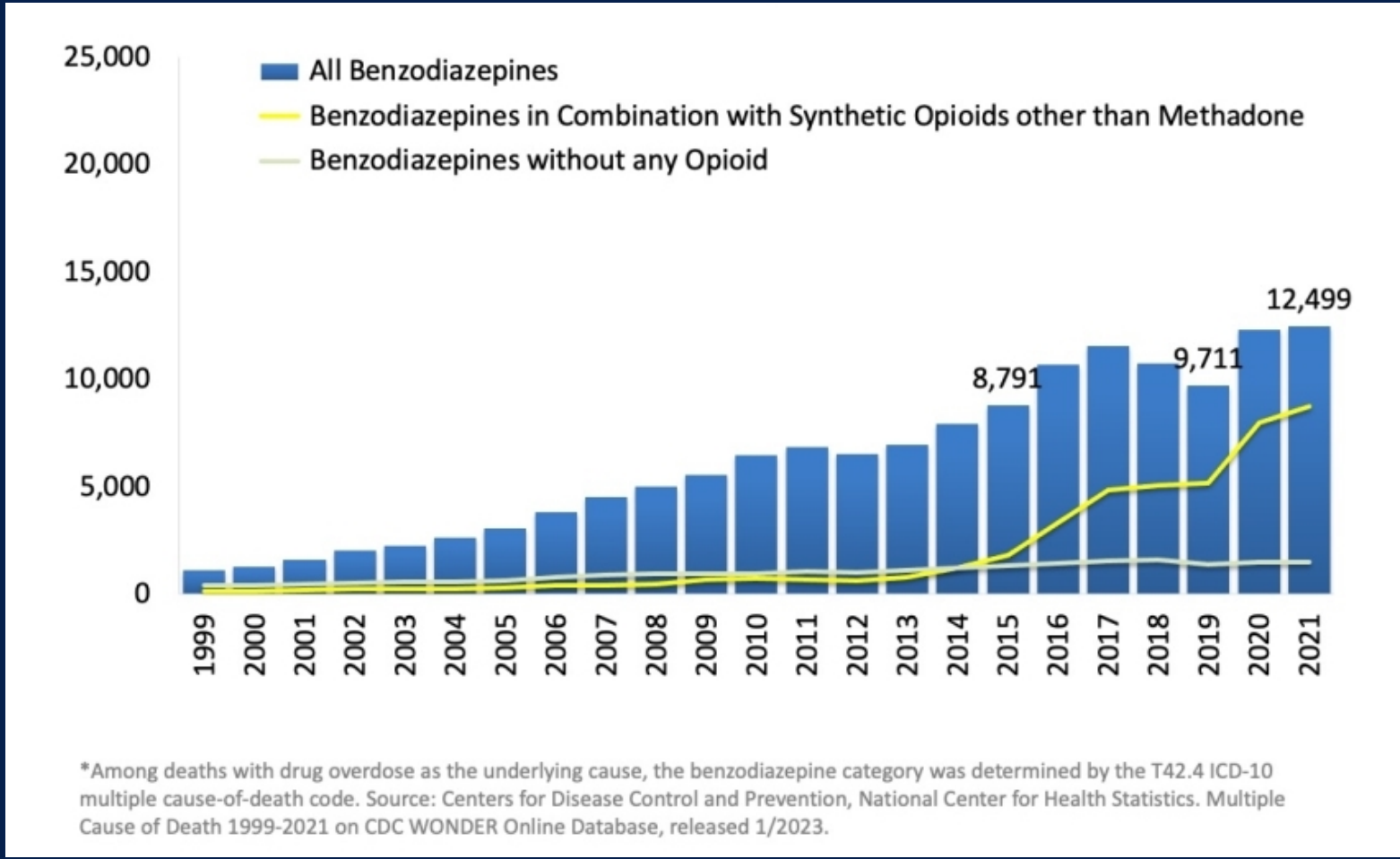
Co-occurring with other SUDs

- High rates of benzodiazepine misuse in patients with other SUDs[5]
  - Patients with OUD: misuse 20x > US general population. 43% reporting last year use
  - Patients with AUD: misuse 3-4x > US general population. 7.6% reporting last year misuse
- Admissions[6]
  - 81% of admissions where BUD is active, it is secondary to another primary SUD
  - Treatment admissions for primary BUD have doubled from 2007 to 2017 (0.5 to 1%)

Votaw et al. *Addictive Behaviors*. 2019
Votaw et al. *Drug Alcohol Depend*. 2019

Benzodiazepine overdose mortality

National Overdose Deaths Involving Benzodiazepines, by opioid involvement, 1999-2021



*Among deaths with drug overdose as the underlying cause, the benzodiazepine category was determined by the T42.4 ICD-10 multiple cause-of-death code. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 1/2023.

National Institute on Drug Abuse. 2023

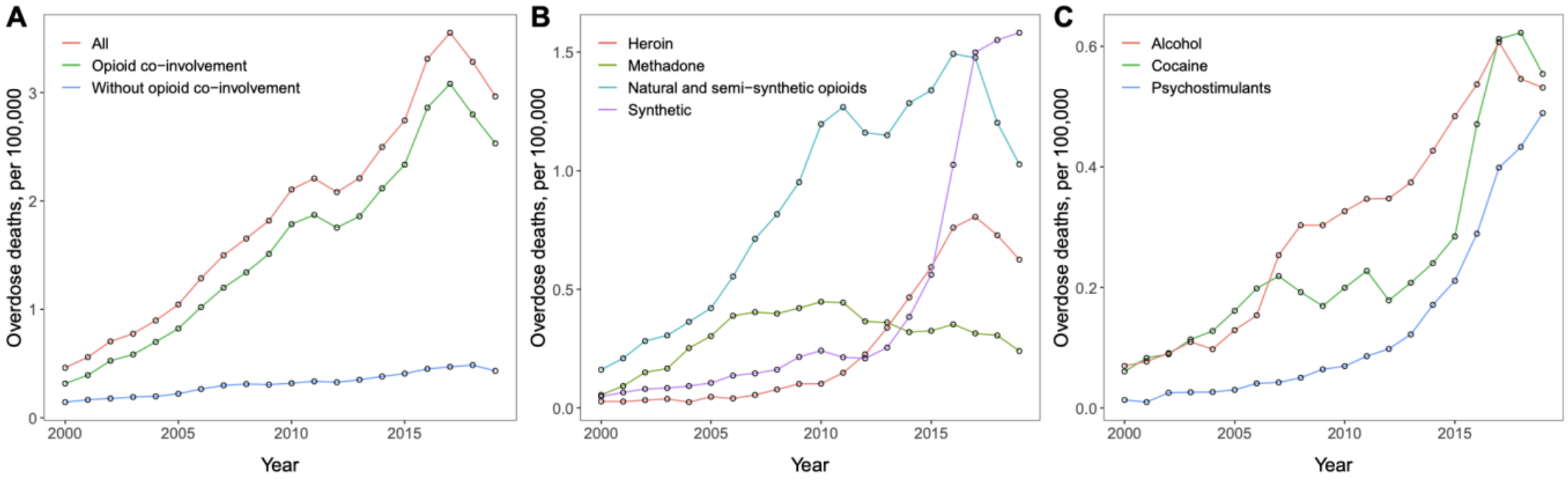


Figure 1 Trends in benzodiazepine-involved overdose mortality rates, by co-involved substances. A Overdose mortality rates by presence of any opioid. B Overdose mortality rates by co-involved opioid. C Overdose mortality rates by co-involved non-opioid. Rates of overdose mortality are presented per 100,000 individuals. Overdose deaths may co-involve multiple substances.

Klienman and Weiss. *J Gen Intern Med.* 2022

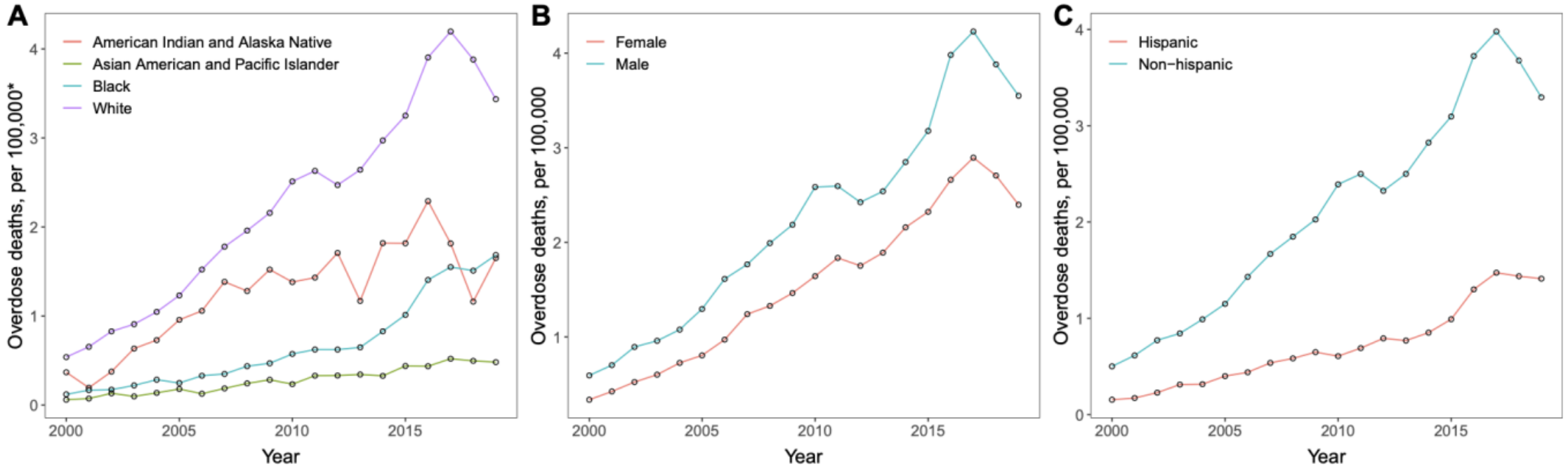


Figure 2 Trends in demographic characteristics of benzodiazepine-involved overdose mortality. A Overdose mortality rates by race. B Overdose mortality rates by sex. C Overdose mortality rates by Hispanic origin. Rates of overdose mortality are presented per 100,000 individuals of the demographic group.

Klienman and Weiss. *J Gen Intern Med.* 2022

Ben's Case Part II: Use Practices

Ben reports that he uses either intranasally or injecting, and rarely intramuscularly when he cannot find veins. He is engaged with a harm reduction/syringe service program, and always uses alcohol swabs, new needles, sterile water, and single use cookers. His harm reduction program has a *Fouirer-transform Infrared Spectroscopy* **(FTIR)** to **check pressed pills**, which he uses regularly to ensure he is getting alprazolam.

Select Harm Reduction Principles:
Understanding pressed pills

Pressed pills:

- Made using a pill press
- Often are diluted
- Can contain adulterants

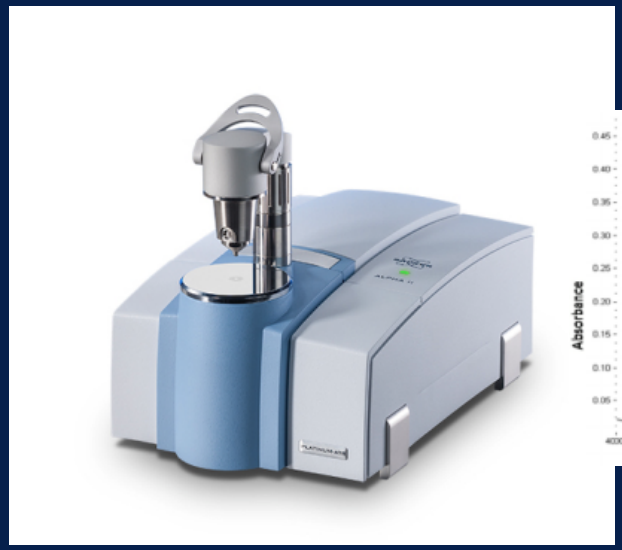
Left: Authentic oxycodone M30 tablets (top) vs. counterfeit oxycodone M30 tablets containing fentanyl (bottom). Center: Authentic Adderall tablets (top) vs. counterfeit Adderall tablets containing methamphetamine (bottom). Right: Authentic Xanax tablets (white) vs. counterfeit Xanax tablets containing fentanyl (yellow).

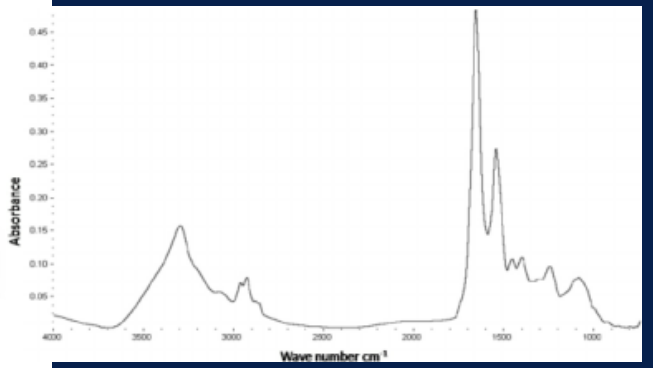
Drug Enforcement Administration. 2021

Select Harm Reduction Principles:
Drug checking

Multiple modalities

- Test strips (fentanyl, xylazine)
- Reagent testing
- Fourier-transform Infrared Spectroscopy **(FTIR)**
- Mass spectroscopy
  - i.e mail in based lab analysis





Select Harm Reduction Principles:
Intranasal Use

- A set of **practical strategies** to **reduce the risk** of mucosal injury, infectious disease transmission, and overdose
- Recommended items:
  - Alcohol swabs
  - Single use straw
  - Sterile water
  - Foil (sterile surface)
- Key points:
  - Do not share supplies
  - Ensure drug is finely crushed to help prevent mucosal injury
  - Rinse nostrils with sterile water or saline
  - Switch nostrils
  - Do not use alone
  - Always carry naloxone
  - Start low and go slow

Benzodiazepine Withdrawal

Objective 2

Identify the signs and symptoms specific to benzodiazepine withdrawal, especially in cases with other withdrawal syndromes

Case Part III

Ben was admitted to the hospital for treatment of pneumonia and started on CIWA with prn lorazepam protocol for benzodiazepine withdrawal. You were consulted on the Addiction Consult Team. He states his anxiety is “through the roof” and endorses the following on review of systems:

- Skin crawling
- Cold sweats
- Restlessness
- Yawning
- Abdominal cramping
- Insomnia
- Photo- and phonophobia
- Peripheral paresthesias

Mechanism of Withdrawal

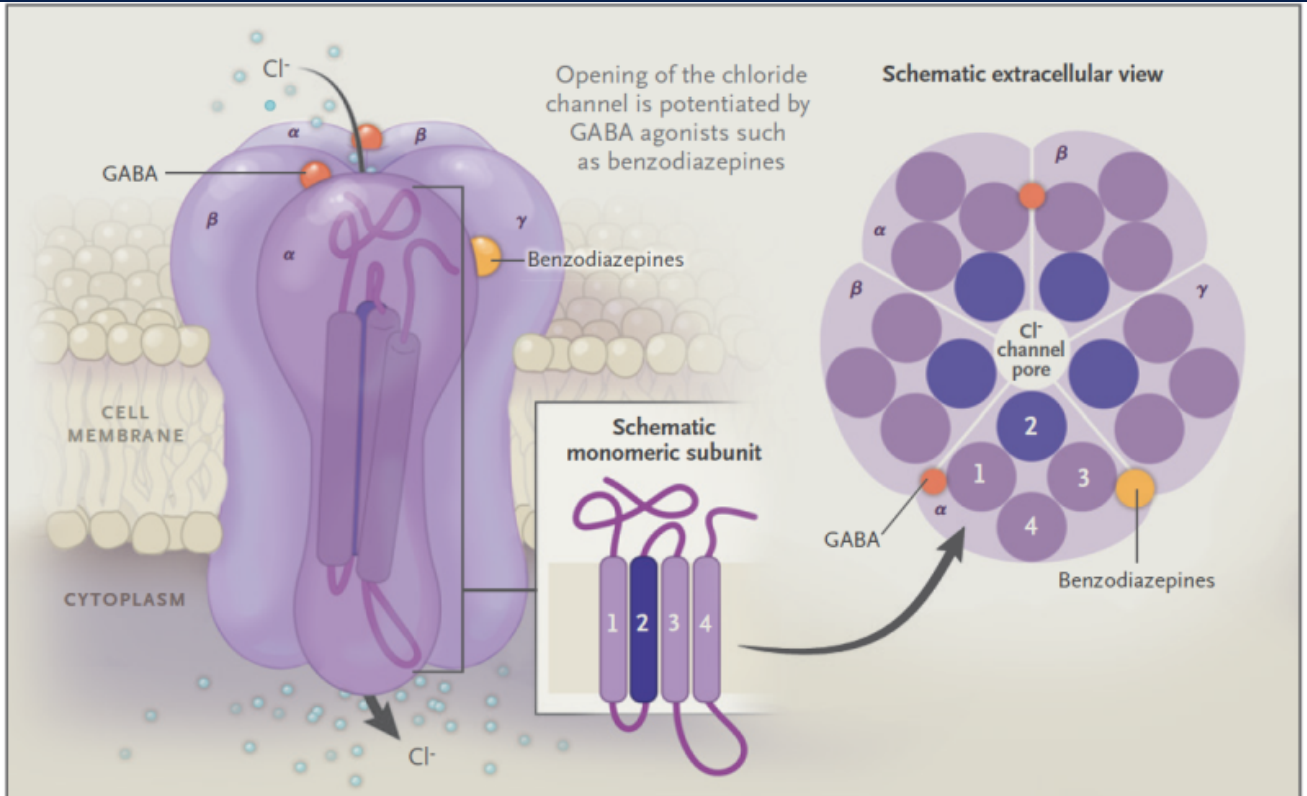


Figure 1. Pharmacologic Characteristics of γ-Aminobutyric Acid Type A ($GABA_A$) Receptors.

The $GABA_A$ receptor consists of five transmembrane glycoprotein subunits arranged around the central chloride channel. Each subunit is composed of four domains (domains 1 through 4); domain 2 (dark purple) is the part of the monomeric subunit that lines the chloride channel. Benzodiazepines increase the affinity of the $GABA_A$ receptor for GABA and the likelihood that the receptor will open for chloride ions (light blue).

Soyka. *N Engl J Med*. 2017

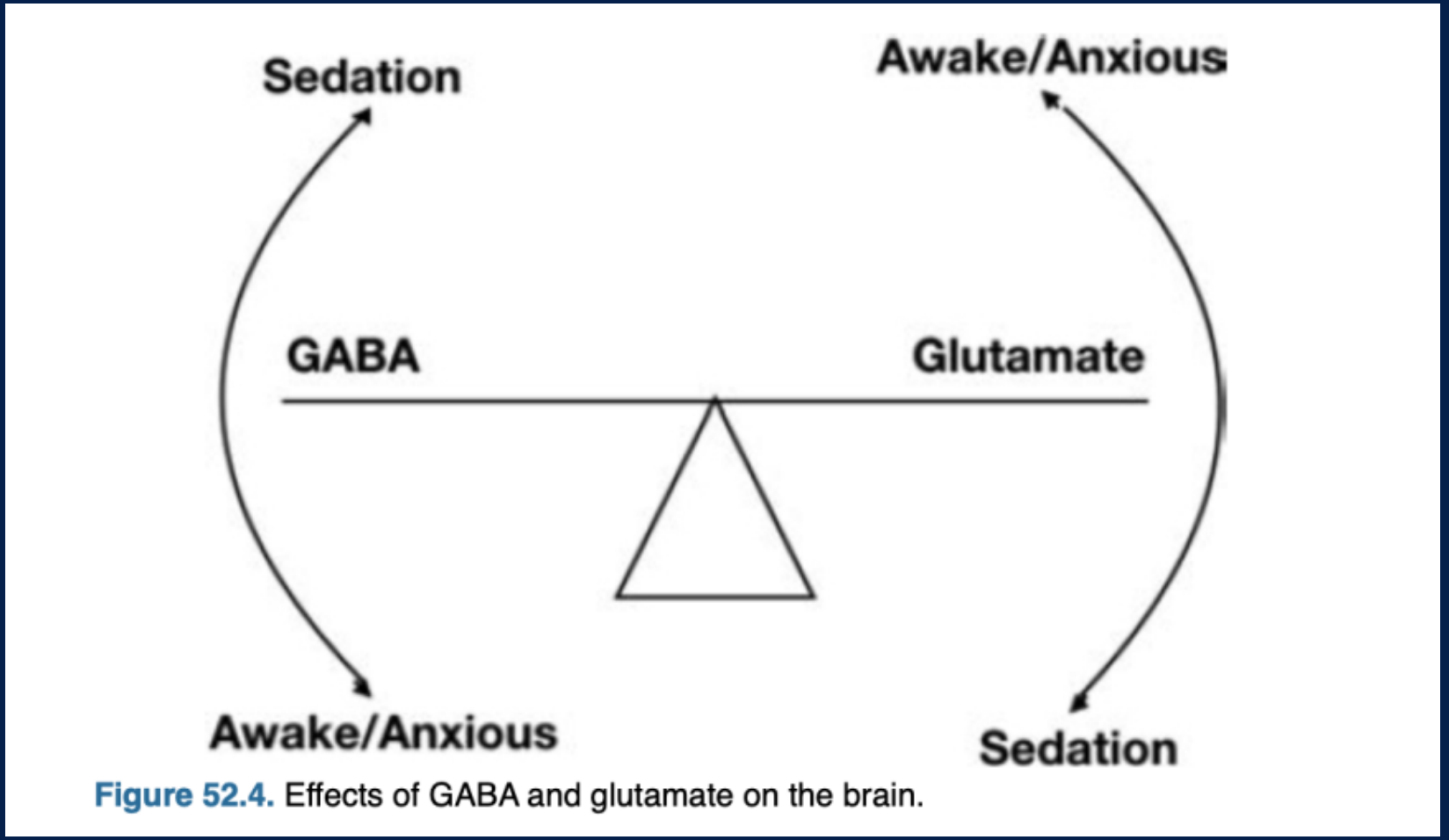


Figure 52.4. Effects of GABA and glutamate on the brain.

After benzodiazepine discontinuation…

Recurrence	Rebound	"Pseudowithdrawal"	Withdrawal
• symptoms return for which it was initially used/rx (i.e. insomnia, anxiety) • can occur days to months • 60-80% in insomnia or anxiety disorders	• symptoms transiently more intense than they were before drug treatment • hours to days • Short duration and self-limited	• Overinterpretation of symptoms with expectations of withdrawal Winokur. J Clin Psychiatry. 1984	

ASAM Principles of Addiction Medicine (6th ed.)

Factors Affecting Withdrawal

- Pharmacokinetics:
  - Short-acting
    - occurs < 24h of last use, peaks 1-5 days
  - Long-acting
    - occurs < 5 days, peaks 1-9 days
- Potency
  - Rapid acting, high potency benzodiazepines = higher tolerance = more intense w/d

Factors Affecting Withdrawal

- Dose and duration
  - Doses within "*therapeutic range*":
    - < 10d – transient insomnia
    - < 2-3 mo – mild withdrawal
    - > 1 year – moderate to severe withdrawal sxs
  - Does > 3-5x upper limit of therapeutic range ("*high dose*"):
    - 2-3 months – moderate in all to severe withdrawal in most

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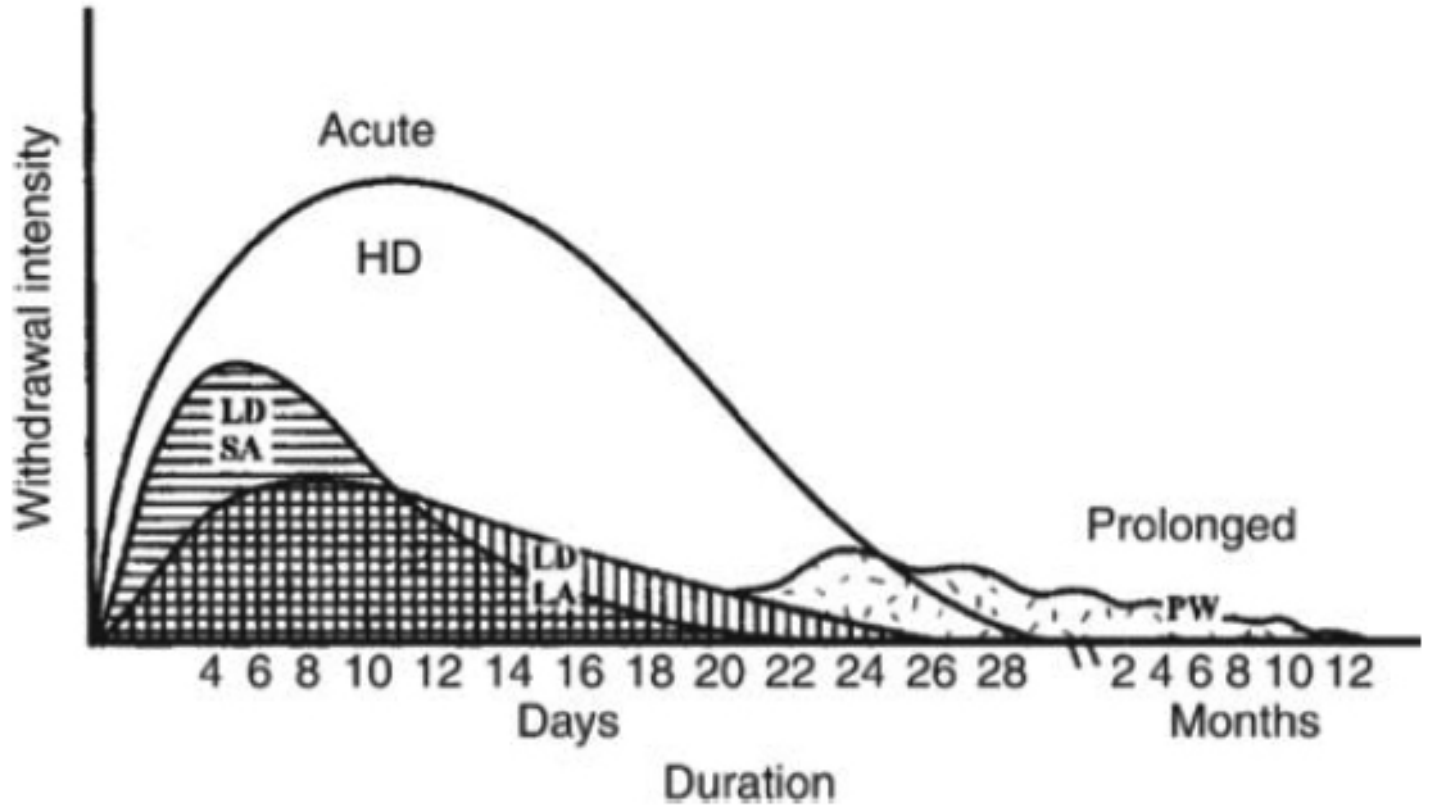

Figure 52.1. Time course of sedative–hypnotic withdrawal. Time course and potential withdrawal intensity as influenced by dose and duration of drug action. HD, high dose; LD, low or therapeutic dose; SA, short acting; LA, long acting; PW, prolonged withdrawal.

TABLE 56.2 Sedative–Hypnotic Withdrawal Symptoms

Mild	Moderate	Severe
• Anxiety • Insomnia • Dizziness • Headache • Anorexia • Perceptual hyperacusis • Irritability • Agitation	• Panic • Decreased concentration • Tremor • Sweating • Palpitations • Perceptual distortions • Muscle fasciculations • Muscle aches • GI upset • Insomnia • Elevated vital signs • Depression	• Hypothermia • Vital sign instability • Muscle fasciculations • Seizures • Delirium • Psychosis

Post Acute Withdrawal Syndrome (PAWS)

- Persisting withdrawal symptoms weeks – months
- Waxes and wanes day-to-day
- Must exclude recurrence of psychiatric disease
- Treatment:
  - Propranolol 10-20mg TID (tremor, anxiety)
  - Gabapentin (insomnia, anxiety)
  - Sedating antidepressants (insomnia)
- Self limited

Symptoms

- Insomnia
- Perceptual disturbances
- Tremor
- Sensitivity to light and touch
- Tinnitus
- Anxiety

CIWA-B

0271-0749/89/0906-0412$02.00/0
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A Clinical Scale to Assess Benzodiazepine Withdrawal

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[3]*Clinical Psychopharmacology, Addiction Research Foundation; and* [1]*Faculty of Pharmacy and*
[3]*Departments of Pharmacology and Medicine, University of Toronto, Ontario, Canada*

Busto et al. *J Clin Psychophramacol*.1989

1	Do you feel irritable?
2	Do you feel fatigued?
3	Do you feel tense?
4	Do you have difficulties concentrating?
5	Do you have any loss of appetite?
6	Have you any numbness or burning in your face, hands or feet?
7	Do you feel your heart racing? (palpitations)
8	Does your head feel full or achy?
9	Do you feel muscle aches or stiffness?
10	Do you feel anxious, nervous or jittery?
11	Do you feel upset?
12	How restful was your sleep last night? (0 = very much so; 4 = not at all)
13	Do you feel weak?
14	Do you think you had enough sleep last night? (0 = very much so; 4 = not at all)
15	Do you have any visual disturbances? (sensitivity to light, blurred vision)
16	Are you fearful?
17	Have you been worrying about possible misfortunes lately?

Clinician observations

18. Observe behaviour for sweating, restlessness and agitation	
0	None, normal activity
1	
2	Restless
3	
4	Paces back and forth, unable to sit still

19. 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

20. Observe 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

TOTAL SCORE FOR ITEMS 1 - 20

1-20 = mild withdrawal | **21-40 = moderate withdrawal** | **41-60 = severe withdrawal** | **61 - 80 = very severe withdrawal**

Busto et al. *J Clin Psychophramacol*.1989

Many other scales…

- Benzodiazepine Dependence Questionnaire
- Benzodiazepine Dependence Self-Report Questionnaire
- Severity of Dependence Scale
- Benzodiazepine Craving Questionnaire Ashton check- list
- Benzodiazepine Withdrawal Symptom Questionnaire
- Penn Physician Withdrawal Checklist
- And more…

Withdrawal Management

Objective 3
Summarize the most common protocols reported for management of benzodiazepine withdrawal

A word of caution on evidence…

- Minimal prospective RCT for BZD withdrawal management
- Lack of literature published in recent decade
- Sporadic case series, uncontrolled prospective data
- Reminder: "*High dose*" vs "*therapeutic dose*"
  - Trials typically enroll patients on therapeutic dose

Determining Setting of Withdrawal Management

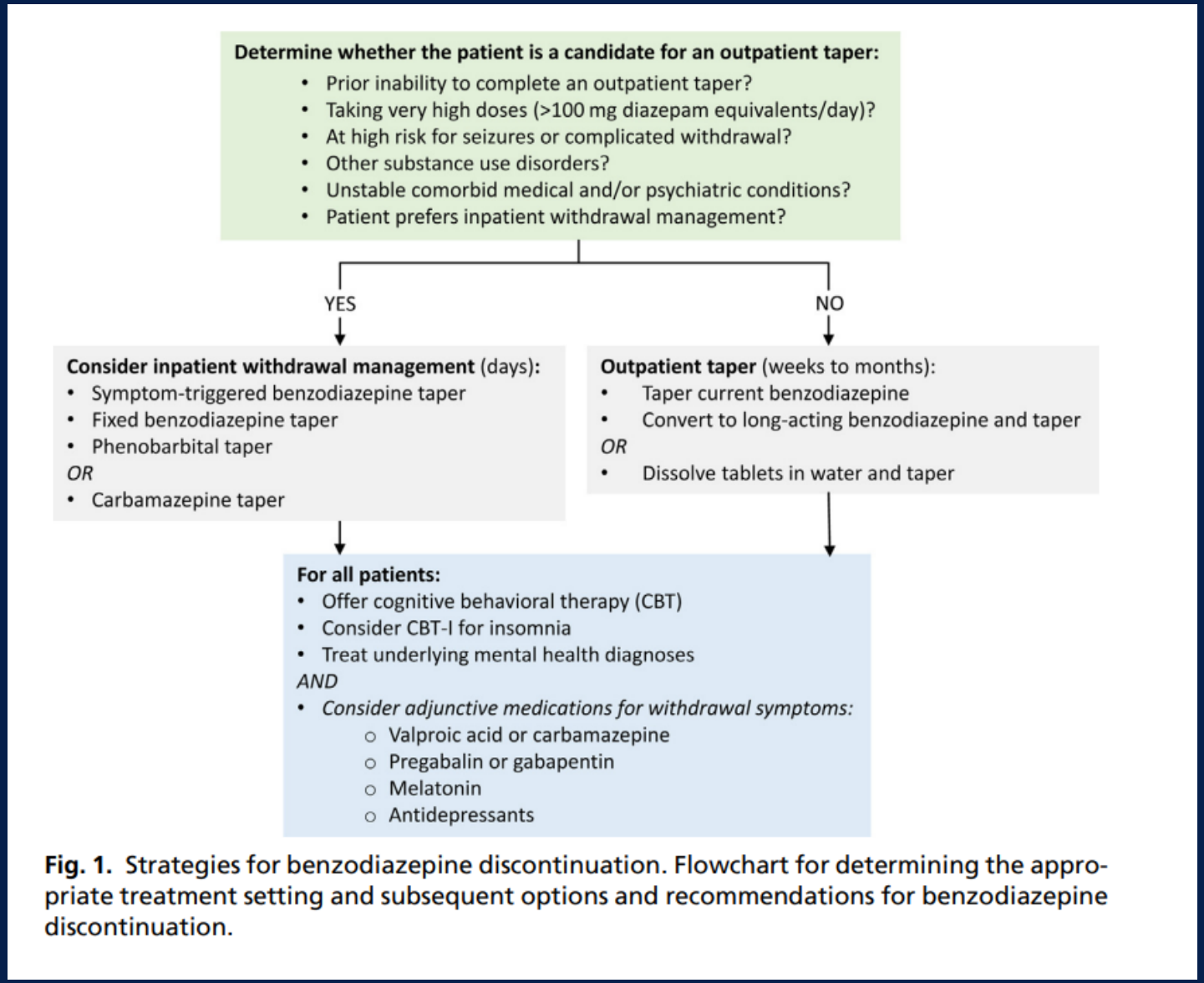


Fig. 1. Strategies for benzodiazepine discontinuation. Flowchart for determining the appropriate treatment setting and subsequent options and recommendations for benzodiazepine discontinuation.

Peng et al. *Med Clin North Am*. 2022

Traditionally, two strategies

1. Simple taper

- Continuity with provider to taper
- Already on a long acting agent
- Patients already on low dose/therapeutic dose

2. Substitution and taper

- On shorter acting agents
- May be better in patients using non-prescribed, high doses

ASAM Principles of Addiction Medicine (6th ed.).

1. Simple Taper

- First ½ of taper typically smoother, quicker and less symptomatic than last ½
- Reduce dose weekly or every other week
- Reduce by 5mg diazepam equivalents or 10% of the prior dose
- For the final 1/3 of the taper, slow the rate of reduction
  - Less tolerated than the initial portion of the taper
  - Can use adjunctive medications, (gabapentin, carbamazepine, etc)

ASAM Principles of Addiction Medicine. 6th ed.

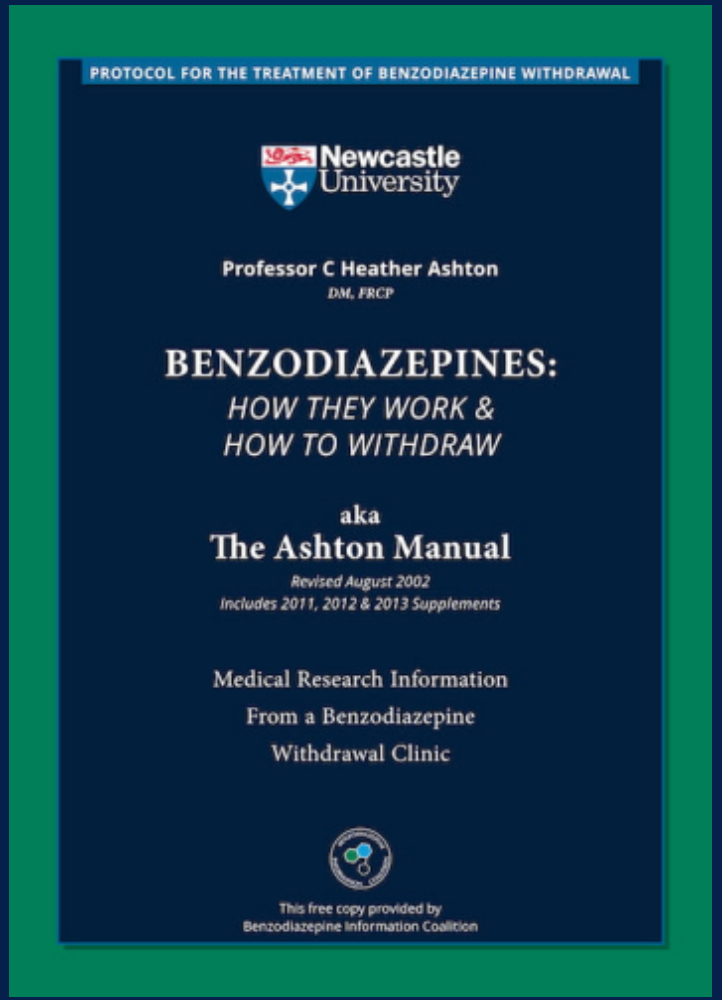
2. Substitution and Taper

- Estimate daily benzodiazepine dose
- Convert to long acting BZD, or phenobarbital
  - Clonazepam, chlordiazepoxide, diazepam
  - Liver dz: oxazepam, lorazepam
- Provide in divided doses

Dose equivalency calculator via MDCalc

Example protocols: Ashton Manual

- Manual used internationally for treatment of benzodiazepine withdrawal
- Example tables describing taper schedule's for low (therapeutic) and high dose benzodiazepine withdrawal
- Taper schedule over several months



Ashton. 2002

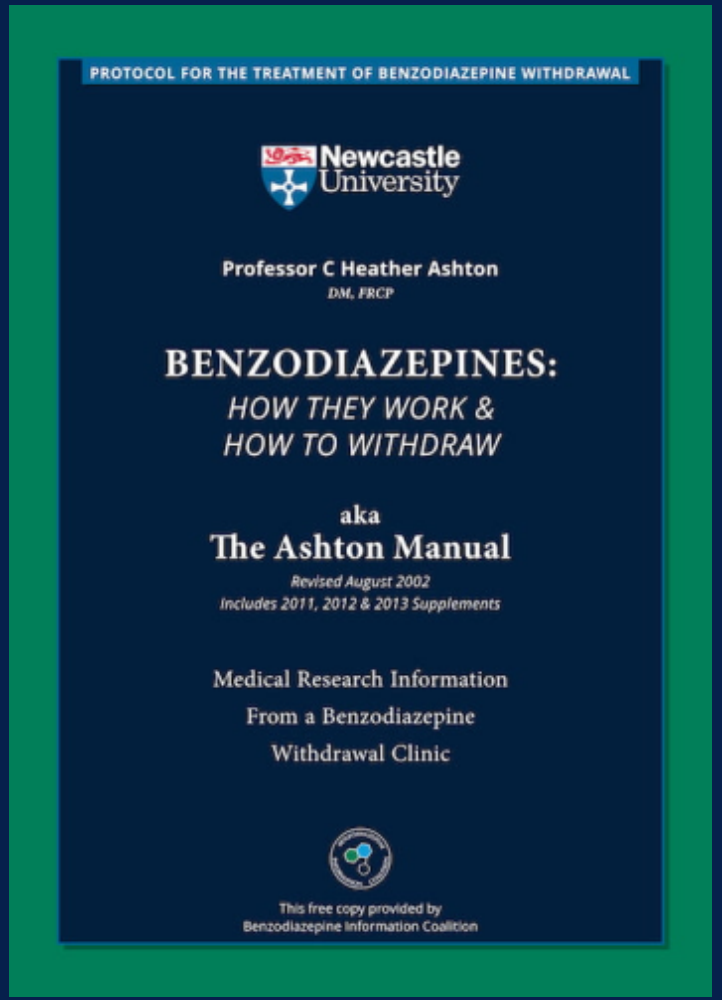
Example protocols: Ashton Manual

- High dose example. Alprazolam 6mg QD

Schedule 1. Withdrawal from high dose (6mg) alprazolam (Xanax daily with diazepam (Valium) substitution. (6mg alprazolam is approximately equivalent to 120mg diazepam)

	Morning	Midday/Afternoon	Evening/Night	Daily Diazepam Equivalent
Starting dosage	alprazolam 2mg	alprazolam 2mg	alprazolam 2mg	120mg
Stage 1 (one week)	alprazolam 2mg	alprazolam 2mg	alprazolam 1.5mg diazepam 10mg	120mg
Stage 2 (one week)	alprazolam 2mg	alprazolam 2mg	alprazolam 1mg diazepam 20mg	120mg
Stage 3 (one week)	alprazolam 1.5mg diazepam 10mg	alprazolam 2mg	alprazolam 1mg diazepam 20mg	120mg
Stage 4 (one week)	alprazolam 1mg diazepam 20mg	alprazolam 2mg	alprazolam 1mg diazepam 20mg	120mg
Stage 5 (1-2 weeks)	alprazolam 1mg diazepam 20mg	alprazolam 1mg diazepam 10mg	alprazolam 1mg diazepam 20mg	110mg
Stage 6 (1-2 weeks)	alprazolam 1mg diazepam 20mg	alprazolam 1mg diazepam 10mg	alprazolam 0.5mg diazepam 20mg	100mg
Stage 7 (1-2 weeks)	alprazolam 1mg diazepam 20mg	alprazolam 1mg diazepam 10mg	Stop alprazolam diazepam 20mg	90mg
Stage 8 (1-2 weeks)	alprazolam 0.5mg diazepam 20mg	alprazolam 1mg diazepam 10mg	diazepam 20mg	80mg

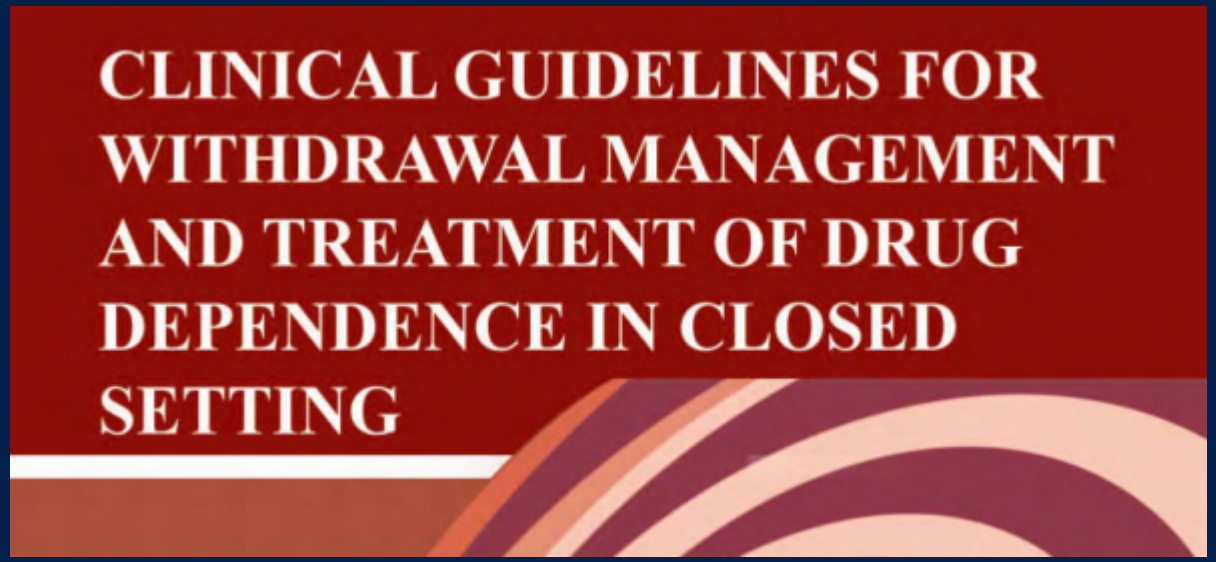
….Etc.



Ashton. 2002

Example protocols, WHO Guidelines:

- Provides treatment protocols in closed facilities (supervised withdrawal treatment, prison, etc)
- Protocols rely on substitution and taper method with diazepam



Geneva: World Health Organization. 2009.

Example protocols, WHO Guidelines:

Table 9 Low-dose benzodiazepine reducing schedule

Patients using less than 40mg/day diazepam equivalent				
	Time of dose			Total daily dose
	08:00	12:00	20:00	
Starting dose	5mg	5mg	5mg	15mg
1st reduction	5mg	2.5mg	5mg	12.5mg
2nd reduction	5mg	-	5mg	10mg
3rd reduction	2.5mg	-	5mg	7.5mg
4th reduction	-	-	5mg	5mg
5th reduction	-	-	2.5mg	2.5mg

Table 10 High-dose benzodiazepine reducing schedule

Patients using more than 50mg/day diazepam equivalent					
	Time of dose				Total daily dose
	08:00	12:00	17:00	21:00	
Starting dose	10mg	10mg	10mg	10mg	40mg
1st reduction	10mg	5 mg	5mg	10mg	30mg
2nd reduction	5mg	-	5mg	10mg	20mg
3rd reduction	-	-	-	10mg	10mg
4th reduction	-	-	-	5mg	5mg

Geneva: World Health Organization. 2009.

Phenobarbital

- Can also be used in “substitution and taper” strategy

- Example protocol of induction and taper when starting dose unknown
  - Can be used when degree of dependence challenging to determine, high dose use, multiple substance use, non prescribed use
  - Induction done in an inpatient setting with 24h medical monitoring and taper can be transitioned to intensive outpatient setting

ASAM Principles of Addiction Medicine. 6th ed.

Step 1

- Phenobarbital 60mg PO given q2h prn for CIWA-Ar > 15
- First 48 hours
- Hold dose for toxicity (somnolence, slurred speech, ataxia), resume if resolved
- Ideally mintored hourly

Step 2

- Total 48 hour dose dived by 2 to get 24h stabilizing dose
- Taper started after first 48 hours

Step 3

- Reduce by 20-30% every day for first half of taper
- Reduce by 10% Second half of taper
- Dose with largest dose at night

ASAM Principles of Addiction Medicine. 6th ed.

Taper Day	7:00	12:00	22:00	Total Dose
1	60 mg	30	120	210
2	30		120	150
3			120	120
4			90	90
5			90	90
6			60	60
7			60	60
8			30	30
9			30	30
10			15	15
11			15	15

ASAM Principles of Addiction Medicine. 6th ed.

Adjunctive medications

Anticonvulsants

- Carbamazepine
- Valproate[17]
- Gabapentin[18]
- Pregabalin[19]

Clonidine

Propranolol

Trazadone

- Decreased anxiety in tapered patients[20]
- ↑ in BZD free days[17]

2018 Cochrane Review concludes:

- Low to very low evidence
- No single intervention with more than 4 trials
- Not many trials on long term outcomes

Rickels et al. *Psychopharmacology.* 1999

Mariani et al. *Am J Drug Alchol Abuse*. 2016

Freynhagen et al. *CNS drugs*. 2016

Annseau et al. *J Clin Psychiatry*. 1993

Baandrup et al. *Cochrane Database Syst Review*. 2018

Evidence for taper

What Agent:

- Data present for benzodiazepine as taper agent
  - No longitudinal data for phenobarbital or head to head trials

Outcomes post taper:

- Varies greatly based on a number of factors[23]
  - Lower daily dose at start of taper
  - Self reduced dose prior to starting
  - Less severe dependence
  - **Worse outcomes for those who used alcohol and over 10mg diazepam equivalent daily**
- High dose use pre taper, approximately 25% BZD free 12 months post taper[24]
- Patients low dose, 80% free post-taper at 6 months[25]

Voshaar et al. *Can J Psychiatry*. 2006
Vorma et al. *Drug Alcohol Depend*. 2003
Curran et al. *Psychol Med.* 2003

What about our hospitalized patients?

Inpatient management

- Challenged by short length of stay
- Often benzodiazepine withdrawal not primary reason for admission
- Multiple withdrawal syndromes
- Medical complexity

It can get complicated, here is what was done in Ben's case…

Day 1

Started on CIWA with PRN lorazepam

(0mg)

Methadone 60mg

Day 2

Standing lorazepam 2mg q4h + CIWA with PRN lorazepam

(total 6mg)

Increase methadone 80mg

Day 3

Morning lorazepam held for sedation x2

<u>24h doses</u>

Methadone 80mg

Lorazepam 10mg

Day 4

Lorazepam PRN discontinued

<u>24h doses</u>

Lorazepam 12mg

Methadone 80mg

Day 5

Increase Methadone 90mg

<u>24h doses</u>

Lorazepam 12mg

Day 6

24h doses

Lorazepam 12mg

Methadone 90mg

Day 7

Increase Methadone 100mg

Switched to Clonazepam 2mg Q6H (TDD 80mg Diazepam equiv)

Re-started home Gabapentin 300mg TID

24h doses

Day 8

Increased gabapentin 600mg TID

Shared decision on Clonazepam taper plan

1 dose prn clonazepam 2mg given for anxiety

Day 9

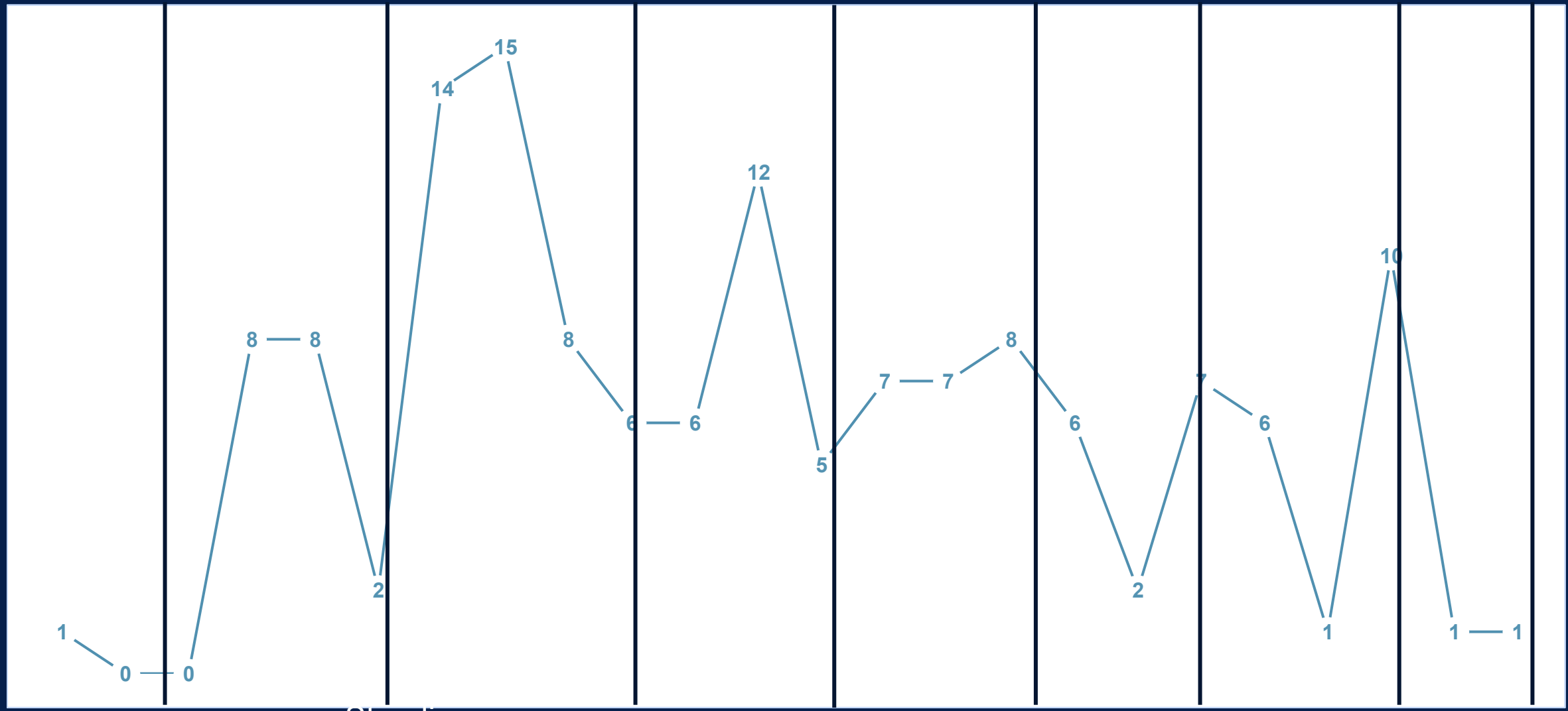
Methadone increased 110mg

Discharged to lower level of care

Hospital Day 1
36h since last BZD use

CIWA-Ar Scores

Day 8



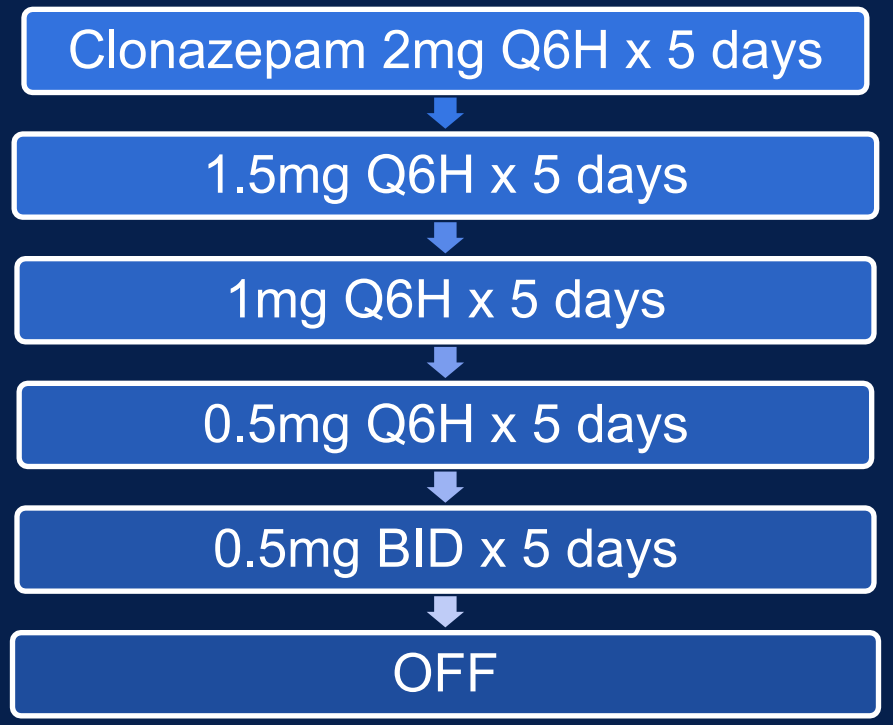
CIWA with sx triggered lorazepam

Standing lorazepam 2mg Q4H

Clonazepam 2mg Q6H

Discharge

- Clonazepam Taper
- Other Meds:
  - Gabapentin 600mg TID
  - Methadone 110mg
- *Self directed discharge 2 hours after arriving to medical respite*



Possible short-term taper options

- When possible best practice for extended taper

When not:

- Rapid substitution and taper
  - Taper long acting BZD by 50% each day over 3-7 days[14]
- Phenobarbital load and taper

Peng et al. *Med Clin North Am*. 2022

ELSEVIER

Journal of Substance Abuse Treatment 43 (2012) 331–334

Journal of Substance Abuse Treatment

Brief article

Safety and effectiveness of a fixed-dose phenobarbital protocol for inpatient benzodiazepine detoxification

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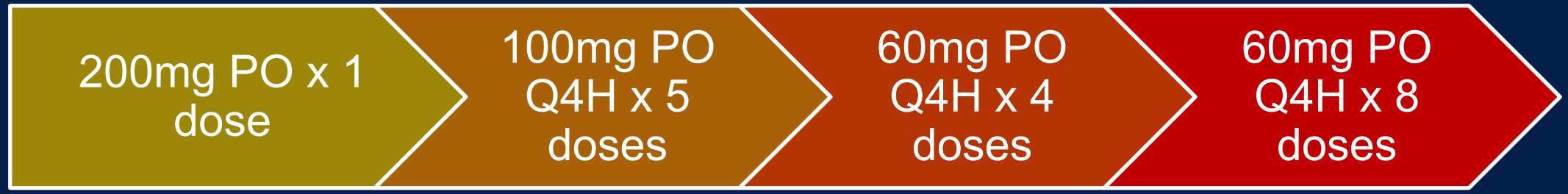
3 Day Phenobarbital Protocol



Kawasaki et al. *J Subst Abuse Treat.* 2013

Table 1
Characteristics of the 310 admissions

Median age (range)	36 (19–62)
Male gender	171 (55.2%)
Prior benzodiazepine detoxification	87 (28.1%)
Concurrent opioid detoxification	177 (57.1%)
Methadone maintenance	78 (25.2%)
Prior seizures	43 (13.9%)
Prior delirium	12 (3.9%)
Median length of stay in days (range)	3 (0–9 days)
Treatment setting	
Chemical dependence unit	276 (89.0%)
General medical service	29 (9.4%)
Psychiatry	4 (1.3%)
Obstetrics/Gynecology	1 (0.3%)

Kawasaki et al. *J Subst Abuse Treat.* 2013

Table 2
Phenobarbital protocol and percentage of doses held

Dose/Interval	No. of doses in protocol	Percentage who received all doses [a]	Percentage of doses held because of sedation [a]
200 mg once	1	86	14
100 mg every 4 hours	5	58	17
60 mg every 4 hours	4	70	14
60 mg every 8 hours	3	56	25

[a] Patients who were discharged against medical advice were not included.

Kawasaki et al. *J Subst Abuse Treat.* 2013

Table 4
Main outcomes

Seizures	0 (0%)
Delirium	3 (1.0%)
Falls	0 (0%)
Sedation	84 (27.1%)
Left against medical advice	53 (17.1%)
ED visits within 30 days	22 (7.1%)
Readmission with 30 days	19 (6.1%)

Note. ED = emergency department.

Kawasaki et al. *J Subst Abuse Treat.* 2013

Management of Benzodiazepine Use Disorder

Objective 4

Discuss the chronic management of benzodiazepine use disorder

Case Part IV

- Ben presents to an outpatient addiction medicine bridge clinic for benzodiazepine use disorder
- Started on a clinic taper protocol:
  - Substitution and taper:
    - Stabilize on maximum dose is 40mg diazepam
  - On day 3 of protocol, returns after feeling his symptoms were unmanaged and using additional non-prescribed benzodiazepines, urine positive for amphetamines
- Discharged from protocol and recommended a higher level of care

Management of Benzodiazepine Use Disorder

- Prevention
- Benzodiazepine discontinuation
  - Brief letters
  - Tapers
  - Behavioral therapies

Prevention

- **Prescribing practices**
  - Has been described as “our other prescription drug problem”[26]
  - Most guidelines suggest short term (2-4 weeks) use rather than long term use
  - *To the contrary*:
    - Evidence for safety in long term BZD treatment for treatment resistant generalized anxiety disorder[27]
    - Cohort of 12598 patients with BZD use over 5 years, **only 3.7%** with dose escalation > 40mg equivalents diazepam[28]
- **Brief interventions in primary care** – tailored patient letter[29], psychoeducation[30], shown to decrease reduction in benzodiazepine use

Lembke et al. *N Engl J Med*. 2018

Stien & Sareen. *N Engl J Med*. 2015

Alessi-Severini et al. *Psychiatr Serv*. 2016

Ten Wolde et al. *Addiction*. 2008

Mugunthan et al. *Br J Gen Pract*. 2011

Discontinuation

- No FDA approved medications for BUD
- Discussed extensively in withdrawal management
  - Taper protocol developed and individualized to patient
- Reminder, long term outcomes vary on discontinuation, likely dependent on low vs high dose use

- **CAUTION:**
  - May be harm associated in tapering patients on chronic benzodiazepine therapy

Original Investigation | Pharmacy and Clinical Pharmacology

December 20, 2023

Benzodiazepine Discontinuation and Mortality Among Patients Receiving Long-Term Benzodiazepine Therapy

Donovan T. Maust, MD, MS[1,2,3]; Kierstdea Petzold, MS[2]; Julie Strominger, MS[2]; et al

» Author Affiliations | Article Information

JAMA Netw Open. 2023;6(12):e2348557. doi:10.1001/jamanetworkopen.2023.48557

- Comparative effectiveness study with trial emulation approach
- Large commercial insurance database 2013 to 2017
- Benzodiazepine discontinuation: defined as no BZD coverage for 31 days after approximately 90% coverage over a year
- **Outcomes:**
  - Small absolute increases in mortality, nonfatal overdose, suicidal ideation, and emergency department use.

Maust et al. *JAMA Network Open*. 2023

Behavioral therapies

- **Cognitive behavioral therapy + Taper**
  - Shown the most benefit in benzodiazepine abstinence in 4 weeks and 3 months though no benefit on 6 and 12 mo follow up (moderate quality)
  - No benefit from CBT alone in discontinuation
- **Motivational Interviewing**
  - Modest benefit in small studies though no significant difference in outcomes (abstinence or reduced use) on metanalysis
- No evidence standardized interview, self-help booklet, relaxation, e-counselling, enhance skills training improve outcomes with or without taper

Darker et al. *Cochrane Database Syst Rev.* 2015

Is abstinence all we can offer?

- How does a harm reduction paradigm fit into this framework?
- Standard of care = complete taper off benzodiazepine
- What is the treatment goal? Is it always abstinence?
- Is there a role for prescribed benzodiazepines as agonist therapy in patients with existing BUD?

"Maintenance" in patients with high dose use?

- Little data to guide practice
- A taper to a therapeutic dose long acting agent
- Could there be a role in some patients
- Naturalistic study of patients on methadone (n=33)
  - BZD misused was switched to clonazepam and either 1) taper completely or 2) taper to maintenance dose
    - Abstinence group: 27% BZD free at 2 mo
    - Maintenance group: 78% without additional BZD use on top of maintenance at 2 mo

Weizman et al. *Aust N Z J Psychiatry*. 2003

Summary

- Rising rates of benzodiazepine involved overdoses
- Consensus guidance is a prolonged taper over weeks to months tailored to the individual
- Role for adjunctive medications and cognitive behavioral therapy to improve outcomes
- No FDA approved pharmacotherapy with limited data for interventions in chronic management of BUD
- Current treatment approaches should be individualized with a harm reduction based approach

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