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Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

BEST PRACTICES FOR MANAGEMENT OF BENZODIAZEPINE USE DISORDER

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SPEAKER DISCLOSURES

✓ No conflict of interest

PLANNER DISCLOSURES

The following series planners have no relevant conflicts of interest to disclose; other disclosures have been mitigated.

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What has been your experience managing chronic benzodiazepines use?

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OBJECTIVES

1. Review the epidemiology of benzodiazepine use disorder
2. Review the current models for management for benzodiazepines use disorder
3. Discuss challenges with management of benzodiazepines use disorder
4. Discuss management of benzodiazepines use disorder through a harm reduction lens

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"THIS HAPPENS ONCE EVERY FEW LIFETIMES…"

M is a 35 y.o F w/ hx of newly diagnosed thyroid ca, recurrent sinus infection, MCV six months ago presented to your clinic for detox from benzodiazepines. She started buying alprazolam from a pharmacy in Mexico while on vacation about two years ago. Her first purchase of 30 tablets of alprazolam 1mg lasted 6 months. More recently, she has been traveling to Mexico every 2-3 months to purchase more tablets. She ran out of supply 2 weeks ago and have been borrowing from her friends.

How would you classify M's benzodiazepine use?

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SEDATIVE HYPNOTIC USE DISORDER

- Benzodiazepines, Barbiturates, Z-drugs and Carbamates
- Use, “mis-use,” Use Disorder
- Co-occurring with other Substance Use Disorders (Votaw et al, 2019)
  - OUD: 20x more misuse than general population
  - AUD: 3-4x more misuse than general population

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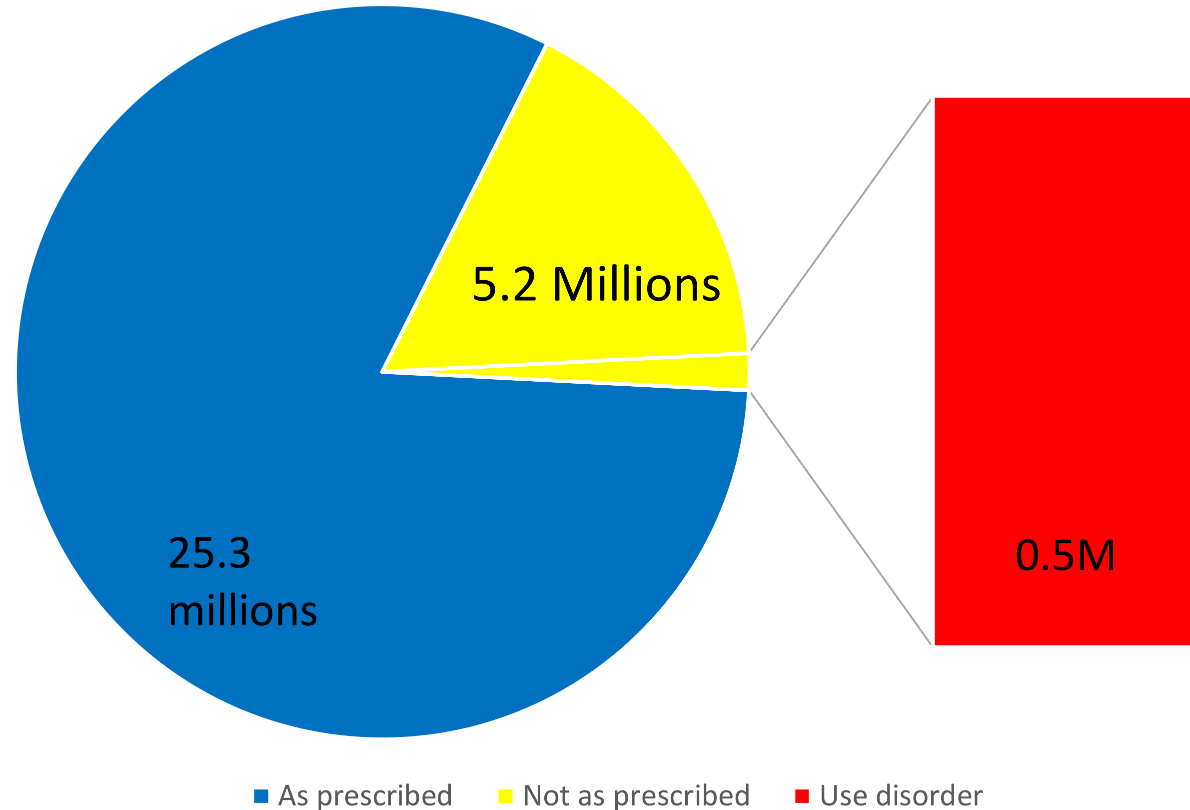

Blanco et al, 2018

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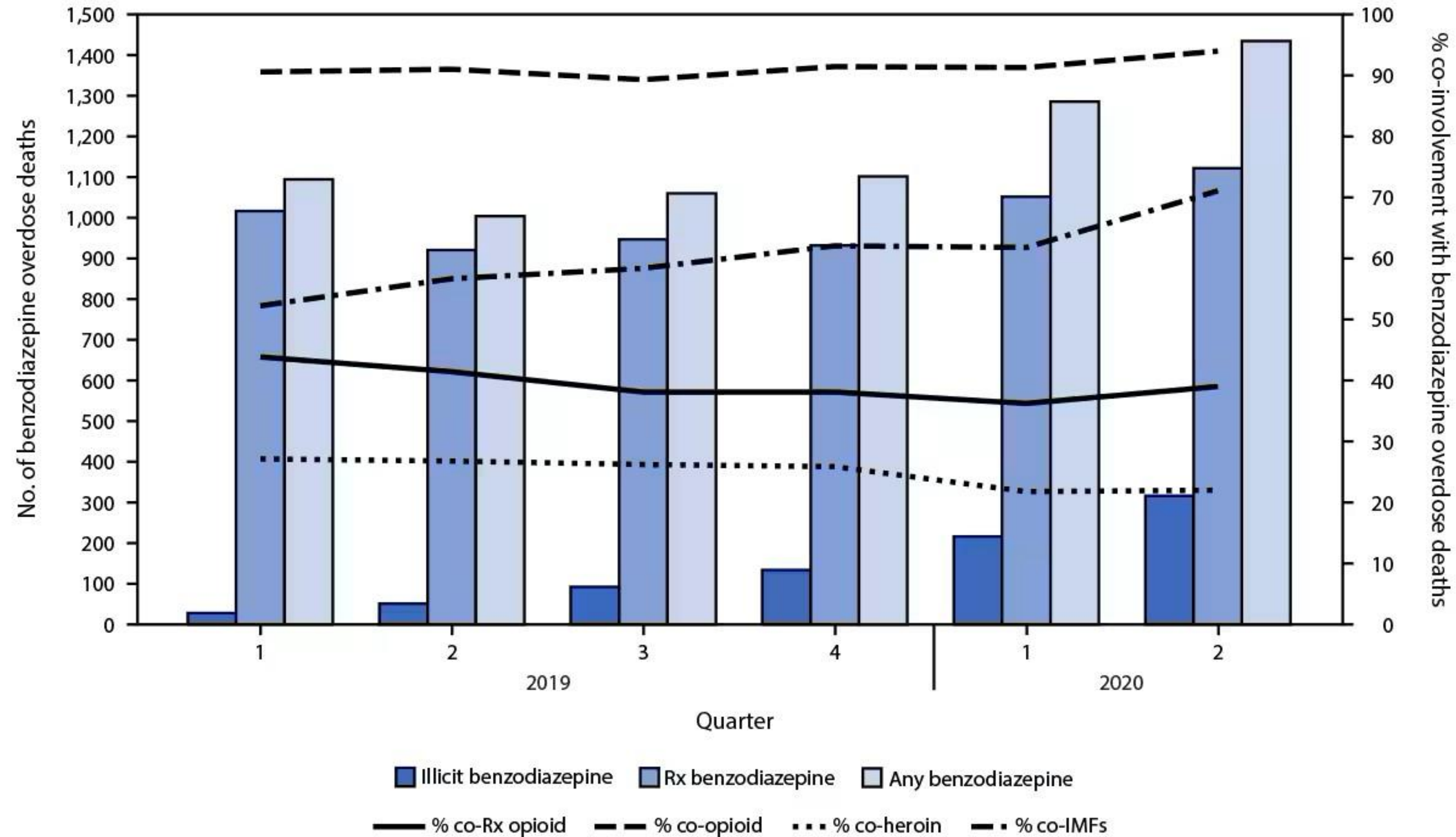
BENZODIAZEPINES OVERDOSE
(STATE UNINTENTIONAL OVERDOSE REPORTING SYSTEM)



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Cl-

GABA

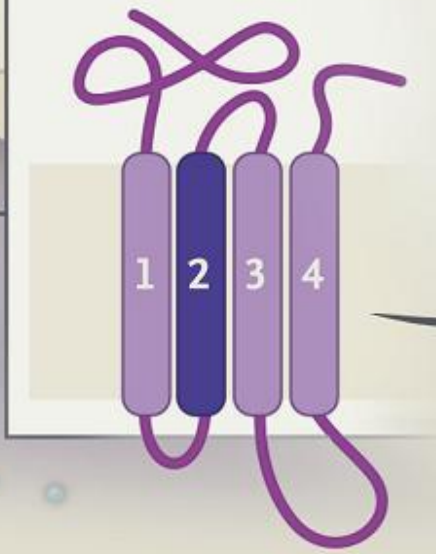
Benzodiazepines

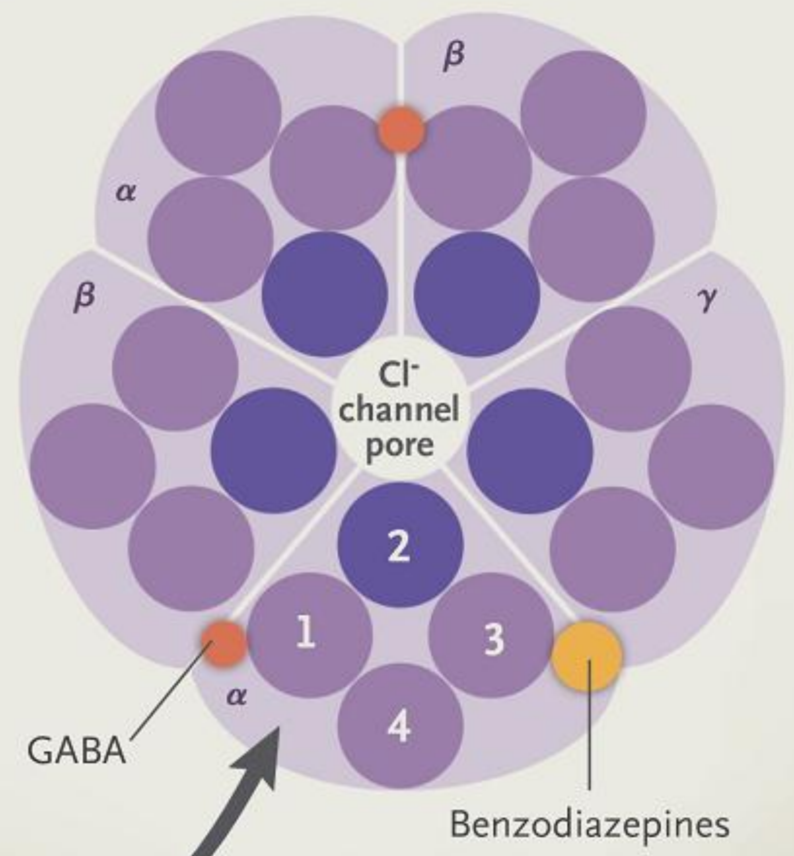
CELL MEMBRANE

CYTOPLASM

Cl-

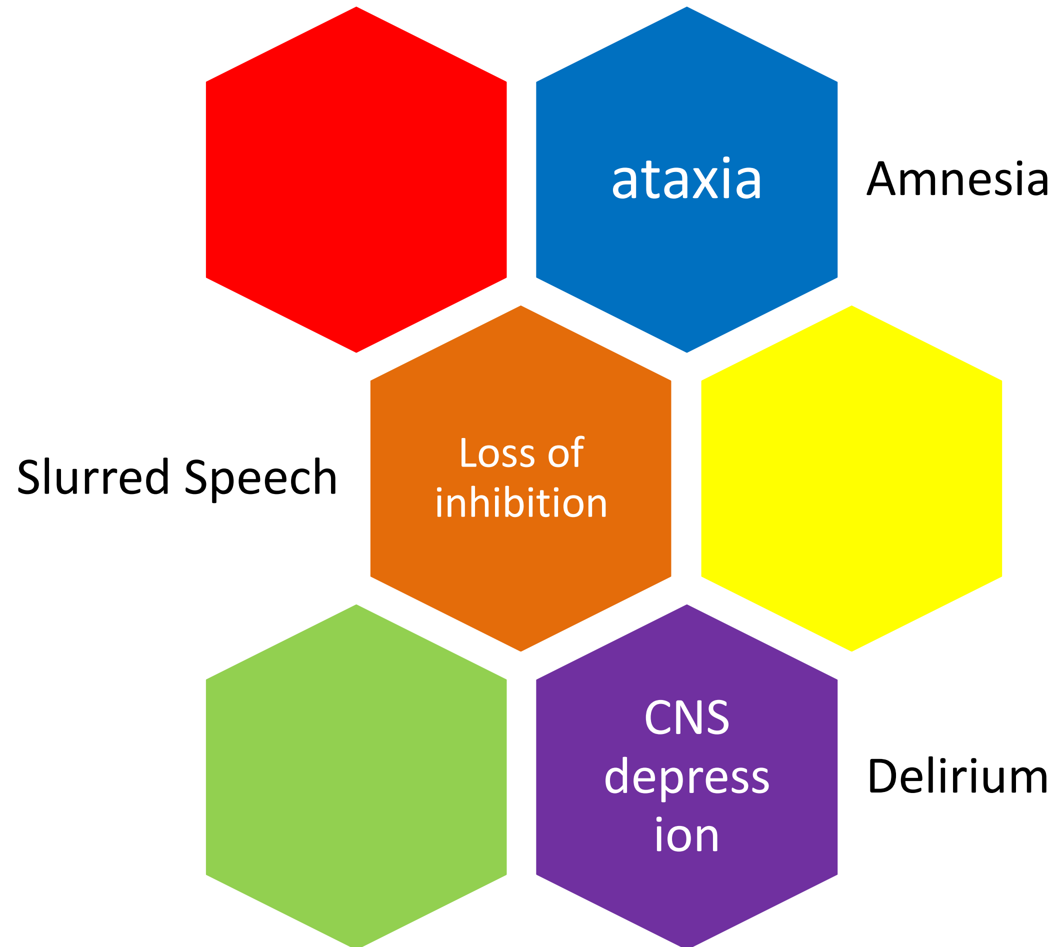
Opening of the chloride channel is potentiated by GABA agonists such as benzodiazepines





"THESE CHEMICALS HIT ME LIKE WHITE WINE" (BENZO INTOXICATION)

- Focusing on the ABCs
- Supportive Care
- Activated charcoal not recommended (risk of aspiration)



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FLUMAZENIL

- reverse the sedative effect of short acting benzodiazepines
- Associated with risk of cardiac arrythmia, seizures
  - Rapid titration of flumazenil
  - Co-ingestion of other substances that lower seizure threshold
  - Patients with physiologic dependence
- Preliminary studies using flumazenil for withdrawal management (due to the partial agonist property)
  - Weak binding, partial agonist at benzodiazepines sites

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How would you manage M's use disorder

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"THE HOSPITAL IS A DRAG…" INPATIENT VS OUTPATIENT MANAGEMENT

- Inability to complete outpatient taper
  - Hx of incomplete tapers prior
  - Severe Use Disorder/more compulsive habits- "…if I had more, I would take more"
- High risk for seizures or complicated withdrawal
- Unstable comorbid medical or psychiatric conditions
- ? Other unstable substance use disorders
- Patient's preference

Peng et al, 2020

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"…WORST SLEEP I EVER HAD" (WHY IS BENZO WITHDRAWAL SO HARD TO MANAGE)

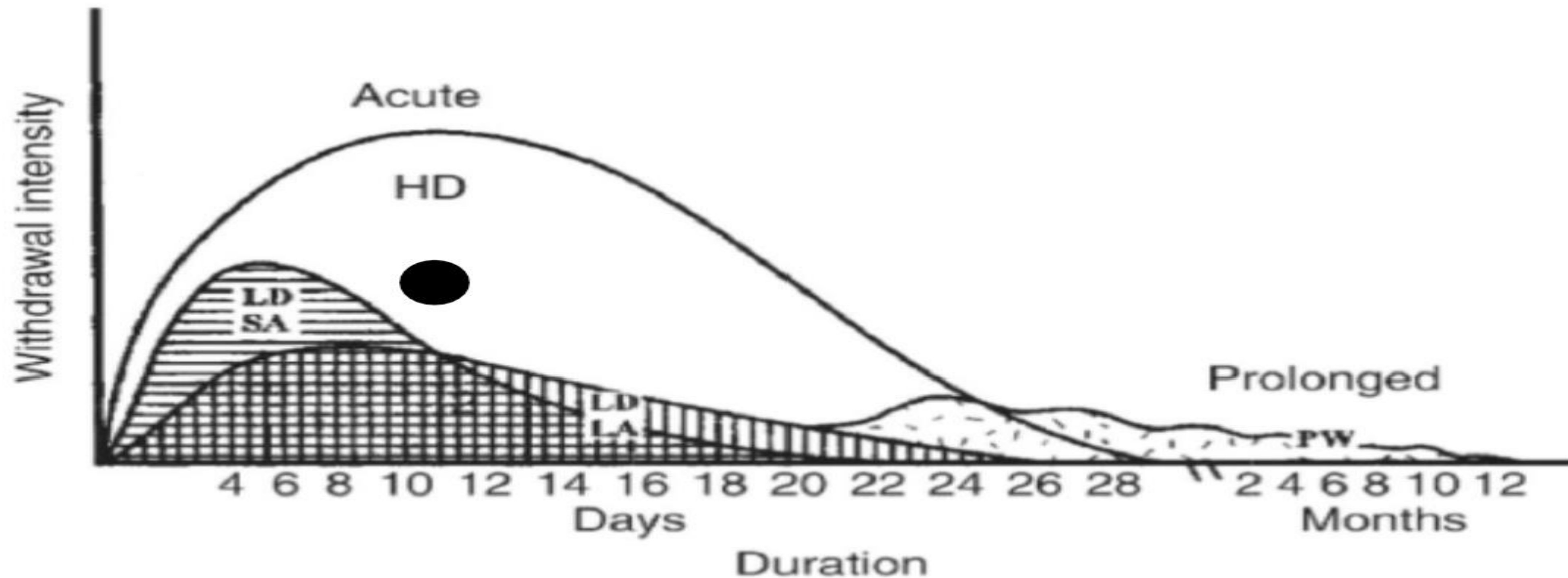

Figure 52-1 Time course of sedative–hypnotic withdrawal. Time course and potential withdrawal intensity as influenced by dose and duration of drug action. HD, high dose; LD, low or therapeutic dose; SA, short acting; LA, long acting; PW, prolonged withdrawal.

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BENZODIAZEPINES WITHDRAWAL

- Factors effecting withdrawal
  - Pharmacokinetics
    - Short acting – occurs <24 hours of last use, peaks 1-5 days
    - Long acting – occurs <5 days, peaks 1-9 days
  - Potency
    - More potent, short acting – higher tolerance, more intense withdrawal
  - Doses and duration
    - Usual prescribed doses
    - Doses > 3-5x of upper therapeutic limits

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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

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POST ACUTE WITHDRAWAL SYMPTOMS

- Self-limited, fluctuating day to day, persisting weeks to months after the acute symptoms
- Symptoms
  - Insomnia
  - Perceptual disturbances
  - Tremors
  - Sensitivity to light and touch
  - Tinnitus
  - Anxiety
- Exclude recurrence of psychiatric condition

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ADJUNCTIVE MEDICATIONS

AEDs
-Carbamazepine
-Valproate
-Gabapentin
-Pregabalin

Clonidine

Prazosin

Trazadone

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"THAT CHILD'S PLAY BACK IN SCHOOL…"

R is a 41 y.o M w/ hx of hypothyroidism, panic disorder, MDD, OUD on methadone, chronic benzodiazepine use and housing instability presented to your outpatient clinic for management of chronic benzodiazepine use. R was started on clonazepam in his teens for panic disorder. He was recommended a taper 3-4 years after the initial prescription, did not tolerate the withdrawal symptoms so started purchasing benzodiazepines on the internet for the next few years. He was incarcerated in 2014 and underwent a rapid taper which resulted in a withdrawal seizure. He resumed non-Rx benzodiazepines after release. He reports currently using several "Xanax bars" daily. He is on 125mg methadone daily and continues to smoke several "blue pills" a day.

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Would you start the patient on a taper?

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What expectations/goals would you set with the patient?

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YOU'RE READY TO TAPER…ARE YOU?

- Patient's buy-in….
- Evaluate and treat co-occurring disorders
- How much time do you have?
  - Aims for weeks – months, slower for higher doses
- Which benzo to use?
  - Stay on current benzo – lower doses, on long acting, patient driven
  - Switch to long acting: clonazepam, chlordiazepoxide, diazepam – from shorter acting benzos, patients using non prescribed benzos
- Adjunctive Medications
- Psychotherapy support
  - CBT+ taper have the most benefit in benzodiazepine abstinence at 4 weeks and 3 months, benefits less clear at 3 and 12 months follow up
  - No benefit for CBT alone
  - MI modest benefit in small studies

Darker et al, 2015

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Study protocol | Open access | Published: 20 March 2013

An educational intervention to reduce the use of potentially inappropriate medications among older adults (EMPOWER study): protocol for a cluster randomized trial

Philippe Martin, Robyn Tamblyn, Sara Ahmed & Cara Tannenbaum

Trials **14**, Article number: 80 (2013) | Cite this article

7602 Accesses | **32** Citations | **1** Altmetric | Metrics

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ADDICTION

SSA SOCIETY FOR THE STUDY OF ADDICTION

Long-term effectiveness of computer-generated tailored patient education on benzodiazepines: a randomized controlled trial

First published: 13 March 2008 | https://doi.org/10.1111/j.1360-0443.2008.02141.x | Citations: 37

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OUTCOME POST TAPER VARIES GREATLY

- High dose use pre-taper, 25% bzd free 12 months post taper
- Low dose use, 80% free-post taper at 6 months
- Worse outcomes for those who used alcohol and over 10mg diazepam equivalent daily
- How we taper matters-
  - Gradual dose reductions and brief interventions provided superior cessation rates at post treatment to routine care
  - Psychological treatment plus GDR were superior to GDR alone
  - Abrupt substitution of benzodiazepines by other pharmacotherapy less effective than GDR alone

Voshaar et al, 2006
Vorma et al, 2003
Parr et al, 2009

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DESIGNING A TAPER PLAN

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Pharmacology of benzodiazepines used to treat anxiety symptoms/disorders

Drug	Adult oral total daily dose (mg)*	Comparative potency (mg)¶	Onset after oral dose (hours)	Metabolism	Elimination half-life (hours)Δ
Alprazolam	0.5 to 6	0.5	1	CYP3A4 to minimally active metabolites.	11 to 15 16 (older adults) 20 (hepatic impairment) 22 (obesity)
Alprazolam extended release	0.5 to 6 once daily	0.5	1		
Bromazepam◊ §	6 to 30	7.5	1	CYP1A2. No active metabolite.	8 to 20
Chlordiazepoxide§	5 to 100	10	1	CYP3A4 to active metabolites.	30 to 100 Prolonged in older adults and hepatic impairment
Clonazepam	0.5 to 4	0.25 to 0.5	0.5 to 1	CYP3A4. No active metabolite.	18 to 50
Clorazepate	15 to 60	7.5	0.5 to 1	CYP3A4 to active metabolite.	36 to 200
Diazepam	4 to 40	5	0.25 to 0.5	CYP2C19 and 3A4 to active metabolites.	50 to 100 Prolonged in older adults and renal or hepatic impairment
Lorazepam immediate release	0.5 to 6 0.5 to 4 (hypnotic)	1	0.5 to 1	Non-CYP glucuronidation in liver. No active metabolite.	10 to 14
Lorazepam extended release	1 to 6 mg¥	1	0.5 to 1	Non-CYP glucuronidation in liver. No active metabolite.	13 to 27
Oxazepam	30 to 120 15 to 30 (hypnotic)	15 to 30	1 to 2	Non-CYP glucuronidation in liver. No active metabolite.	5 to 15
Prazepam◊ §	15 to 60	15	2 to 3	CYP3A4 to active metabolites.	30 to 200 Prolonged in older adults

Data on drug metabolism and activity of metabolite(s) are for assessment of potential for CYP drug interactions and risk of accumulation. Risk of accumulation is greater, and dose reduction necessary, for older or debilitated adults and for patients with renal or hepatic insufficiency.

* Range of usual **total** daily dose for treatment of adults with anxiety or panic disorder typically given in divided doses two to four times daily.

¶ Important: Data shown are approximate equal potencies relative to lorazepam 1 mg orally and are NOT recommendations for initiation of therapy or for conversion between agents.

Δ Half-life of parent drug and pharmacologically active metabolite, if any.

◊ Not available in the United States.

§ Use only when other preferred agents are unavailable or not tolerated.

¥ To be used only when converting from immediate release lorazepam. Total daily dose is equal to the current total daily dose of immediate release lorazepam. Dose is given once daily in the morning after discontinuing immediate dose lorazepam tablets the night before.

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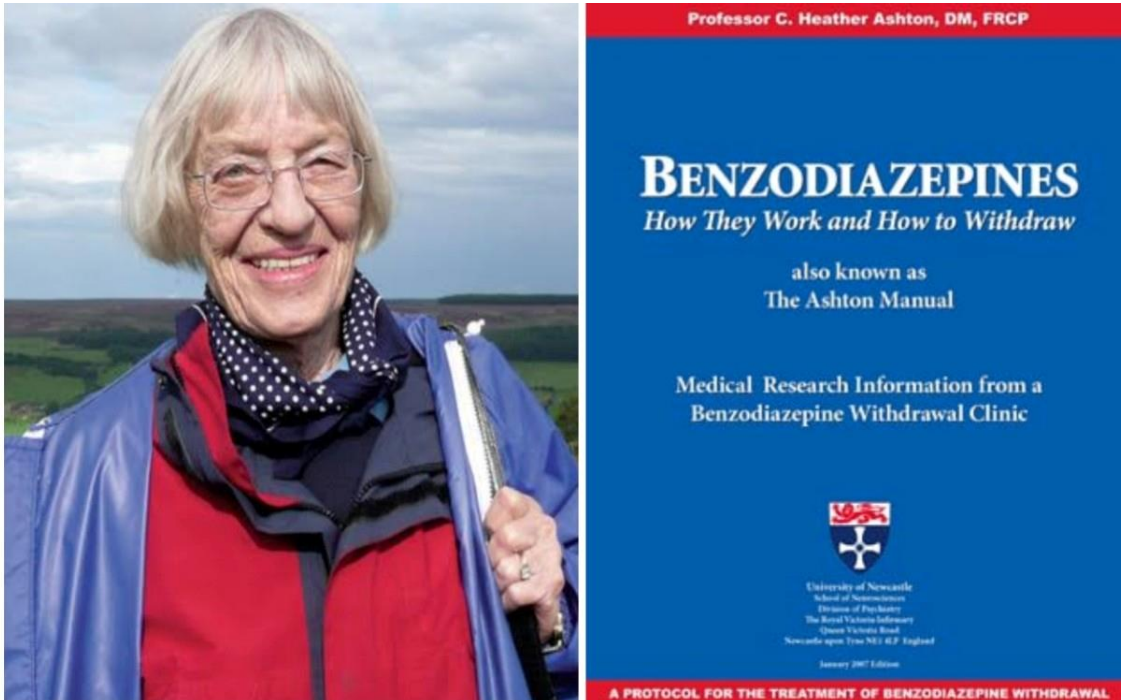
EXAMPLES OF SLOW TAPERS OVER MONTHS USING SIMPLE TAPER OR SUBSTITUTION AND TAPER STRATEGIES

benzo.org.uk : Benzodiazepines: How They Work & How to Withdraw, Prof C H Ashton DM, FRCP, 2002



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

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"THERE WAS NO CHANCE TRYING TO BE THE GREATEST IN THE LEAGUE"

? Phenobarbital Substitution taper

- Helpful when degree of dependence is difficult to determine (non Rx use, unknown amount, multiple substances, high doses)
- Requires (at least) initial inpatient monitoring
- No head to head trial for bzd vs phenobarbital
- Contraindicated in hepatic impairment

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SYMPTOMS TRIGGERED

Phenobarbital 60mg PO q2H PRN x 48H for CIWA-Ar >15

- Hold doses for signs of toxicity
- Monitored hourly

Total dose from previous 48H divided by 2 to get the 24 hours stabilizing dose

Reduce the 24 hours stabilizing dose by 20-30% everyday for the first half of the taper. Then 10% every other other day for the second half of the taper

FIXED DOSE

200mg

100mg q4H x 5 doses

60mg q4H x 4 doses

60mg q8H x 3 doses

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KAWASAKI ET AL, 2012

- Record review of 310 patients treated w/ 3 days fixed dose phenobarbital taper for benzodiazepines dependence between 2004-2009
- Taper was well tolerated, ¼ patients had at least one dose held due to sedation

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.

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"WHERE'S THE TROPHY?"

- R is started on clonazepam 2mg TID (a previously stable dose per patient) and levothyroxine 25mcg daily. At his 2 weeks follow up, patient reports increased anxiety, diarrhea, GI upset which he attributes to opioid withdrawal so have been increasing his fentanyl use. He has not been using non-Rx benzo.

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How would you manage his clonazepam dose at this point

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- Patient was continued on clonazepam 2mg TID, levothyroxine lowered by 25% total weekly dose. Unfortunately, he did not return for the next follow up.
- He was later admitted to the hospital due to opioid overdose. He was incarcerated during the period of absence. Methadone was not continued and he was put on a rapid diazepam taper during the incarceration. He used an unknown amount of fentanyl on release (with the intention to overdose). He also reports use of non Rx benzodiazepines. Methadone was restarted and patient was placed on CIWA-B with lorazepam by the primary team

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Addiction Medicine was consulted. How would you manage his benzodiazepines use?

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"WHO ARE WE TO FIGHT THE ALCHEMY?" (?BENZODIAZEPINES MAINTENANCE THERAPY)

Weizman et al, 2003

- Open, naturalistic study on patients in methadone maintenance treatment with benzodiazepines dependence (DSM IV criteria)
- N=66
- Patients with benzodiazepines dependence were given a choice of clonazepam detoxification (CDTX) or clonazepam maintenance (CMT)
- Both groups started with 6mg clonazepam daily. CDTX group had a taper over 6 weeks. CMT group was gradually tapered until a dose that patient reports is effective for their symptoms, takes 4-8 weeks
- Failure = benzo use above what is prescribed by the clinic on two consecutive days

Table 1. *Success and failure rates of clonazepam detoxification (CDTX) and maintenance (CMT) at 2, 4, 6, 8, 10 and 12 months*

	2 months	4 months	6 months	8 months	10 months	12 months
CDTX	n = 33	n = 31	n = 30	n = 30	n = 29	n = 29
Success	9 (27.3%)	7 (22.6%)	5 (16.7%)	5 (16.7%)	4 (13.8%)	4 (13.8%)
Failure	24 (72.7%)	24 (77.4%)	25 (83.3%)	25 (83.3%)	25 (86.2%)	25 (86.2%)
CMT	n = 33	n = 33	n = 32	n = 29	n = 28	n = 26
Success	26 (78.8%)	25 (75.8%)	24 (75%)	20 (69%)	19 (65.5%)	17 (65.4%)
Failure	7 (22.2%)	8 (24.2%)	8 (25%)	9 (31%)	9 (34.5%)	9 (34.6%)

Mean maintenance clonazepam dose 2.64 (SD 1.46)

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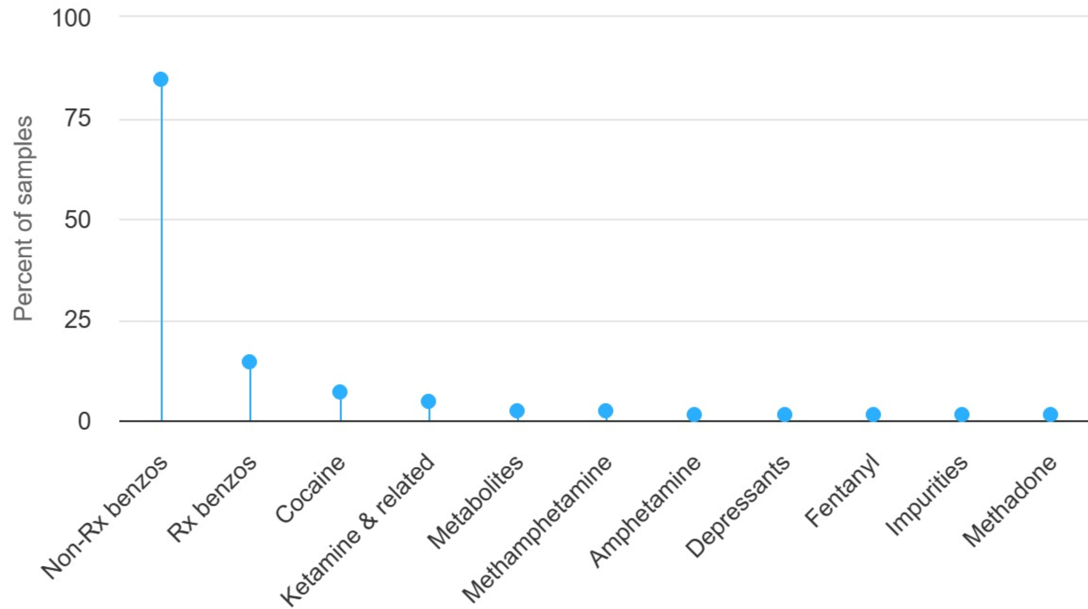
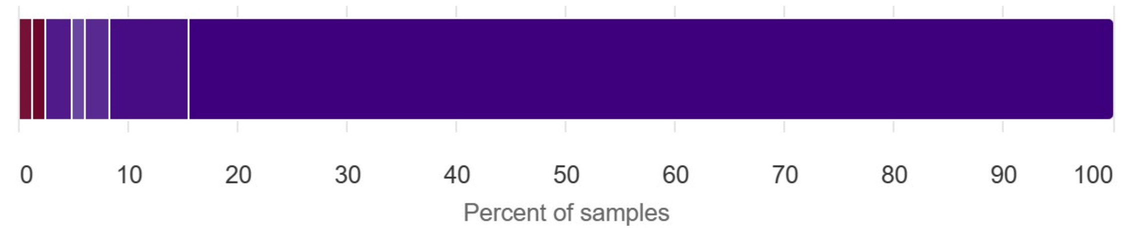
“HE JOKES THAT IT’S HEROIN, BUT THIS TIME WITH AN E”





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SELECTED SAFER USE STRATEGIES

- Drug Checking
  - Can influence drug use behaviors (Betzlet et al, 2021)
- Avoid Using Alone
  - Virtual Spotting App
- Naloxone

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TOUCH DOWN…

- Benzodiazepines tapering can be a long and challenging process. Patient engagement is important
- Cognitive Behavior Therapy has a role in long term outcome
- No current pharmacological treatment for benzodiazepine use disorder although some patients may benefit from benzodiazepine maintenance therapy.

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