

Benzodiazepines: Should We Worry About Them?

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Learning Objectives

At the completion of this activity, participants will be able to:

1. Explain the basic pharmacology of benzodiazepines
2. Identify the therapeutic role and potential risks associated with benzodiazepine use
3. Recognize the management of benzodiazepine use disorder/physiologic dependence

Outline

- Benzodiazepines (BZDs) and nonbenzodiazepines (“z-drugs”), “designer” BZDs
- Pharmacologic properties
- Therapeutic uses
- Potential risks with BZD use
- Use and misuse, physiologic dependence, withdrawal
- Strategies for withdrawal management

Disclosures

- Dr. Gandhi, faculty for this activity, has no financial relationship(s) to disclose. None of the planners for this activity have financial relationships to disclose.



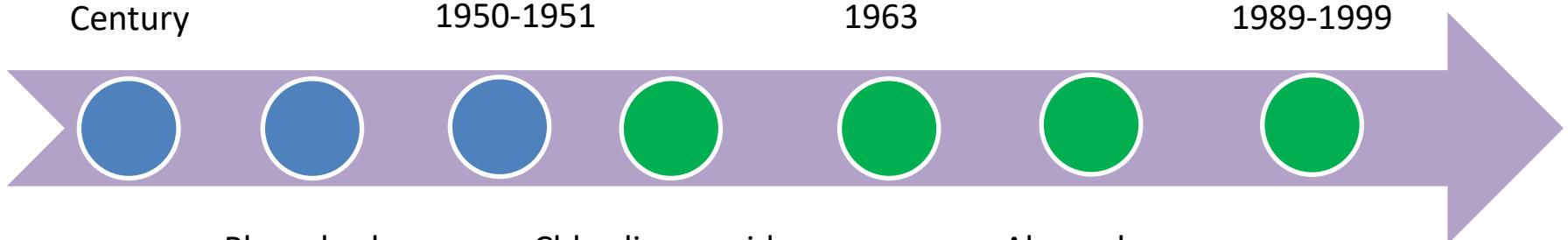
Timeline of Sedative-Hypnotics/Anxiolytics

Bromides,
chloral,
paraldehyde,
barbituric
acid: 19th
Century

Meprobamate/
methaqualone:
1950-1951

Diazepam:
1963

“Z- drugs”:
1989-1999



Phenobarb:
1912

Chlordiazepoxide
(Leo Sternbach):
1955

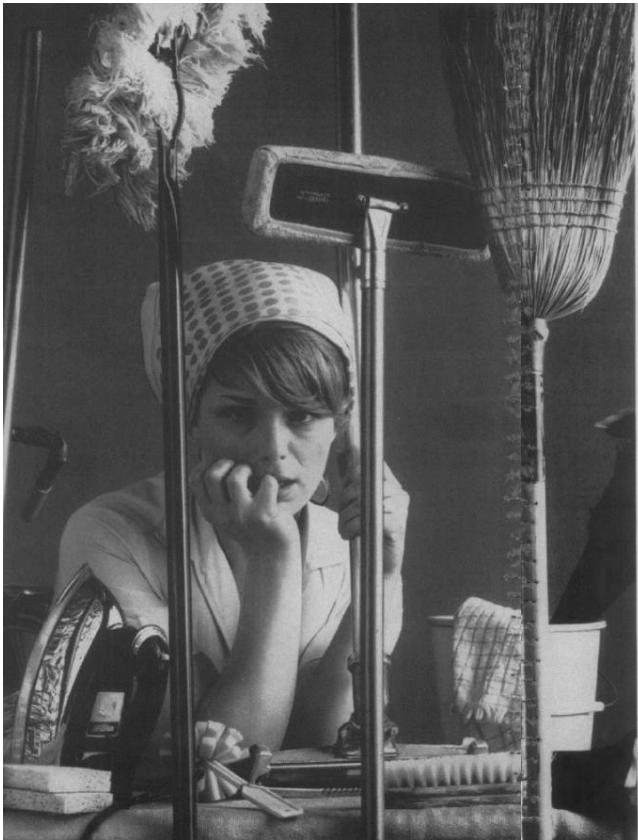
Alprazolam:
1971

A Troubled History of Aggressive Marketing...



Newspaper Headline: "*The Drug That Tames Tigers - What Will It Do For Nervous Women?*"

...Specifically Targeting Women



You can't set her free. But you can help her feel less anxious.

You know this woman.

She's anxious, tense, irritable. She's felt this way for months. Beset by the seemingly insurmountable problems of raising a young family, and confined to the home most of the time, her symptoms reflect a sense of inadequacy and isolation. Your reassurance and guidance may have helped some, but not enough. SERAX (oxazepam) cannot change her environment, of course. But it can help relieve anxiety, tension, agitation and irritability,¹ by strengthening her ability to cope with day-to-day problems. Eventually—when she regains confidence and composure—your counsel may be all the support she needs.

Indicated in anxiety, tension, agitation, irritability, and anxiety associated with depression.

May be used in a broad range of patients, generally with considerable dosage flexibility.

Contraindications: History of previous hypersensitivity to oxazepam. Oxazepam is not indicated in psychoses.

Precautions: Hypotensive reactions are rare, but use with caution where complications could ensue, such as in blood pressure, especially in the elderly. One patient exhibiting drug dependency by taking a chronic overdose developed upon cessation questionable withdrawal symptoms. Carefully supervise dose and amounts prescribed, especially for patients prone to overdose; excessive prolonged use in susceptible patients (e.g., alcoholics, etc.) may result in tolerance. No tolerance is induced; dosage gradually after prolonging; excessive dosage to avoid possibility of epileptiform seizures. Caution patients against driving or operating machinery. In absence of drowsiness or dizziness is assumed. When possible, gradual possible reduction in dosage is recommended. Safety for use in pregnancy has not been established. Not indicated in children under 6 years; absolute dosage for 6 to 12 year-olds not established.

Side Effects: Therapy-interrupting side effects are rare. Transient mild drowsiness is common initially; if persistent, reduce dosage. Dizziness, vertigo and headache have also occurred infrequently; syncope, rarely. Mild paradoxical reactions (excitement, stimulation of affect) are reported. Transient rash, hives, urticaria, and angioedema (especially in children and/or popular) are rare. Nausea, lethargy, edema, slurred speech, tremor and altered libido are rare and generally controllable by dosage reduction. Although rare, leukopenia and hepatic dysfunction, jaundice, hepatitis, and hepatitis have been reported. Periodic complete blood and liver function tests are advised. Anuria, reported rarely, does not appear related to dose or age. These side reactions, noted with related compounds, are not yet reported; paradoxical excitation with severe rage reactions, hallucinations, menstrual irregularities, change in EEG pattern, blood dyscrasias (including agranulocytosis), blurred vision, diplopia, incontinence, stupor, disorientation, fever, euphoria and dysmetria.

Availability: Capsules of 10, 15 and 30 mg. oxazepam.

To help you relieve anxiety and tension

Serax[®] (oxazepam)



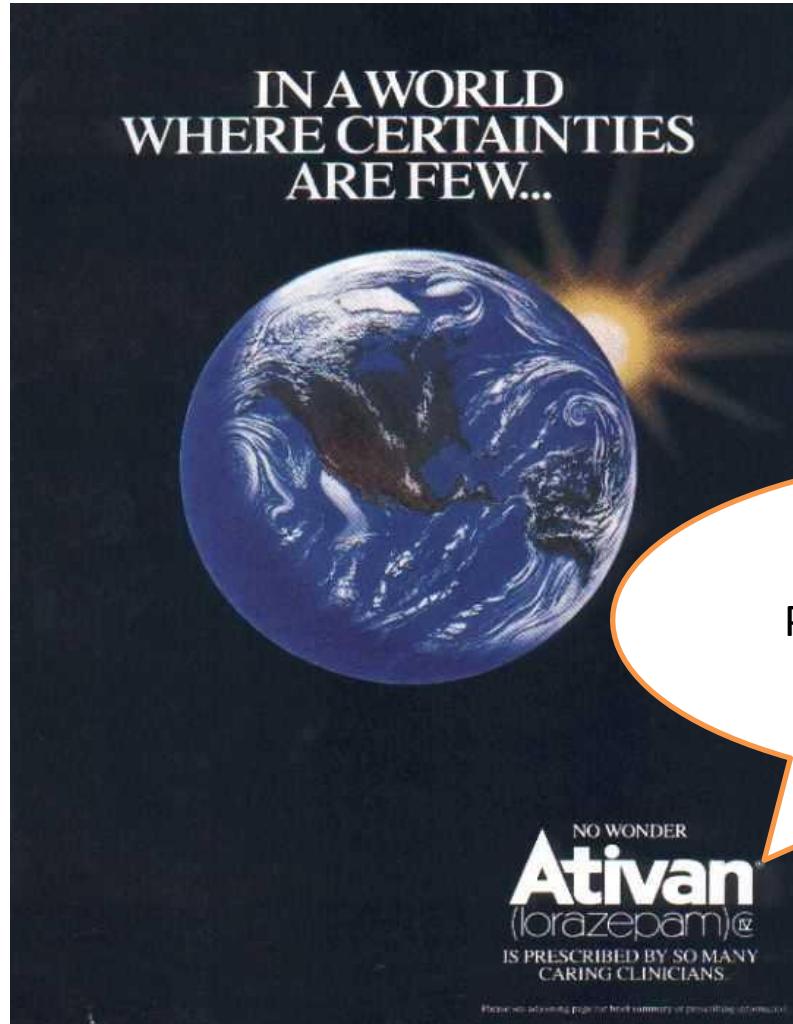
Wyeth Laboratories
Philadelphia, Pa.

Made It Into Pop Culture



- “*Kids are different today, I hear ev'ry mother say
Mother needs something today to calm her down
And though she's not really ill, there's a little yellow pill*
*She goes running for the shelter of a mother's little helper
And it helps her on her way, gets her through her busy day*”





A marketing strategy that still works, maybe in more subtle ways: pathologizing normal conditions, normalizing pill-taking, promising a better life

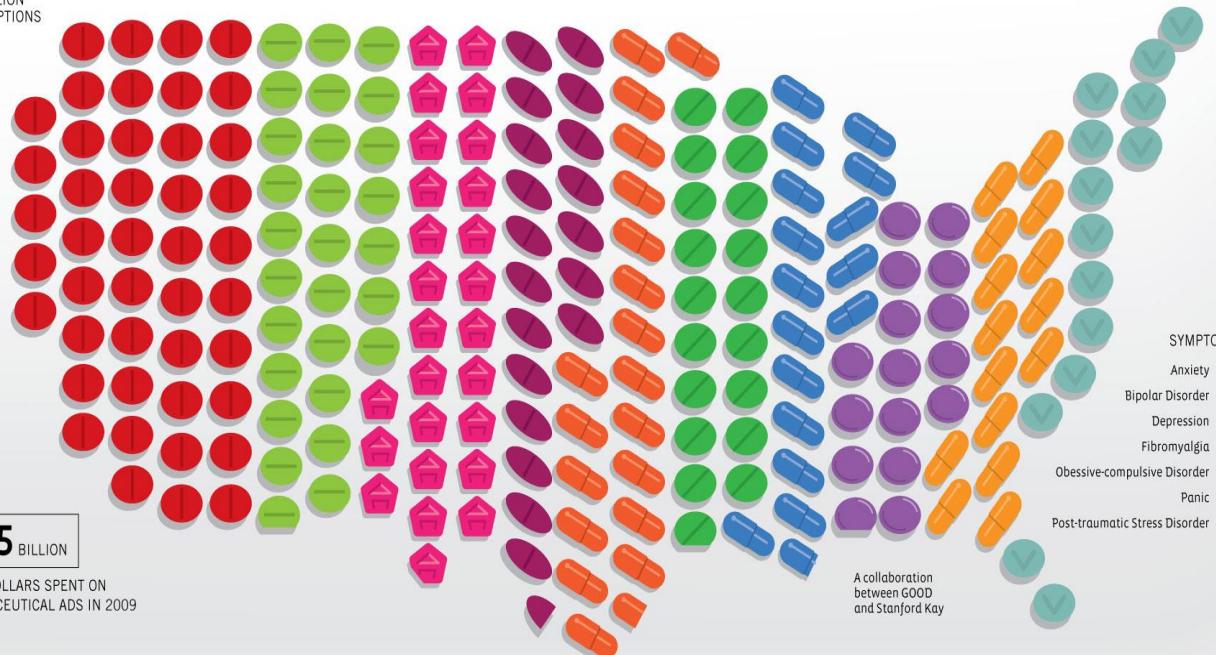
DRUGGED CULTURE

The pharmaceutical industry spends a lot of money marketing their newest psychiatric drugs to Americans. And we take a lot of them. In fact, in 2009 alone, U.S. doctors wrote more psychiatric prescriptions than there are people in this country. This is a look at 2009's 10 most prescribed psychiatric drugs. Don't worry, there's a pill for that.

AMERICA'S MOST PRESCRIBED PSYCHIATRIC DRUGS

In both their brand-name and generic forms

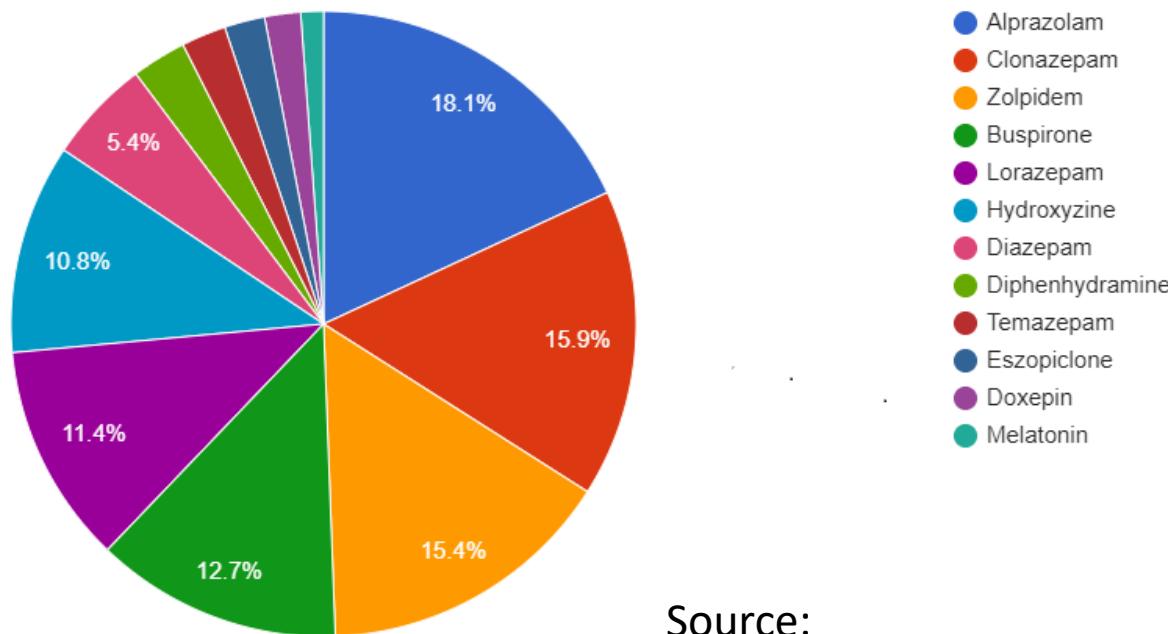
DRUG	Xanax	Lexapro	Ativan	Zoloft	Prozac	Desyrel	Cymbalta	Seroquel	Effexor XR	Valium
SYMPTOMS	A	AD	AP	ADOT	AD	AD	ADF	BD	ADP	AP
ONE PILL = ONE MILLION PRESCRIPTIONS	44	27.7	25.9	19.5	19.5	18.9	16.6	15.8	15	14



CHANGE IN RANK FOR TOTAL FILLED U.S. PRESCRIPTIONS	2009	2008
1	1	
2	3	
3	5	
4	2	
5	4	
6	NA	
7	16	
8	13	
9	6	
10	9	

SOURCE: IMS Health

Most Prescribed Anxiolytic, Sedative, Hypnotics in 2020



Source:

[https://clincalc.com/DrugStats/TC/Anxiolytics
SedativesandHypnotics](https://clincalc.com/DrugStats/TC/AnxiolyticsSedativesandHypnotics)

Prescription Trends

- Annually during 2014–2016, benzodiazepines were prescribed at approximately 65.9 million office-based physician visits, increasing with age
- 35% of these also involved a co-prescription of an opioid

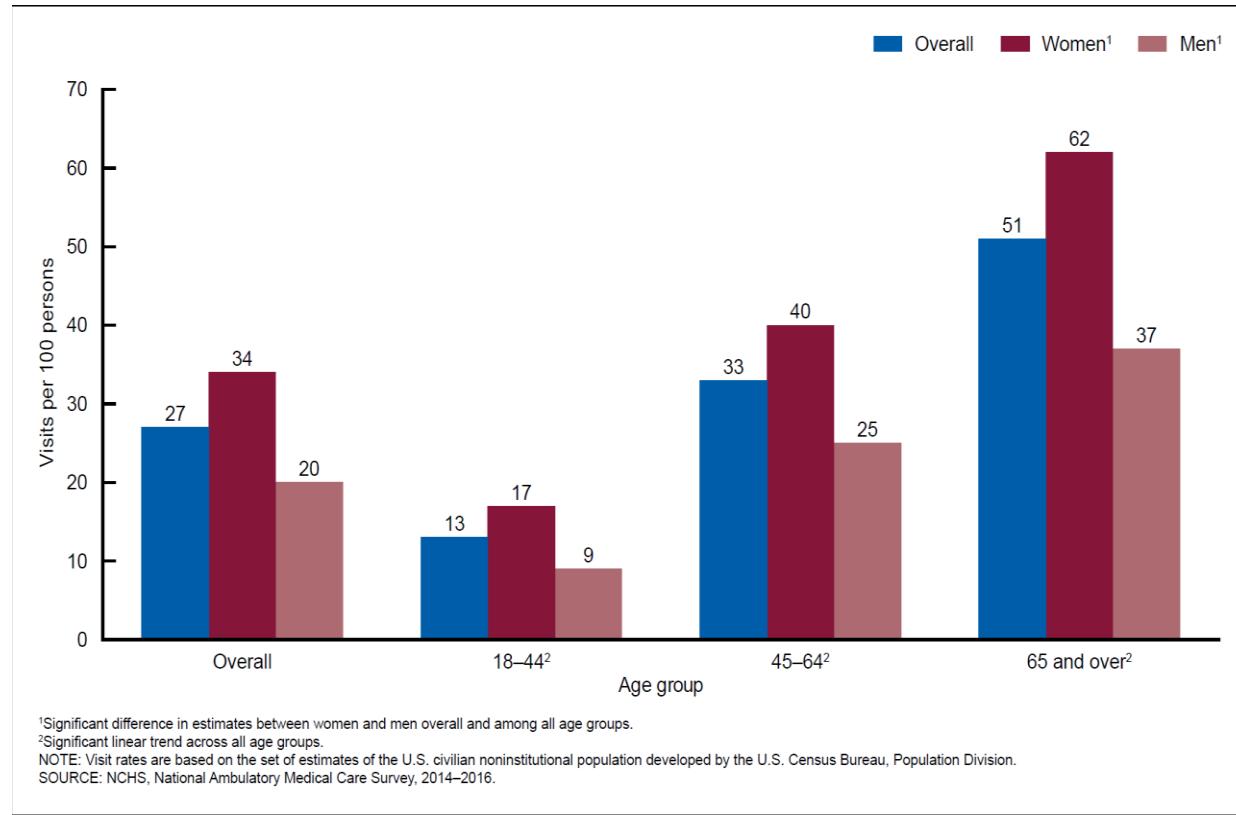
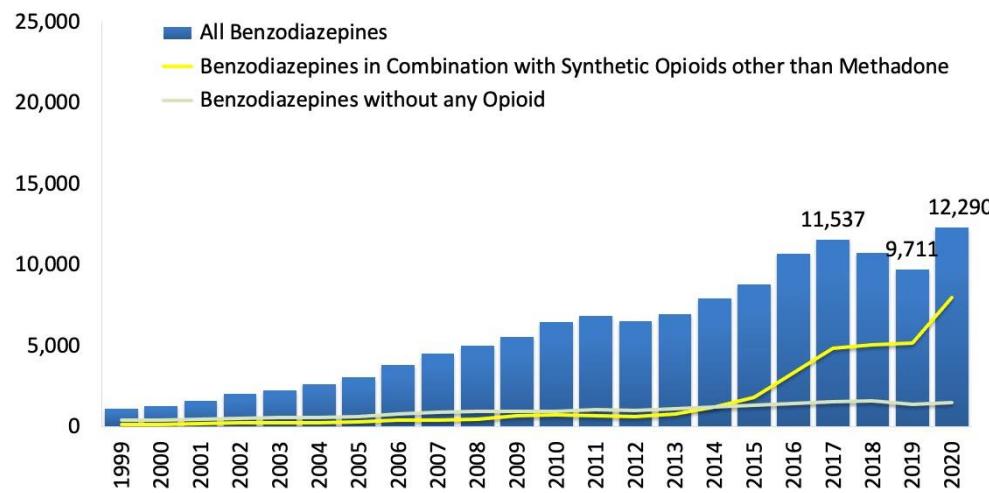


Figure 1. Visit rates at which benzodiazepines were prescribed for adult patients aged 18 and over, by age and sex: United States, 2014–2016

Santo L, Rui P, Ashman JJ. Physician Office Visits at Which Benzodiazepines Were Prescribed: Findings From 2014–2016 National Ambulatory Medical Care Survey. *Natl Health Stat Report*. 2020 Jan;(137):1-16. PMID: 32510318.

- In 2019, about 1 in 6 overdose deaths involving opioids also involved benzodiazepines.
- Drug overdose deaths involving benzodiazepines have steadily increased from 1,135 in 1999 to 11,537 in 2017.
- Between 2017 and 2020, deaths declined, and then rose again to 12,290.

Figure 8. National Drug Overdose Deaths Involving Benzodiazepines*, by Opioid Involvement, Number Among All Ages, 1999-2020



*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 1999-2020 on CDC WONDER Online Database, released 12/2021.

BZD + Opioid Co- prescription

- The overdose death rate among patients receiving both high-dose opioids and benzodiazepines was 10 times higher than among those only receiving opioids in a statewide study in NC*

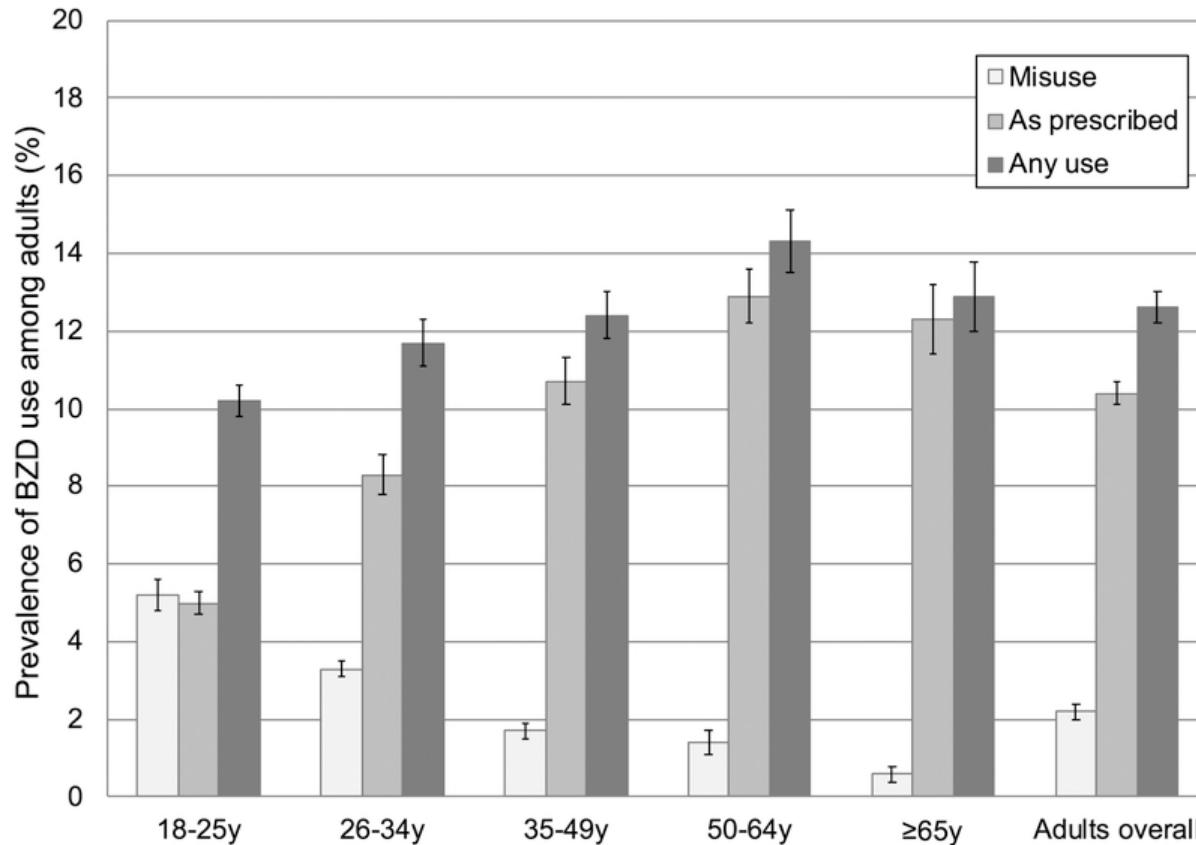
*Dasgupta N, Funk MJ, Proescholdbell S, Hirsch A, Ribisl KM, Marshall S. Cohort Study of the Impact of High-Dose Opioid Analgesics on Overdose Mortality. *Pain Med Malden Mass.* 2016;17(1):85-98. doi:10.1111/pme.12907

Use, Misuse, Use Disorder: NSDUH Data

- Among US adults in 2015-2016:
 - 12.5% used benzodiazepines,
 - 2.1% misused benzodiazepines at least once
 - 0.2% had benzodiazepine use disorders
- Among those using benzodiazepines:
 - 17.1% misused benzodiazepines,
 - 1.5% had benzodiazepine use disorders
- Benzodiazepine use was associated with emergency room visits, suicidal ideation, use of most substances, and mental disorders

Blanco C, Han B, Jones CM, Johnson K, Compton WM. Prevalence and Correlates of Benzodiazepine Use, Misuse, and Use Disorders Among Adults in the United States. *J Clin Psychiatry*. 2018 Oct 16;79(6):18m12174. doi: 10.4088/JCP.18m12174. PMID: 30403446.

BZD Use and Misuse by Age



Prevalence of Benzodiazepine Prescription Use and Misuse among NSDUH Respondents by Age Group in 2015 and 2016

Maust DT, Lin LA, Blow FC. Benzodiazepine Use and Misuse Among Adults in the United States. Psychiatr Serv. 2019 Feb;70(2):97-106. doi: 10.1177/003332221800321. Epub 2018 Dec 17. PMID: 30554562; PMCID: PMC6358464.

FDA requiring Boxed Warning updated to improve safe use of benzodiazepine drug class

Includes potential for abuse, addiction, and other serious risks

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Drug Safety and Availability

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Food and Drug Administration
Overdose Prevention

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[Drug Safety Communication \(PDF - 134KB\)](#)

09-23-2020 FDA Drug Safety Communication

What safety concern is FDA announcing?

To address the serious risks of abuse, addiction, physical dependence, and withdrawal reactions, the U.S. Food and Drug Administration (FDA) is requiring the *Boxed Warning* be updated for all benzodiazepine medicines. Benzodiazepines are widely used to treat many conditions, including anxiety, insomnia, and seizures. The current prescribing information for benzodiazepines does not provide adequate warnings about these serious risks and harms associated with these medicines so they may be prescribed and used inappropriately. This increases these serious risks, especially when benzodiazepines are

Content current as of:

10/02/2020

Regulated Product(s)

Drugs

Topic(s)

Safety - Issues, Errors, and
Problems

FDA Boxed Warning: Still DEA Schedule IV*

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS; ABUSE, MISUSE, AND ADDICTION; and DEPENDENCE AND WITHDRAWAL REACTIONS

- **Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death.** Reserve concomitant prescribing of these drugs for patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation [see Warnings and Precautions (5.1), Drug Interactions (7.1)].
- The use of benzodiazepines, including [DRUG], exposes users to **risks of abuse, misuse, and addiction, which can lead to overdose or death.** Abuse and misuse of benzodiazepines commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes. Before prescribing [DRUG] and throughout treatment, assess each patient's risk for abuse, misuse, and addiction [see Warnings and Precautions (5.2)].
- The continued use of benzodiazepines, including [DRUG] , may lead to clinically significant **physical dependence.** The risks of dependence and **withdrawal** increase with longer treatment duration and higher daily dose. Abrupt discontinuation or rapid dosage reduction of [DRUG] after continued use may precipitate acute withdrawal reactions, which can be life-threatening. **To reduce the risk of withdrawal reactions, use a gradual taper** to discontinue [DRUG] or reduce the dosage [see Dosage and Administration (2.2), Warnings and Precautions (5.3)].

***"Low potential for abuse and low risk of dependence"**

The Good News: Alprazolam Rx Trends

Year	Rank*	# of Rxs
2017	21	25,516,329**
2018	36	20,859,430
2019	41	17,533,262
2020	37	16,780,805

*Among all prescribed drugs
**vs
>44 million in 2009

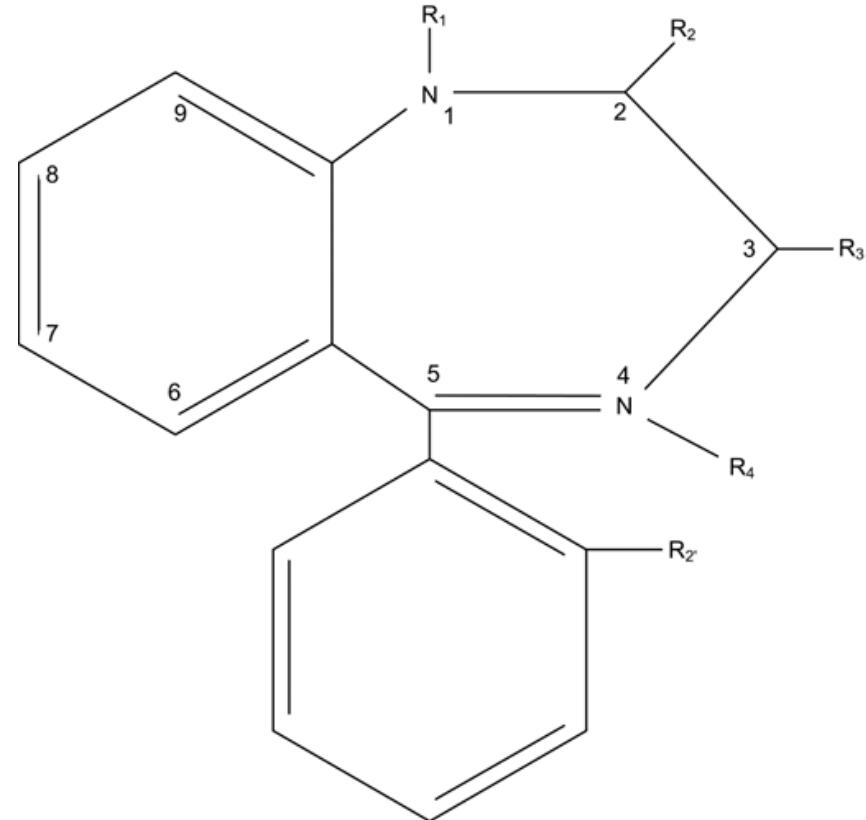
Source:
<https://clincalc.com/DrugStats/Drugs/Alprazolam>



Pharmacology

Basic Pharmacology

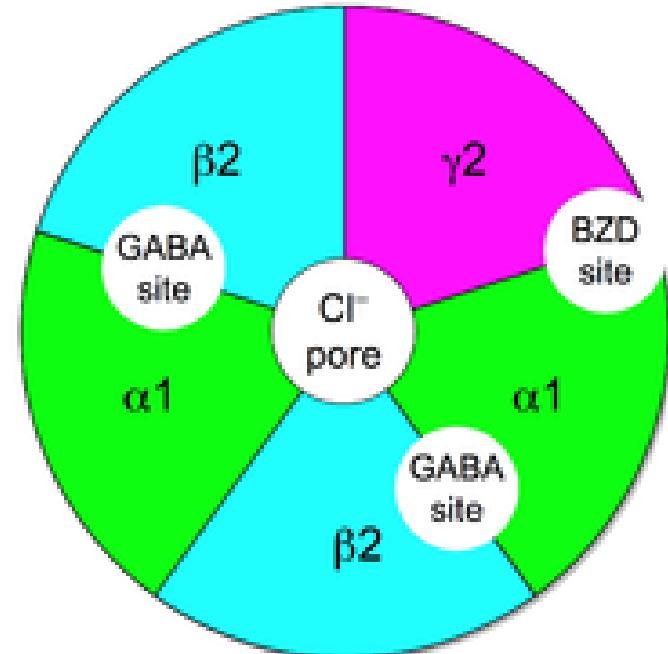
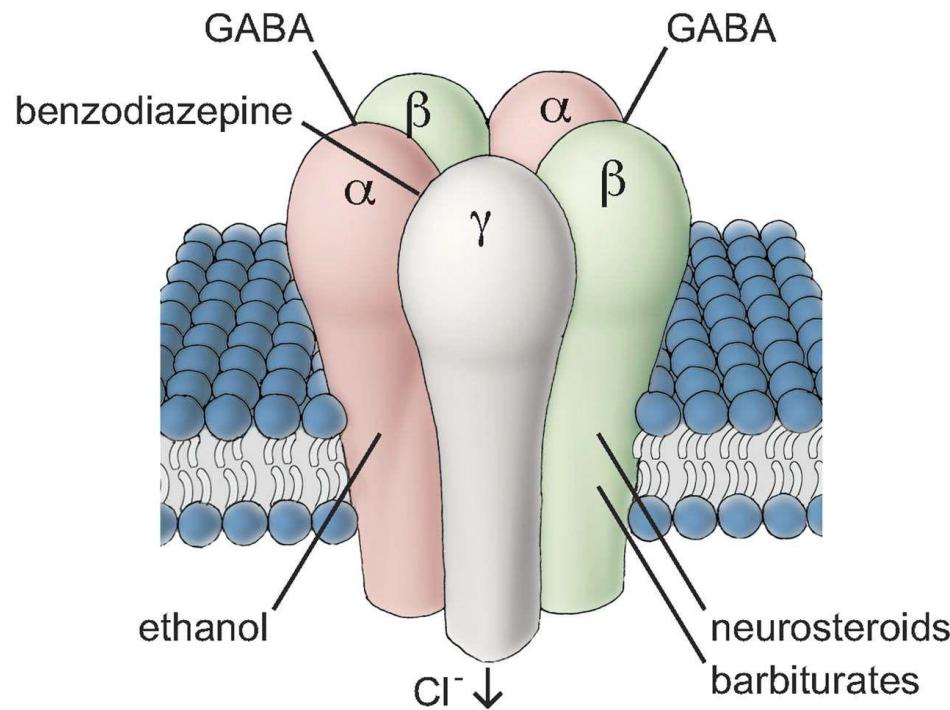
- Benzodiazepines (BZDs) are derived by the fusion of a benzene ring with a diazepine ring
- Side chains at Rx give unique properties to different benzodiazepines
- Much of this discussion also applies to non-benzodiazepines, the so-called “z-drugs”
- All are CNS depressants



Receptor Action of BZDs

- BZDs act on GABA –A receptors, but not on GABA –B
- Bind to a specific site on the receptor that is distinct from the site for GABA binding
- Do not activate GABA-A receptors directly, but modulate the effect of GABA by increasing the frequency of opening of chloride ion channel causing a rapid, large, increase in neuronal inhibition
- These effects are exerted by modulating the Cl- current generated by GABA –A activation

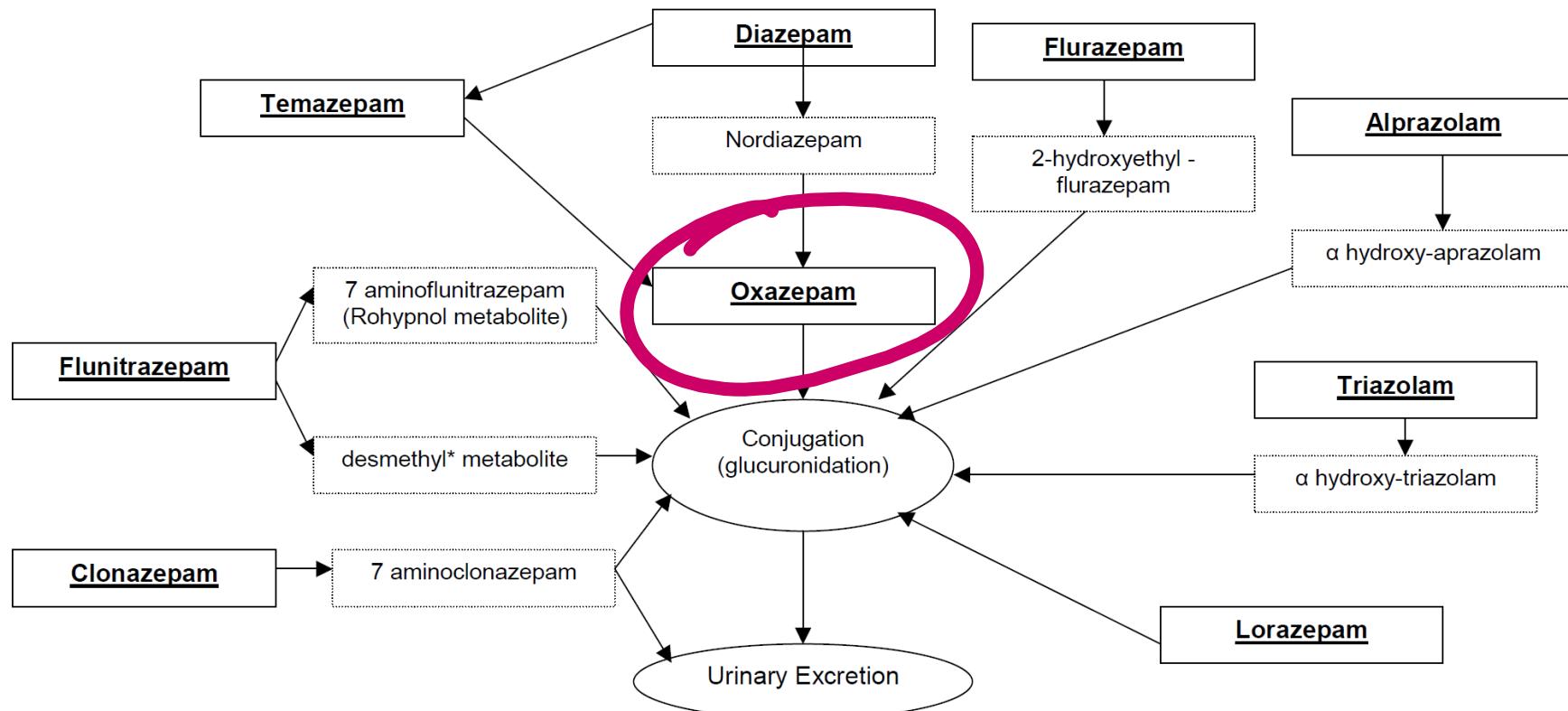
GABA-A Receptor Structure



Metabolism: CYP450 and BZDs

- Clinically most relevant: 3A4
- 3A4 inhibitors- e.g., keto/itraconazole, macrolide antibiotics, fluoxetine, nefazodone, cimetidine, grapefruit juice, etc- may increase levels (diazepam, alprazolam, triazolam, clonazepam, zaleplon, zolpidem)
- 2C19 inhibitors- e.g., oral contraceptives- may increase levels of some benzodiazepines (diazepam, chlordiazepoxide)
- Many are converted to active metabolites, which may have significantly longer half-lives than the parent compound
- Oxazepam, lorazepam, temazepam, triazolam, and midazolam are inactivated by the initial reaction and have short duration of action

Benzodiazepine Metabolism



Benzodiazepine Classes

- Long-acting:
 - Diazepam
 - Chlordiazepoxide
- Short-acting:
 - Lorazepam
 - Clonazepam
 - Alprazolam
 - Oxazepam
- Ultra-short acting:
 - Midazolam
- Z Drugs (non-benzodiazepines)
 - Zolpidem
 - Eszopiclone
 - Zaleplon

Moderate risk for misuse
High risk for misuse

Benzodiazepines by Common Uses

Anxiolytic

- Alprazolam
- Chlordiazepoxide
- Diazepam
- Clonazepam
- Lorazepam
- Oxazepam

Alcohol Withdrawal

- Chlordiazepoxide
- Diazepam
- Lorazepam
- Oxazepam

Hypnotic

- Flurazepam
- Flunitrazepam
- Nitrazepam
- Triazolam
- Temazepam

Sedation

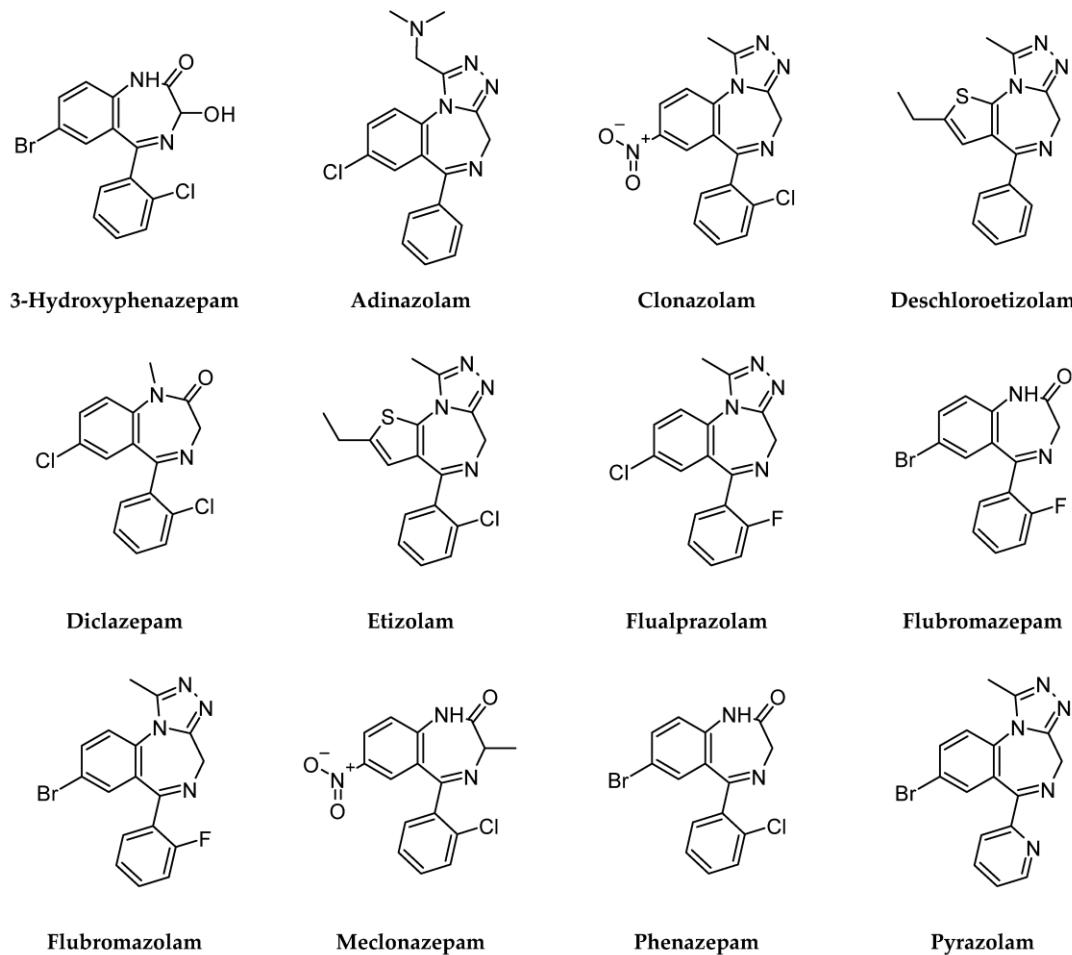
- Lorazepam
- Midazolam
- Diazepam

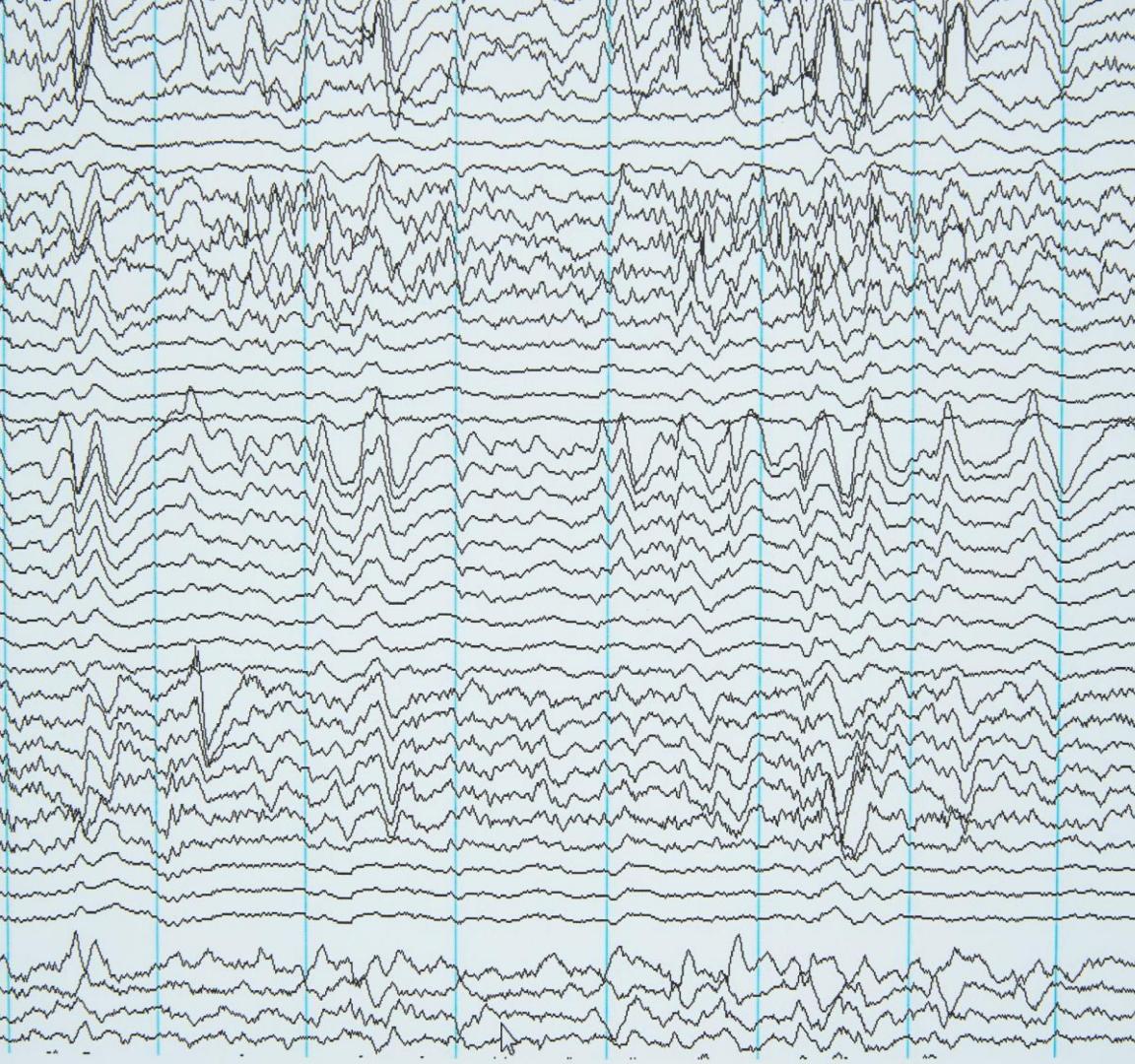
Anticonvulsant

- Clorazepate
- Clonazepam
- Diazepam
- Lorazepam
- Clobazam

“Designer” Benzodiazepines

Brunetti P, Giorgetti R, Tagliabracci A, Huestis MA, Busardò FP. Designer Benzodiazepines: A Review of Toxicology and Public Health Risks. *Pharmaceuticals (Basel)*. 2021 Jun 11;14(6):560. doi: 10.3390/ph14060560. PMID: 34208284; PMCID: PMC8230725.





Effects on Sleep

- EEG: Decrease in alpha activity, and increase in low-voltage fast activity
- Decrease in sleep latency
- Decrease in REM, Stage 1/3/4
- Increase in total sleep time, esp. Stage 2
- Increase in total REM cycles
- Increase in REM upon discontinuation

Short-term Adverse Effects

Risk of respiratory depression/oversedation, esp with other CNS depressants

Risk of falls and fractures, esp in older patients

Risk of MVCs*, work-place accidents

Worsening depression, PTSD, suicidal behaviors**

Cognitive and psychomotor impairment, ataxia

Complex sleep-related behaviors

Paradoxical reactions, agitation, disinhibition

*Smink BE, Egberts AC, Lusthof KJ, Uges DR, de Gier JJ. The relationship between benzodiazepine use and traffic accidents: A systematic literature review. *CNS Drugs*. 2010 Aug;24(8):639-53. doi: 10.2165/11533170-00000000-00000. PMID: 20658797.

**Dodds TJ. Prescribed Benzodiazepines and Suicide Risk: A Review of the Literature. *Prim Care Companion CNS Disord*. 2017 Mar 2;19(2). doi: 10.4088/PCC.16r02037. PMID: 28257172.

Long-term Use: Hazardous to Health?

- Though some studies show continuing effectiveness, relatively stable or decreasing doses, and few problems over long-term use, other studies show high proportions of patients on chronic bzds meet criteria for bzd dependence*.
- Concerns about potential long-term effects on cognition**, increase in all-cause mortality***.
- Most patients will need a taper after 2-4 weeks on bzds, 30% in one study had withdrawal after 8 weeks on a bzd.

*Guerlais M, Grall-Bronnec M, Feuillet F, Gérardin M, Jollet P, Victorri-Vigneau C. Dependence on prescription benzodiazepines and Z-drugs among young to middle-aged patients in France. *Subst Use Misuse*. 2015 Feb;50(3):320-7. doi: 10.3109/10826084.2014.980952. Epub 2014 Dec 4. PMID: 25474727.

**He Q, Chen X, Wu T, Li L, Fei X. Risk of Dementia in Long-Term Benzodiazepine Users: Evidence from a Meta-Analysis of Observational Studies. *J Clin Neurol*. 2019 Jan;15(1):9-19. doi: 10.3988/jcn.2019.15.1.9. Epub 2018 Oct 26. PMID: 30375757; PMCID: PMC6325366.

***Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. *BMJ Open*. 2012 Feb 27;2(1):e000850. doi: 10.1136/bmjopen-2012-000850. PMID: 22371848; PMCID: PMC3293137.

Why Are BZDs So Popular?

- Effective
- Rapid onset of action
- Well-tolerated
- Perceived as safe
- Insufficient education about bzds- among prescribers and patients
- Marketing

Considerations When Prescribing

- Not recommended for > 2-4 weeks of use due to risk of tolerance, withdrawal and misuse
- Not first line treatment for anxiety or insomnia
- Not ideal for patients with substance use disorders
- Risky in patients on opioids
- Avoid in the elderly- risk of falls, confusion, oversedation
- Not recommended for patients with compromised pulmonary function
- Avoid in patients in high-risk occupations- e.g., transportation, heavy machinery operation

Management of Withdrawal

Abrupt Cessation

- Rebound anxiety and panic
- Symptoms similar to alcohol withdrawal
- Delirium (similar to DTs)
- Seizures
- Self-harm, violence, psychosis, catatonia
- Can be life-threatening

Symptoms/Signs of Benzodiazepine Withdrawal

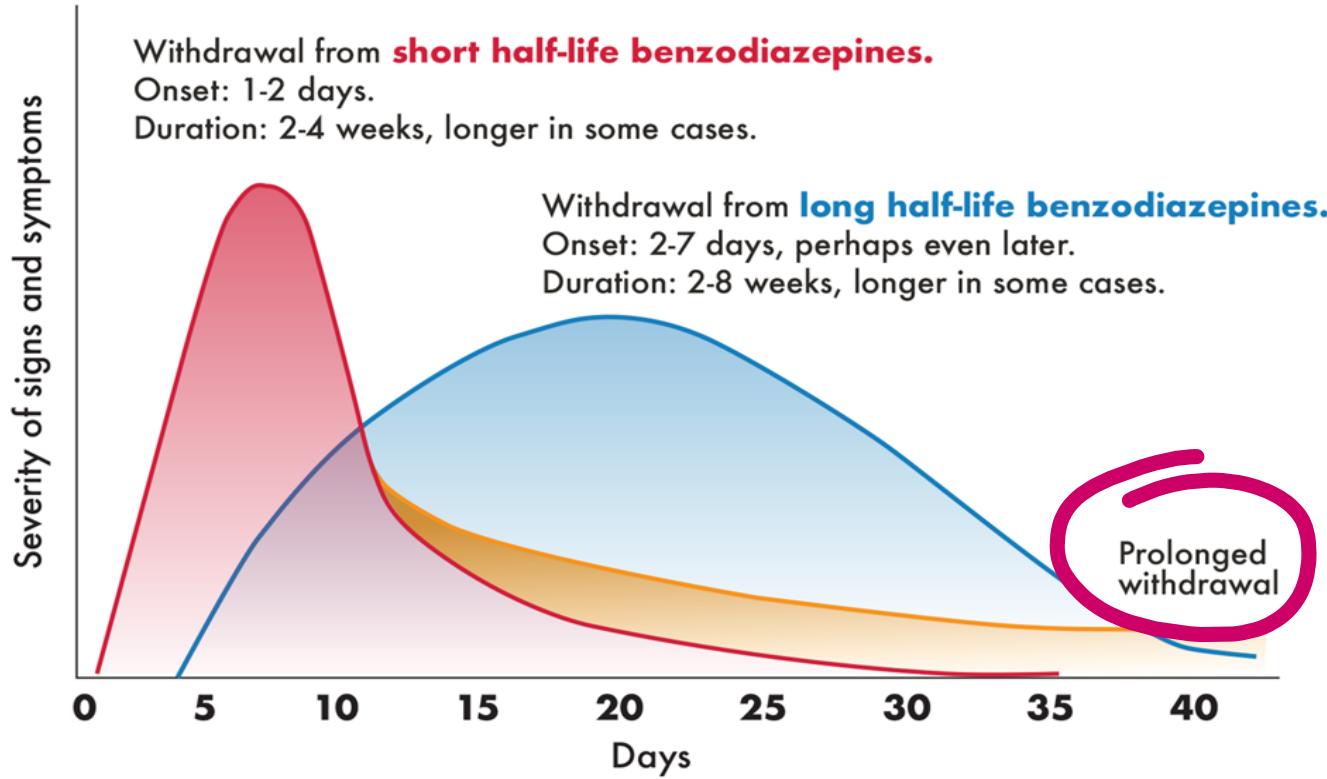
Psychological

- **Insomnia/nightmares**
- **Anxiety/ panic**
- **Depersonalization/derealization**
- Depression
- **Hallucinations**
- Paranoia
- Rage/ irritability
- **Poor concentration**
- Cravings
- **Confusion/Delirium**

Physical

- Headache
- **Tingling, numbness, altered sensation**
- **Muscle twitches, jerks, "electric shocks"**
- **Tremor**
- **Tinnitus**
- **Hypersensitivity to sensory inputs**
- Flushing/sweating/palpitations
- Hyperventilation
- **Seizures**

Course of Benzodiazepine Withdrawal



Source: Howell, E. ACAAM
Presentation 2020

Protracted Withdrawal

May last from months to a year or more, with waxing and waning course

- **Insomnia**
- **Anxiety**
- Depression
- **Cognitive difficulty**
- **Paresthesia/Tinnitus**
- **Oversensitivity to sensory inputs**
- **Tremor/muscle twitches**
- Muscle spasms

Intense preoccupation, misattribution of symptoms

Strategies to Manage Withdrawal

- Gradual dose reduction/taper
- Switch to a long-acting BZD and taper
- Switch to a barbiturate and taper
- Switch to an anticonvulsant and taper
- Use adjuncts

Management of Benzodiazepine Withdrawal

Table 5. Management of Benzodiazepine (BZD) Withdrawal.

Situation	Treatment Approach	Level of Evidence
Approach to BZD dependence in general	Gradual withdrawal over a period of several weeks or months	High
Use of several BZDs or sedatives	Switch to use of only one BZD for detoxification (diazepam)	Good
Choice of BZD for detoxification	Switch to a long-acting BZD (diazepam)	Low
BZD withdrawal in a patient receiving opioid maintenance therapy	Adjustment of opioid dose to prevent opioid withdrawal; switch to a partial agonist (buprenorphine)	Good for adjustment of opioid dose; moderate for switch to partial agonist
Concomitant pharmacotherapy for BZD withdrawal	Carbamazepine, 200 mg twice a day	Moderate
Sleep disorders	Antidepressants, antihistaminergic drugs, melatonin; improved sleep hygiene, sleep restriction, relaxation techniques	Moderate
Other drugs for treatment of withdrawal symptoms	Pregabalin, gabapentin, beta-blockers; flumazenil	Low for pregabalin, gabapentin, and beta-blockers; experimental for flumazenil
Psychotherapy	Cognitive behavioral therapy and other approaches	Good

Soyka M. Treatment of Benzodiazepine Dependence. *N Engl J Med.* 2017 Mar 23;376(12):1147-1157. doi: 10.1056/NEJMra1611832. PMID: 28328330.

**TABLE 3. Sedative-Hypnotic Withdrawal
Substitution Dose Conversions**

Drug	Dose Equal to 30 mg of Phenobarbital (mg)
Benzodiazepines	
Alprazolam (Xanax®)	0.5-1
Chlordiazepoxide (Librium®)	25
Clonazepam (Klonopin®)	1-2
Clorazepate (Tranxene®)	7.5
Diazepam (Valium®)	10
Estazolam (ProSom®)	1
Flurazepam (Dalmane®)	15
Lorazepam (Ativan®)	2
Oxazepam (Serax®)	10-15
Quazepam (Doral®)	15
Temazepam (Restoril®)	15
Triazolam (Halcion®)	0.25
Barbiturates	
Pentobarbital (Nembutal®)	100
Secobarbital (Seconal®)	100
Butalbital (Fiorinal®)	100
Amobarbital (Amytal®)	100
Phenobarbital	30
Nonbarbiturates-Nonbenzodiazepines	
Ethchlorvynol (Placidyl®)	500
Glutethimide (Doriden®)	250
Methyprylon (Noludar®)	200
Methaqualone (Quaalude®)	300
Meprobamate (Miltown®)	1,200
Carisoprodol (Soma®)	700
Chloral Hydrate (Noctec®)	500

Taper Schedules

- Can last from a few days to a few months, and occasionally, longer
- Depends on the type, duration, and amount of BZD being used
- Very difficult to withdraw from the short-acting BZDs (alprazolam, lorazepam)- not recommended
- May need inpatient stay

Withdrawal Scales

- Benzodiazepine Withdrawal Symptom Questionnaire*
 - 20 items, scored 0-2
 - Self-report
- CIWA-B**
 - 22 items, scored 0-4
 - 17 self-report, 3 observation
 - Mild (1-20), moderate (21-40), severe (41-60), very severe (61-80)

*Tyrer P, Murphy S, Riley P. The Benzodiazepine Withdrawal Symptom Questionnaire. *J Affect Disord.* 1990 May;19(1):53-61.

**Busto, U.E., Sykora, K. & Sellers, E.M. (1989). A clinical scale to assess benzodiazepine withdrawal. *Journal of Clinical Psychopharmacology*, 9 (6), 412-416.

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 intended
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?	Total CIWA-B Score:
22 How many minutes do you think it took you to fall asleep last night?	_____

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

Withdrawal scales were developed to assist the monitoring and management of withdrawal

To download more of this resource visit www.insight.qld.edu.au

insight
Centre for alcohol and other drug
training and evidence development

Source: Bustos UE, Sykora K, Sellers EM. A clinical scale to assess benzodiazepine withdrawal. Journal of Clinical Psychopharmacology. 1989;9(6):412-6. doi: 10.1097/00004567-198912000-00005

Factors Impacting Taper Strategy

Consider BZD

-Type- long vs short half-life

-Dose- low vs high dose

-Duration of use- short vs long

-Prescribed vs non-prescribed

-Motivated patient vs not

-Co-morbid psychiatric conditions

-Level of care- inpatient vs outpatient

General Principles For Tapers

Scheduled, not PRN, dosing

Decrease total *original* dose 25% q 1-2 weeks

Consider holding dose at 50% total original dose for several weeks to a month

Decrease 10-25% *current* dose q 1-2 weeks thereafter

Hardest part is the last 25%

May need to temporarily stop taper or even reverse course

May not be able to taper off entirely, but less is better (harm reduction)

Adapted from: Ilse Wiechers, MD, US Department of Veterans Affairs

Example Taper Schedule

Milestone Suggestions

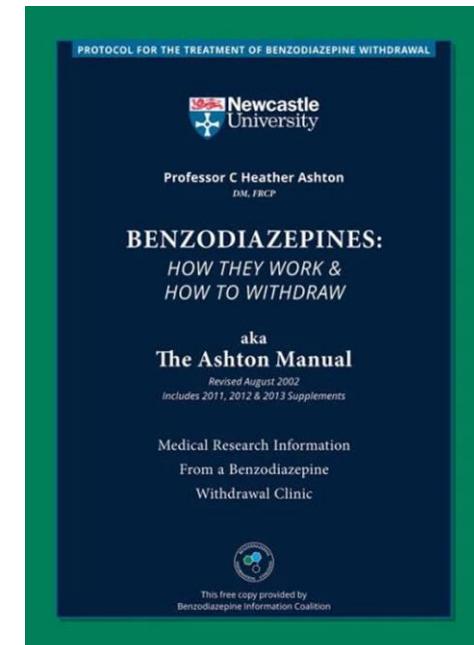
Example: Alprazolam 2 mg bld
Convert to 40 mg diazepam daily

Week 1		35 mg/day
Week 2	Total dose decrease by 25%	30 mg/day (25%)
Week 3		25 mg/day
Week 4	Total dose decrease by 50%	20 mg/day (50%)
Week 5-8	Hold dose	Continue at 20 mg/day for 1 month
Week 9-10	Current dose reduction of 25% every two weeks	15 mg/day
Week 11-12		10 mg/day
Week 13-14		5 mg/day
Week 15		discontinue

National Center for PTSD
2013

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
Stage 9 (1-2 weeks)	alprazolam 0.5mg diazepam 20mg	alprazolam 0.5mg diazepam 10mg	diazepam 20mg	80mg
Stage 10 (1-2 weeks)	alprazolam 0.5mg diazepam 20mg	Stop alprazolam diazepam 10mg	diazepam 20mg	60mg
Stage 11 (1-2 weeks)	Stop alprazolam diazepam 20mg	diazepam 10mg	diazepam 20mg	50mg
Stage 12 (1-2 weeks)	diazepam 25mg	Stop midday dose; divert 5mg each to morning and night doses	diazepam 25mg	50mg
Stage 13 (1-2 weeks)	diazepam 20mg	--	diazepam 25mg	45mg
Stage 14 (1-2 weeks)	diazepam 20mg	--	diazepam 20mg	40mg



<https://www.benzo.org.uk/manual/>

	Morning	Night	Total Daily Dosage
Starting dosage	diazepam 20mg	diazepam 20mg	40mg
Stage 1 (1-2 weeks)	diazepam 18mg	diazepam 20mg	38mg
Stage 2 (1-2 weeks)	diazepam 18mg	diazepam 18mg	36mg
Stage 3 (1-2 weeks)	diazepam 16mg	diazepam 18mg	34mg
Stage 4 (1-2 weeks)	diazepam 16mg	diazepam 16mg	32mg
Stage 5 (1-2 weeks)	diazepam 14mg	diazepam 16mg	30mg
Stage 6 (1-2 weeks)	diazepam 14mg	diazepam 14mg	28mg
Stage 7 (1-2 weeks)	diazepam 12mg	diazepam 14mg	26mg
Stage 8 (1-2 weeks)	diazepam 12mg	diazepam 12mg	24mg
Stage 9 (1-2 weeks)	diazepam 10mg	diazepam 12mg	22mg
Stage 10 (1-2 weeks)	diazepam 10mg	diazepam 10mg	20mg
Stage 11 (1-2 weeks)	diazepam 8mg	diazepam 10mg	18mg
Stage 12 (1-2 weeks)	diazepam 8mg	diazepam 8mg	16mg
Stage 13 (1-2 weeks)	diazepam 6mg	diazepam 8mg	14mg
Stage 14 (1-2 weeks)	diazepam 5mg	diazepam 8mg	13mg
Stage 15 (1-2 weeks)	diazepam 4mg	diazepam 8mg	12mg
Stage 16 (1-2 weeks)	diazepam 3mg	diazepam 8mg	11mg
Stage 17 (1-2 weeks)	diazepam 2mg	diazepam 8mg	10mg
Stage 18 (1-2 weeks)	diazepam 1mg	diazepam 8mg	9mg
Stage 19 (1-2 weeks)	--	diazepam 8mg	8mg
Stage 20 (1-2 weeks)	--	diazepam 7mg	7mg
Stage 21 (1-2 weeks)	--	diazepam 6mg	6mg
Stage 22 (1-2 weeks)	--	diazepam 5mg	5mg
Stage 23 (1-2 weeks)	--	diazepam 4mg	4mg
Stage 24 (1-2 weeks)	--	diazepam 3mg	3mg

- Schedule 2. Simple withdrawal from diazepam (Valium) 40mg daily (follow this schedule to complete [Schedule 1](#))**

Phenobarbital Taper

- 310 admissions
 - Age range: 19-61 years; median age 36 years
 - 78 (25.2%) on MMT; 177 (56.1%) on buprenorphine taper
 - 3-day inpatient taper
 - 200 mg x1, followed by 100 mg q4 hours x5 doses
 - 60 mg q4 hours x4 doses
 - 60 mg q8 hours x3 doses
 - 25.8% had at least 1 dose held due to sedation
 - 11.6% received at least 1 extra dose of phenobarbital

Kawasaki SS, Jacaprarro JS, Rastegar DA. Safety and effectiveness of a fixed-dose phenobarbital protocol for inpatient benzodiazepine detoxification. *J Subst Abuse Treat.* 2012 Oct;43(3):331-4.

Adjunctive Medications/ Therapy

- Carbamazepine
- Valproate
- Propranolol
- Clonidine
- Trazodone
- Hydroxyzine
- Buspirone
- CBT
- Complementary and Alternative therapies

Taper + CBT

65 adults, mean age 67, mean bzd use 12+ years

8-week intervention

RCT with 2 arms:

- Taper alone (25% q1-2 weeks)
- Combination taper + CBT (weekly small groups)

Combined taper +CBT was better than taper alone (77% vs 38% completely stopped bzd use)

Improvement sustained at 12-month follow up

Baillargeon L, Landreville P, Verreault R, Beauchemin JP, Grégoire JP, Morin CM. Discontinuation of benzodiazepines among older insomniac adults treated with cognitive-behavioural therapy combined with gradual tapering: a randomized trial. CMAJ. 2003 Nov 11;169(10):1015-20. PMID: 14609970; PMCID: PMC236226.)

Evidence For Combining Taper and CBT-I

76 adults mean age 62, mean benzo use (for sleep) 19+ years

10-week intervention at research-based sleep clinic

RCT with 3 arms:

- Supervised benzo taper
- CBT-I alone (weekly small group)
- Combination taper + CBT-I

Combination was best (85% bzd-free), vs CBT- I alone (54%) vs taper alone (48%)

Improvement sustained over 12 months

Morin CM, Bastien C, Guay B, Radouco-Thomas M, Leblanc J, Vallières A. Randomized clinical trial of supervised tapering and cognitive behavior therapy to facilitate benzodiazepine discontinuation in older adults with chronic insomnia. Am J Psychiatry. 2004 Feb;161(2):332-42. doi: 10.1176/appi.ajp.161.2.332. PMID: 14754783.

Direct Patient Education

EMPOWER (Eliminating Medications Through Patient Ownership of End Results) cluster randomized trial

- Community pharmacies randomized to intervention
- Participants: 65+ yo, receiving long-term benzo therapy (3 mo of Rx fills prior to study)

Intervention: patient education booklet about dangers of benzos with taper recommendations & instructions to talk to a pharmacist or physician

Key result: 62% of intervention group initiated conversation about taper; 27% (vs 5% of the control group) had discontinued benzos at 6 mos; 11% had reduced dose.

Tannenbaum C, Martin P, Tamblyn R, Benedetti A, Ahmed S. Reduction of inappropriate benzodiazepine prescriptions among older adults through direct patient education: the EMPOWER cluster randomized trial. *JAMA Intern Med.* 2014 Jun;174(6):890-8. doi: 10.1001/jamainternmed.2014.949. PMID: 24733354.

Monitoring

- Treatment agreement
- Predefined “exit strategy”
- Frequent, short visits
- Tight control over prescriptions
- Drug tests
- Communication with other providers and family
- Checking PDMP database

Prevention

- Exercise caution in prescribing BZDs; avoid, if possible, especially in patients taking any opioids, or those with SUD
- Set clear expectations for duration of use, discuss risks of long-term use with patients
- Limit to the lowest effective dose for the shortest duration- generally no more than a few weeks
- Do not exceed therapeutic doses
- Consider safer alternatives for anxiety/panic (e.g., SSRIs/SNRIs, non-pharmacologic techniques, CBT), sleep (trazodone, CBT-I, sleep hygiene), seizures (anticonvulsants)
- Taper off when no longer needed

Question 1

Benzodiazepines primarily bind to which of the following receptors?

- A. Glutamate- NMDA receptors
- B. GABA- A receptors
- C. Serotonin- 5HT-1A receptors
- D. GABA-B receptors

Question 2

Individuals in which age group are most likely to misuse prescribed benzodiazepines?

- A. 26-34 years
- B. 35-49 years
- C. >65 years
- D. 18-25 years

Question 3

Symptoms of protracted benzodiazepine withdrawal may include all of the following, except:

- A. Insomnia
- B. Anxiety
- C. Seizures
- D. Hypersensitivity to sensory inputs

Question 4

Management options for benzodiazepine use disorder include all of the following, except:

- A. Gradual dose reduction
- B. Switch to a long-acting benzodiazepine and slow taper
- C. Abrupt discontinuation
- D. Switch to phenobarbital and taper

Answers

Question 1: B

Question 2: D

Question 3: C

Question 4: C

Take-away Message

Managing BZD withdrawal can be an arduous and protracted process

Can challenge both the patient and the clinician- obtain a consultation if necessary

Can be among the most difficult clinical problems one may have to deal with

Prevention is much better than cure- handle BZDs with great caution

**SHOULD WE WORRY
ABOUT
BENZODIAZEPINES??**

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