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PSYCHIATRY ACADEMY

Benzodiazepines (BZP)

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Faculty Disclosure

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Some of the medications discussed may not be FDA approved in the manner in which they are discussed including diagnosis(es), combinations, age groups, dosing, or in context to other disorders (e.g., substance use disorders)

Some slides courtesy of R. Althoff MD, PhD



BPZ Case

- Susan is 35 yo with h/o well treated opioid use disorder on buprenorphine
- She has longstanding Panic disorder with agoraphobia; and generalized anxiety disorder. She reports being on antidepressants in the past “that didn’t work” but admits that she was using opioids at the time.
- Over the past year, she has been using clonazepam purchased on the streets (UDS+ for bzp periodically)
- Susan is employed, has been adherent to her buprenorphine and visits but insists she requires the clonazepam to function



BZP Case: Next Steps

- What would appropriate next steps for Susan ?
 - **Discharging Susan from the clinic**
 - **Immediately admitting Susan for BZP detox**
 - **Trying buspirone, a serotonergic, or serotonergic / noradrenergic agent**
 - **Trying an antipsychotic (e.g. quetiapine)**
 - **Starting Susan on a BZP other than clonazepam**
 - **Starting Susan on a BZP - clonazepam**

Sedative/Hypnotics are 5th Most Common Drug : Past Year Illicit Drug Use Among People >12 yrs; 2023

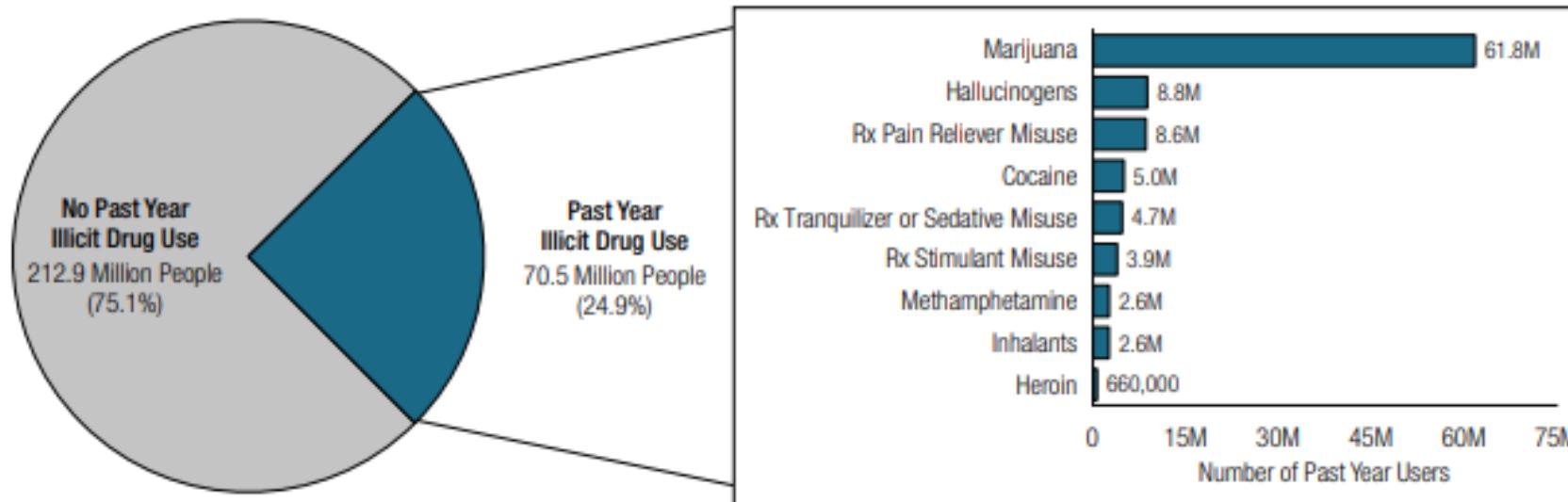
NSDUH 2023; SAMSHA Report 2024



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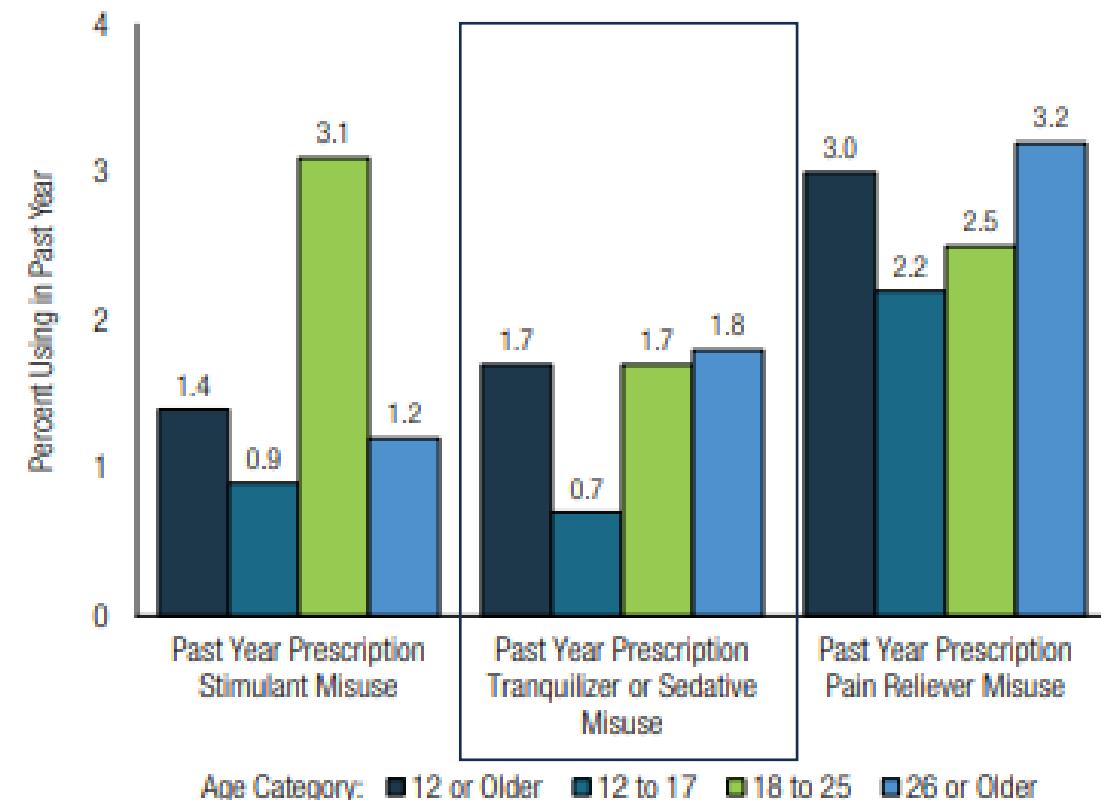
Figure 12. Past Year Illicit Drug Use: Among People Aged 12 or Older; 2023



Rx = prescription.

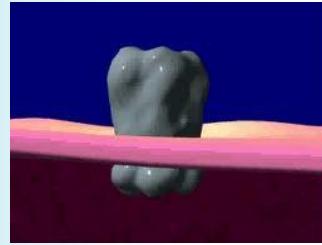
Note: The estimated numbers of past year users of different illicit drugs are not mutually exclusive because people could have used more than one type of illicit drug in the past year.

Figure 19. Past Year Prescription Stimulant Misuse, Past Year Prescription Tranquillizer or Sedative Misuse, or Past Year Prescription Pain Reliever Misuse: Among People Aged 12 or Older; 2023



NSDUH 2024 (SAMSA)

Effects of Barbiturates and BZP on the GABA Receptor



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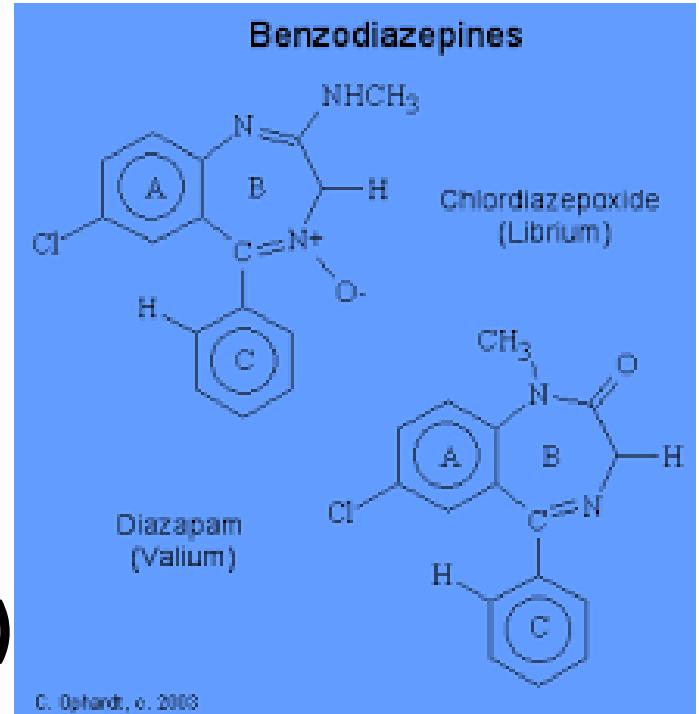
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- Both drugs bind to GABA-A receptor subunits at different sites
- Neither binds specifically to the agonist site
- Benzodiazepines **INCREASE** the frequency of channel opening but do not alter conductance or duration of opening
- Barbiturates **PROLONG** the duration of channel opening



McGill University: http://thebrain.mcgill.ca/flash/i/i_04/i_04_m/i_04_m_peu/i_04_m_peu.html

- Traditional BZP
 - **Diazepam (Valium)**
 - **Clonazepam (Klonopin)**
 - **Alprazolam (Xanax)**
- “Z” Drugs
 - **Zaleplon (trade: Sonata)**
 - **Zolpidem (trade: Ambien, Edluar, Intermezzo)**
 - **Zopiclone (trade: Zimovane)**





BZP Half-Lives

- Long half life benzo's (e.g., >100 hrs)
 - Chlordiazepoxide
 - **Clorazepate**
 - Diazepam
- Intermediate half life
 - Clonazepam
- Short Half Life benzo's (<12 hours)
 - Alprazolam
 - Lorazepam
 - Triazolam

Potency of BZP's

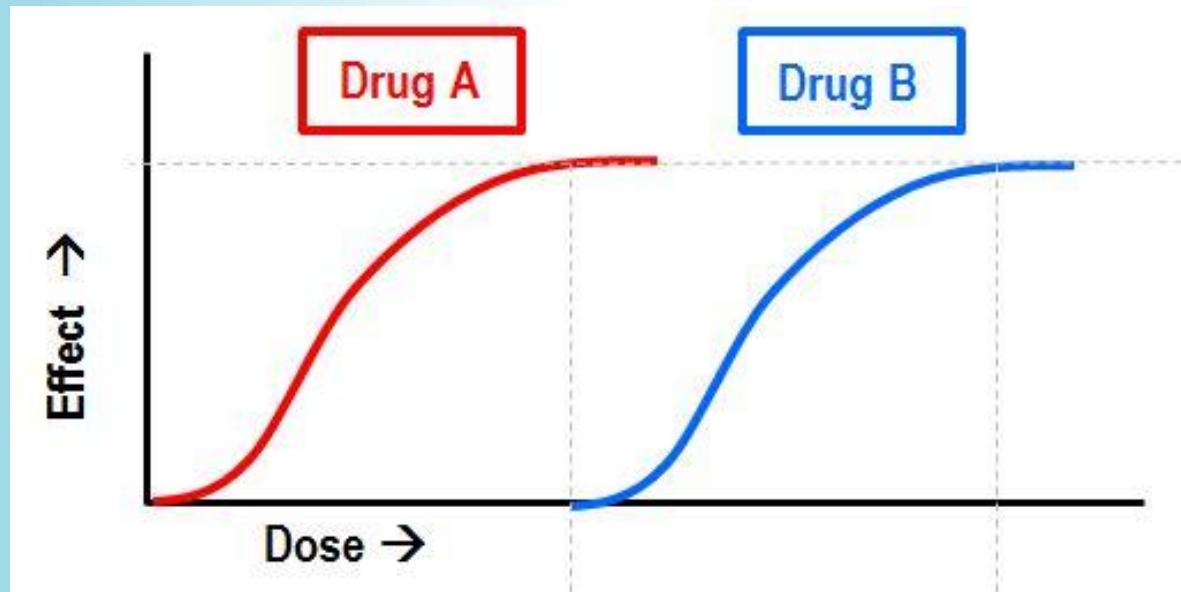
(Measure of drug activity expressed in terms of the amount required to produce an effect of given intensity)

- **High Potency (Drug A)**

- Clonazepam (Klonopin)
- Alprazolam (Xanax)
- Lorazepam (Ativan)
- Triazolam (Halcion)

- **Low Potency (Drug B)**

- Chlordiazepoxide (Librium)
- Clorazepate (Tranxene)
- Diazepam (Valium)





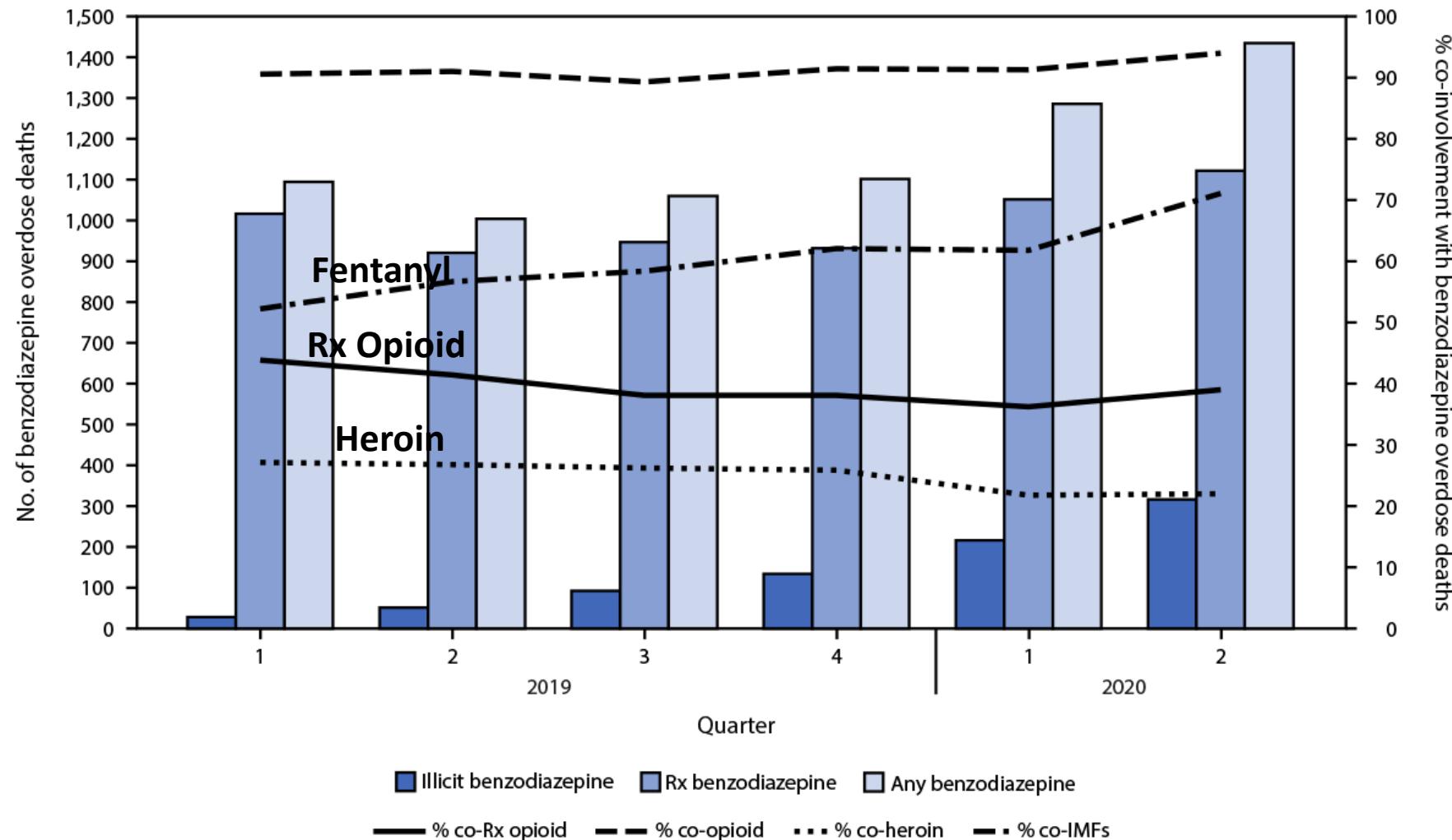
Benzodiazepine: General Info

- Controlled IV DEA classification.
- Although more than 2,000 different benzodiazepines have been produced worldwide, only about 15 are currently FDA-approved in the United States.
- The use of benzodiazepines during pregnancy is a risk factor for cleft lip or palate, lower muscle tone, and withdrawal symptoms in the developing fetus.

Bachhuber, et al. *American Journal of Public Health*. April 2016;106.

Jone and McAnnich. *Am J Prev Med*. 2015 Oct;49(4):493-501. E-medicine Health.

FIGURE 2. Benzodiazepine Overdose Deaths with Opioid Co-involvement — State Unintentional Drug Overdose Reporting System, 23 States,* January 2019–June 2020[†]



Abbreviations: co = co-involved; IMFs = illicitly manufactured fentanyl; Q = quarter; Rx = prescription.

Liu et al., MMWR, 70(34) 1136-41; 2021



Longer Term Outcomes of Tranquilizer Use (e.g., BZP) in Middle Aged Americans

- **Design:** Up to 15 year Monitoring the Future longitudinal study of 19,209 HS students
- Focus on medical & medical+misuse of tranquilizers (e.g., BZP)
- **Findings** (Age 35 to 50 years old):
- At age 35, 30% used BZP: 11% medically only, 7.9% medically + misuse, and 12% misuse only
- Among those with medical BZP use at age 35:
 - **11% developed prescription BZP misuse**
 - **42% developed two or more SUD symptoms**
- **BZP misuse was associated with an even higher SUD risk**

McCabe et al. *JAMA Netw. Open* 2022 Jan 4; 5:e2141995.



BZP Use in Drug Use Disorders

- Danish Registry Study
- N=33203 patients admitted to outpatient SUD treatment receiving BZP
- After first year of treatment, 26% of pts receiving BZP
 - Of these, 36% on higher than average doses
- Among those with Opioid Use Disorders-> 43% on BZP compared to 12% of those with Cannabis Use Disorder
- Almost 30% of patients were NEW users of BZP
- Conclusion: Concerns about inappropriate use of BZPs



BZP Demographics in Context to SUD

- NSDUH Study (N = 86,186)
- 13% of adults with past year BZP use (10.4% as prescribed and 2.2% misuse; misuse accounts for 17.2% of overall use)
- Highest misuse in 18-25 years
- Friend/relative most likely supplier of Rx BZP
- Misuse and abuse/dependence of Rx opioids or stimulants associated with BZP misuse/use disorders

BZP Use in SUD Debate: Yes



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- Generalized Anxiety Disorder (GAD) is a serious disorder necessitating treatment
- BZP are effective treatments for GAD
- Use in pts with opioid use disorder most frequently cited as GAD Tx
- Risk of BZP may be overstated
- Low level of BZP escalation in general population

(Park, TW; Debate. J Addiction Medicine 11(2): p 87-89 2017

BZP Use in SUD Debate: Yes



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- Data that BZP escalation in patients with SUD (alcohol) is similar to that in general population (e.g. Mueller et al 1996)
- Other data suggesting SUD=Psychiatric Disorders > General population (but not robustly)
- Confound related to stats on overdose deaths with opioids, other in combination with BZP due to high level of GAD in SUD groups (and treatment with BZP therapeutically). Interestingly, antidepressants also linked to OD in other SUD (Zedler et al. 2014)—confound?

(Park, TW; Debate. J Addiction Medicine 11(2): p 87-89 2017



Detection of Sedative/Hypnotics

- Benzodiazepines
 - Major metabolites detected in urine
 - Detection based on $\frac{1}{2}$ lives:
Long acting-diazepam (10d), intermediate acting-lorazepam, clonazepam (5 days), short acting-triazolam (2d)
 - Saliva testing—2-3 days for all (may improve with time)
 - Some difficulties with higher potency BZPs (e.g. lower mg exposure leads to false negatives)

Weizman et al. *Australian and New Zealand Journal of Psychiatry*. 2003;37:458–463.

O'Brient et al. *J Clin Psych*. 2006;66:28-33.



Treatment of BZP Use Disorder

- Determination of level of care
- Detoxification from benzodiazepine (inpatient or outpatient)
- Evaluation of comorbidities (e.g., anxiety, depression, SUD, medical)
- Psychotherapies
 - Cognitive Behavioral Therapy
 - Supportive Care
- Pharmacotherapy

Weizman et al. *Australian and New Zealand Journal of Psychiatry*. 2003;37:458–463.

O'Brient et al. *J Clin Psych*. 2006;66:28-33.



BZP Withdrawal (Acute)

- Similar to alcohol withdrawal
- Management settings:
 - Outpatient (slow taper; exogenous BZP)
 - Inpatient (benzodiazepine or phenobarbital challenge and taper)
 - Suggest use of higher potency benzodiazepines
 - Suggest use of CIWA
- Chronic benzodiazepine withdrawal symptoms



BZP (Alcohol, Barbiturate) Withdrawal Inpatient Management

1. Institute CIWA monitoring at minimum q4H. CIWA monitoring may be performed more frequently per nursing discretion. Clonazepam should be initiated for CIWA > 8.
2. Clonazepam 0.5-1 mg po q 2-4 hr PRN s/sx of BZP withdrawal during initial 36 hours from time of admission. Once withdrawal period begins and first dose of clonazepam is administered, patient has 24 hours to complete clonazepam challenge. Call MD to exceed 4 mg/24 hr challenge period.
3. Taper from day 1 total dose of clonazepam by 0.5-1 mg/day in divided doses (BID-QID as tolerated).

Wilens TE, Herzog L, Renner J. *J Am J Addict.* 1993;2(4):325-329.



Treatment of BZP Use Disorder

- Use of nonbenzodiazepines
 - Topirimate for core urges/cravings
 - Buspirone (pearl-use higher dose [e.g., 20 mg TID])
 - SSRI, SNRI
 - Beta blockers, alpha agonists
 - Gabapentin, pregabalin, low dose quetiapine (refractory cases)
- Benzodiazepines
 - RCT evidence of therapeutic clonazepam acceptable in past BZP use disorders (Weizman)
 - Use of lower abuse liability BZP (e.g., clorazepate; Tranxene)

Weizman et al. *Australian and New Zealand Journal of Psychiatry*. 2003;37:458–463.

O'Brient et al. *J Clin Psych*. 2006;66:28-33.



BZP Case: Return to Next Steps

- What would appropriate next steps for Susan include
 - Discharging Susan from the clinic
 - Immediately admitting Susan for BZP detox
 - Trying buspirone, a serotonergic, or serotonergic / noradrenergic agent
 - Trying an antipsychotic (e.g. quetiapine)
 - Starting Susan on a BZP other than clonazepam
 - Starting Susan on a BZP - clonazepam



Chronic BZP Withdrawal (W/D) Symptoms

- **50-80% of BZP use > 3-6 weeks results in some W/D symptoms**
- **Lower risk for W/D symptoms when detoxing with BZP vs beta blockers**
- **Acute W/D 2-5d, then up to 2 weeks; more chronic symptoms may be return of anxiety**
- **Chronic, low level post-acute “withdrawal” symptoms reported in minority of patients trying to discontinue BZP**
 - Some anecdotal evidence of successful management with very low dose high potency BZP taper over months; use of gabapentin or topiramate

Petursson H. *Addiction*. 1994;89:1455-59.

Cantopher et al. *Br J Psych*. 1990;156(3):406-411.



Summary: Benzodiazepines

- Cross tolerance between BZP (and alcohol)
- Rapid development of tolerance, physiological dependence; sometimes addiction
- Abuse liability varies among BZPs
- BZPs can be (carefully) used in patients with SUD-consider clorazepate (Tranxene)
- Often short- and longer-term withdrawal symptoms
- Treatment combines MI/CBT, pharmacotherapy, and treatment of underlying comorbidities