Benzodiazepines

July 1, 2019

Agenda

12:00 to 12:05 PM
Welcome/Housekeeping Rules
Liezel Lago, Continuing Education Program Coordinator

12:05 to 12:10 PM
Introduction
Jeffrey DeVido MD, MTS; *Chief, Addiction Services*,
Marin County; Clinical Behavioral Health Director

12:10 to 12:45 PM
Benzodiazepines
Jeffrey DeVido MD, MTS; Chief, Addiction Services,
Marin County; Clinical Behavioral Health Director, Partnership HealthPlan of California (PHC)

Alex Threlfall, MD; Chief of Psychiatry, Santa Rosa Community Health

David Kan, MD; Chief Medical Officer, Bright Heart Health

12:45 to 12:55 p.m.
Question & Answer Discussion
Presenter Name

12:55 PM
Adjourn

No Conflict of Interest

Presenters have signed the Conflict of Interest form and have declared there is no conflict of interest and nothing to disclose for this presentation.

**This Live activity, It Takes a Team: PHC Clinician Trainings on Substance Use Disorder, from 03/13/2019-12/31/2019, has been reviewed and is acceptable for up to 1.00 Prescribed credit(s) by the American Academy of Family Physicians. Physicians should claim only the credit commensurate with the extent of their participation in the activity.*

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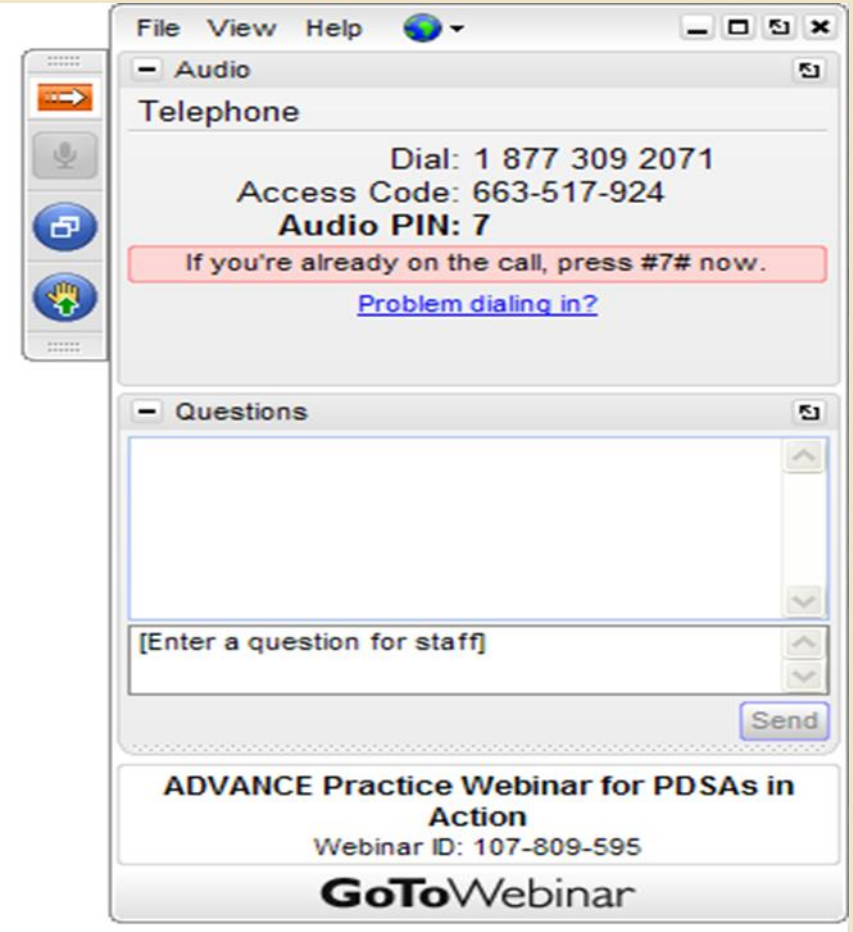

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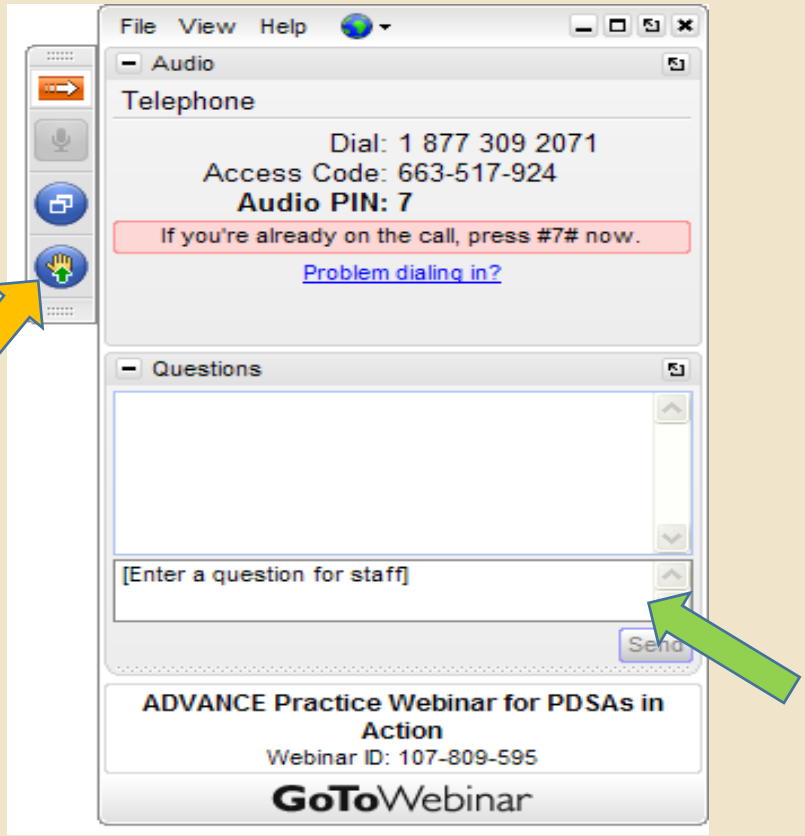
Webinar Instructions



- All participants have been muted to eliminate any possible noise interference/distraction.

- If you have a question or would like to share your comments during the webinar, **please type your question in the "question" box or click on the "raised hand" icon.**

Jeffrey DeVido, MD, MTS

Presenters

- **Jeffrey DeVido MD, MTS**; Chief, Addiction Services, Marin County; Clinical Behavioral Health Director, Partnership HealthPlan of California (PHC)
- **David Kan, MD**; Chief Medical Officer, Bright Heart Health
- **Alex Threlfall, MD**; Chief of Psychiatry, Santa Rosa Community Health

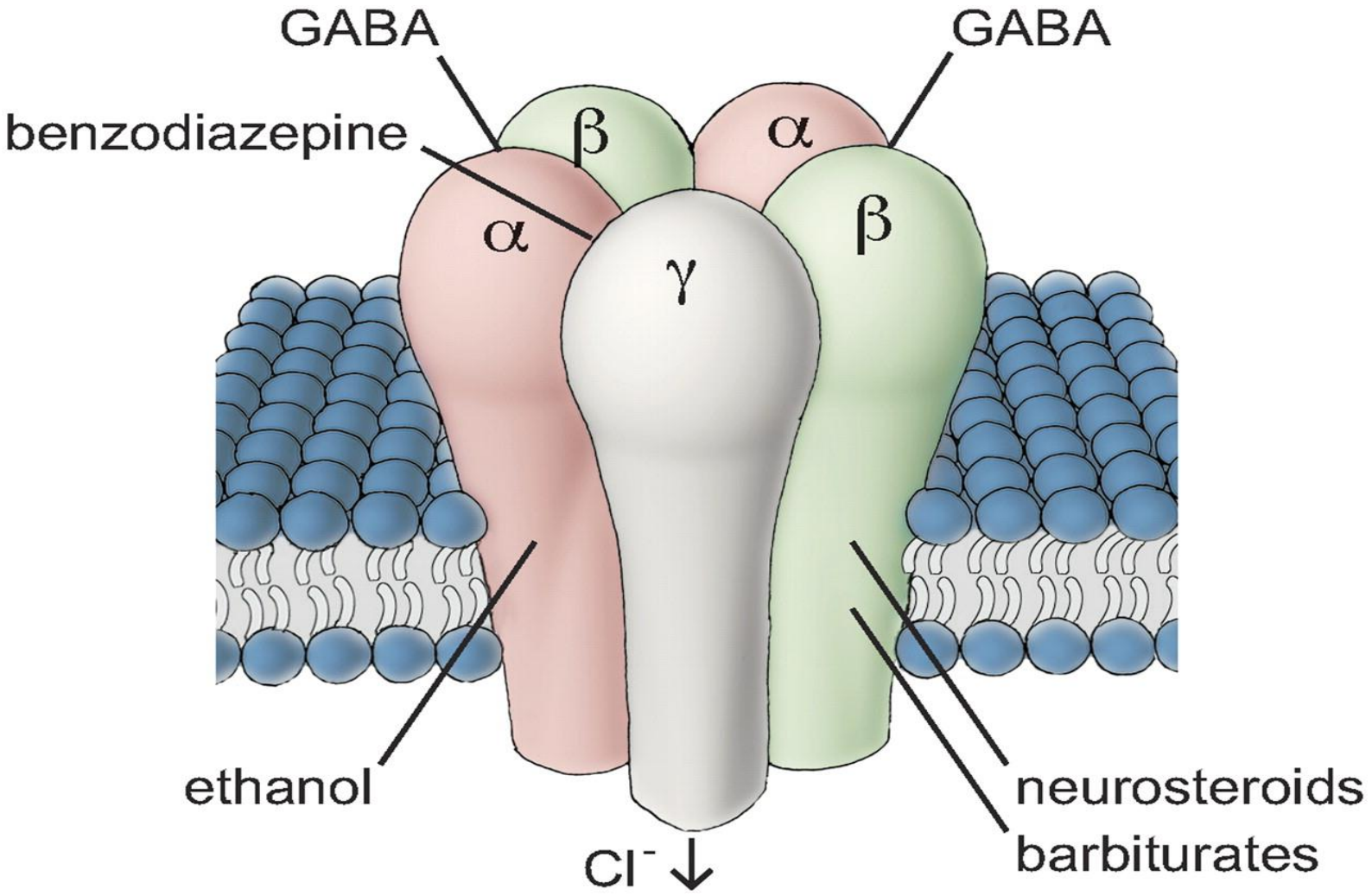
Objectives

- Pharmacology of benzodiazepines
- Physiologic responses to use of benzodiazepines
- Risks of benzodiazepine use
- Prescribing considerations: new starts vs. chronic long-term users vs. illicit/BUD users
- Anxiety and insomnia considerations
- Prescribing approaches
- Adjunctive medications

What are benzodiazepines?

- Sedative-hypnotic medications
  - Uses: anxiety and panic disorders, insomnia, muscle spasm, withdrawal states (especially from alcohol), anesthesia, and seizures
- Heterogenous class of medications that modulate the receptor for the primary inhibitory neurotransmitter (gamma-aminobutyric acid, or GABA) in the brain: the GABA-A receptor.

What are benzodiazepines?



Z-Drugs

The so-called “Z-Drugs” (zolpidem, zopiclone, zaleplon) are technically **not** benzodiazepines (chemically), but their mechanism of action is at the benzodiazepine subsite on the GABA-A receptor, similar to “benzodiazepines”

Differentiating benzodiazepines

How do we differentiate benzodiazepines? Duration of action and potency.

- **Long Acting ($t_{1/2}$ >24hrs)**:
  - Clonazepam 0.5mg
  - Chlordiazepoxide 25mg
  - Diazepam 10mg

- **Medium Acting ($t_{1/2}$ between 12 and 24hrs)**:
  - Lorazepam 1mg
  - Temazepam 20mg
  - Alprazolam 0.5mg

- **Short Acting ($t_{1/2}$ <12hrs)**:
  - Midazolam 2.5mg
  - Oxazepam 20mg
  - Zolpidem 20mg*
  - Zaleplon 20mg*
  - Zopiclone 15mg*

Differentiating benzodiazepines

PHARMACOKINETICS AND PHARMACODYNAMICS

Benzodiazepine	Onset of Action[1]	Peak Onset (hrs)	Half-life parent (hrs)	Half-life metabolite (hrs)	Comparative Oral Dose
Long Acting					
Chlordiazepoxide	Int. (po)	2-4(po)	5-30	3-100	**10 mg**
Diazepam	Rapid (po, IV)	1(po)	20-50	3-100	**5 mg**
Flurazepam	Rapid	0.5-2	inactive	47-100	**30 mg**
Intermediate Acting					
Alprazolam	Int.	0.7-1.6	6-20	-	**0.5mg**
Clonazepam	Int.	1-4	18-39	-	**0.25mg**
Lorazepam	Int. (po), Rapid (sl, IV)	1-1.5 (po)	10-20	-	**1mg**
Oxazepam	Slow	2-3	3-21	-	**15mg**
Temazepam	Slow	0.75-1.5	10-20	-	**30mg**
Short Acting					
Midazolam	Most Rapid IV	0.5-1 (IV)	1-4	-	**-**
Triazolam	**Int.**	**0.75-2**	**1.6-5.5**	**-**	**0.5mg**

Benzodiazepine Drug Interactions

BENZODIAZEPINE DRUG INTERACTIONS	Clinical Concern
CNS depressants (ex: opioids, alcohol)	Increased risk of overdose and death. Avoid concomitant use.
CYP3A4 inducers (ex: carbamazepine, phenytoin)	Decreases levels of alprazolam, clonazepam and diazepam which are metabolized by CYP3A4.
CYP3A4 inhibitors (ex: fluconazole, diltiazem, grapefruit juice)	Increases levels of alprazolam, clonazepam and diazepam which are metabolized by CYP3A4.
Omeprazole	Increases the concentration of diazepam and prolongs its half-life.
Estrogen containing contraceptives	Increases the concentration of alprazolam. Decreases the concentration of lorazepam, oxazepam and temazepam which are metabolized via glucuronidation.

Physiologic tolerance and withdrawal

What can happen when you take benzodiazepines?

- **Physiologic tolerance**:
  - Speed of development is dependent on individual factors, amount of benzodiazepine used, and type of benzodiazepine.

- **Withdrawal**:
  - Potentially life-threatening acute withdrawal syndrome
  - Months-long, “protracted withdrawal”

Withdrawal

- **Acute Withdrawal**
  - Onset (from hours to days after discontinuation).
  - Generally, the longer the $t_{1/2}$, the more delayed the onset of acute withdrawal symptoms may be.
    - 40% of people on benzodiazepines for more than 6 months will have a moderate to severe withdrawal, and the remaining 60% will have a relatively mild withdrawal syndrome, if stopped suddenly.
- **Protracted Withdrawal**
  - 15–44% of chronic benzodiazepine users experience protracted moderate to severe withdrawal symptoms (emergent anxiety and depressive symptoms).
  - 10–25% of chronic benzodiazepine users suffer protracted withdrawal symptoms upon cessation

Withdrawal

- Acute withdrawal syndrome presentation can vary greatly from individual to individual, with common symptoms including:
  - Tremors
  - Anxiety
  - Perceptual disturbances
  - Dysphoria
  - Psychosis
  - Seizures

Alex Threlfall, MD

Other Benzodiazepine Risks

- Benzodiazepines can be misused/abused for both non-medical and recreational purposes.
  - Diversion from legitimate prescriptions is a common source
  - Illicitly manufactured benzodiazepines are increasingly common, oftentimes adulterated with other potentially harmful fillers and additives, such as the potent synthetic opioid, fentanyl.
- Benzodiazepine overdose can result in **death from respiratory depression/arrest**, most typically when co-ingested with other substances that can also decrease respiratory drive, such as opioids, barbiturates, and/or alcohol. Intravenous benzodiazepine use particularly increases the risk of respiratory depression/arrest

Other Benzodiazepine Risks

- Falls
- Over-sedation
- Cognitive impairment (may not remit after discontinuation)
- Confusion/delirium (especially in elderly or medically compromised)
- Floppy infant syndrome/possible fetal malformations (eg, anal atresia with Ativan, esp during 2nd trimester)
- Addiction, amnesia, paradoxical stimulation, impaired motor control, impaired sleep architecture, decreased inhibitions, mood changes

- Some individuals are at higher risk of negative consequences:
  - Mental health conditions associated with trauma
  - History of substance use disorders
  - Elderly or cognitively impaired
  - TBI
  - Compromised pulmonary function
  - Women of childbearing age
  - Patients with chronic pain, with or without opioid use

Regulation of Benzodiazepines

- **DEA Schedule IV controlled substances**
  - California prescribers working outside of inpatient acute care settings are mandated to check the California CURES database within 24 hours of prescribing a benzodiazepine medication, and every 4 months if benzodiazepines are being prescribed on an ongoing basis.
  - If co-prescribed with an opioid, California prescribers are also mandated to offer naloxone prescription

Prescribing Considerations

- New starts

vs.

- Chronic long-term users (prescribed)

vs.

- Illicit benzo users/benzodiazepine use disorder

Prescribing Considerations: New Starts

- Historically, commonly prescribed for **insomnia** and **anxiety/panic**
- Benzodiazepines are **NOT** considered first-line pharmacologic interventions for these conditions.
- Many clinics are restricting or eliminating new starts
- For seizures or muscle spasm (ie, MS), consider specialty consultation

Prescribing Considerations: Anxiety

- 2019 meta-analysis, short-term use of benzodiazepines was not found to be effective in the treatment of generalized anxiety disorder.
- **3rd Line** intervention for anxiety, after failing 1st and 2nd line (SRCH):
  - **1st line pharmacotherapy** +/- CBT for anxiety/PTSD/panic, Mindfulness, Meditation, DBT and/or other evidenced based psychotherapy
    - SSRI/SNRI
    - Buspirone (target dose range 10-30mg TID standing or prn)
  - **2nd line pharmacotherapy** +/- CBT for anxiety/PTSD/panic, Mindfulness, Meditation, DBT and/or other evidenced based psychotherapy
    - Gabapentin, pregabalin, propranolol, clonidine
    - Amitriptyline/nortriptyline
    - Hydroxyzine, diphenhydramine
  - **Individual or group therapy requirements**
    - Documentation of attending at least 2 sessions in full *and* documentation of why further psychotherapy, if indicated, is inappropriate or not recommended for the identified patient.

Prescribing Considerations: Anxiety

- Both diphenhydramine and hydroxyzine should be avoided in elderly individuals and those with cognitive impairment, owing to the propensity of anticholinergic medications to cause delirium.

- Gabapentin (off label) and pregabalin (off label in US, but approved for generalized anxiety disorder in European countries) both have abuse potential and have also been tied to increased risk of respiratory depression when used with opioids, so use these medications with attention to these risks.

Prescribing Considerations: Insomnia

- The American Association of Family Physicians (AAFP) recommends against using any benzodiazepine as a first-line option for insomnia

- Both the American Academy of Sleep Medicine and the European Sleep Research Society task forces indicate that behavioral interventions (i.e., CBT-I) should be considered first-line with only weak evidence to support the use of benzodiazepines in the treatment of insomnia longer than 4 weeks.

- The European Sleep Research Society task force also supported the notion that non-benzodiazepine Z-Drugs were equally effective as benzodiazepines during this short initial treatment period. Neither task force supported the use of benzodiazepines or non-benzodiazepine Z-Drugs for longer than 4 weeks.

Prescribing Considerations: Insomnia

- 4th line = benzodiazepines (SRCH)
- **1st line**
  - CBTi
    - Required documentation of attending at least 2 sessions in full *and* documentation of why further psychotherapy, including mindfulness, meditation and/or other CBTs, is inappropriate or not recommended for the identified patient.
- **2nd line**
  - Trazodone > mirtazapine > doxepin*> amitriptyline*/nortriptyline
  - Prazosin (nightmares)
  - Melatonin
  - Non-formulary (NF): ramelteon (Rozerem), suvorexant (Belsomra)
- **3rd line**
  - Hydroxyzine*, diphenhydramine*
  - Non-BZD-receptor agonist (NBRA) hypnotics: Zolpidem* > eszopiclone* > zaloplon* (med holidays highly encouraged – dispense < 14d supply for 2 weeks)

* NOT RECOMMENDED IN OLDER ADULTS and CONTRAINDIATED IN INDIVIDUALS WITH COGNITIVE IMPAIRMENT

Prescribing Approaches: If You Are

- Should be exceedingly rare
- ONLY for short-term symptomatic relief of severe anxiety/panic (2-4 weeks), and short-term relief of chronic insomnia (1-2 weeks)
- Obtain consultation from a psychiatrist who can review the chart and advise
- Explicitly advise the patient regarding the short duration and limited goal of treatment.
- Review with the patient the risks and side effects, including the risk of dependence.

Prescribing Approaches: If You Are

- Discuss exit strategies, such as short tapering or switching to alternative treatments.
- Agree on need for only one provider to be the benzodiazepine prescriber
- The prescribing provider should document clearly the list of failed attempts at more appropriate 1st, 2nd, and 3rd line treatments.
- Acquire UDS with send out for reflex confirmation and check CURES
- Treatment agreement (see next slide)
- <u>Limit TDD as below:</u>
  - Lorazepam 2mg TDD
  - Clonazepam 1.5mg TDD
  - Diazepam 15mg TDD
  - Temazepam 30mg TDD

Prescribing Approaches: If You Are

- Keep medications safe = lockboxes, safe disposal options
- Document clear treatment plan
- Document coordination of care with other providers
- Obtain peer consultation if indicated

Prescribing Approaches: If You Are

- Treatment agreements-- https://www.drugabuse.gov/sites/default/files/files/SamplePatientAgreementForms.pdf

Prescribing Approaches: If You Are

Patient Agreement Form

Patient Name:
Medical Record Number: **Addressograph Stamp:**

AGREEMENT FOR LONG TERM CONTROLLED SUBSTANCE PRESCRIPTIONS

The use of_____(print names of medication(s)) may cause addiction and is only one part of the treatment for:_____(print name of condition—e.g., pain, anxiety, etc.).

The goals of this medicine are:

- ☐ to improve my ability to work and function at home.
- ☐ to help my_____(print name of condition—e.g., pain, anxiety, etc.) as much as possible without causing dangerous side effects.

I have been told that:

1. If I drink alcohol or use street drugs, I may not be able to think clearly and I could become sleepy and risk personal injury.
2. I may get addicted to this medicine.
3. If I or anyone in my family has a history of drug or alcohol problems, there is a higher chance of addiction.
4. If I need to stop this medicine, I must do it slowly or I may get very sick.

I agree to the following:

- I am responsible for my medicines. I will not share, sell, or trade my medicine. I will not take anyone else's medicine.
- I will not increase my medicine until I speak with my doctor or nurse.
- My medicine may not be replaced if it is lost, stolen, or used up sooner than prescribed.
- I will keep all appointments set up by my doctor (e.g., primary care, physical therapy, mental health, substance abuse treatment, pain management)
- I will bring the pill bottles with any remaining pills of this medicine to each clinic visit.
- I agree to give a blood or urine sample, if asked, to test for drug use.

Refills

Refills will be made only during regular office hours—Monday through Friday, 8:00AM-4:30 PM. No refills on nights, holidays, or weekends. I must call at least three (3) working days ahead (M-F) to ask for a refill of my medicine. **No exceptions will be made**. I will not come to Primary Care for my refill until I am called by the nurse.

I must keep track of my medications. No early or emergency refills may be made.

Pharmacy

I will only use one pharmacy to get my medicine. My doctor may talk with the pharmacist about my medicines.
The name of my pharmacy is_____.

1

Prescriptions from Other Doctors

If I see another doctor who gives me a controlled substance medicine (for example, a dentist, a doctor from the Emergency Room or another hospital, etc.) I must bring this medicine to Primary Care in the original bottle, even if there are no pills left.

Privacy

While I am taking this medicine, my doctor may need to contact other doctors or family members to get information about my care and/or use of this medicine. I will be asked to sign a release at that time.

Termination of Agreement

If I break any of the rules, or if my doctor decides that this medicine is hurting me more than helping me, this medicine may be stopped by my doctor in a safe way.

I have talked about this agreement with my doctor and I understand the above rules.

Provider Responsibilities

As your doctor, I agree to perform regular checks to see how well the medicine is working.

I agree to provide primary care for you even if you are no longer getting controlled medicines from me.

_____ _____
Patient's signature Date

_____
Resident Physician's signature

_____
Attending Physician's signature

☐ This document has been discussed with and signed by the physician and patient. (A signed copy stamped with patient's card should be sent to the medical records department and a copy given to the patient.)

David Kan, MD

Prescribing Considerations

- Illicit benzo users/benzodiazepine use disorder

Vs.

- Chronic long-term users (prescribed)

Prescribing Considerations: Illicit Benzo Users/BUD

- Distinguished by presence of 2 or more of the diagnostic criteria for SUD set forth in the DSM-5. Note that the presence of tolerance or withdrawal alone do not constitute sedative-hypnotic use disorder (addiction).
- Certain patient populations appear to be at higher risk of developing sedative-hypnotic use disorder, especially those with histories of other substance-related and addictive disorders, as well as those who have sustained trauma
- **Tapers will be nearly always indicated**, although tapering approaches and considerations will be the same as those of long-term users of benzodiazepines who do not meet diagnostic criteria for sedative-hypnotic use disorder (addiction).
- Adjunctive SUD counseling and services can be helpful in addressing behavioral aspects of SUD.

Prescribing Considerations

For chronic long-term users (prescribed)

- **Explore diagnostic clarification**
  - Long term benzodiazepine treatment (longer than 4 weeks) is rarely indicated and diagnostic clarification may prove helpful.
  - For patients on long term benzodiazepines for medical reasons (e.g., seizure disorders, muscle spasm), clarification of diagnosis and treatment plan with specialty care (e.g., neurology) is important.

Prescribing Considerations

For chronic long-term users (prescribed)

- Engage patient in conversation regarding risks/benefits/alternatives of benzodiazepine use as above
- Document clear **treatment plan** with goals of care, duration, measures by which treatment effect will be monitored
- Small quantities, no automatic refills, frequent check-ins with clinic of provider directly, urine drug testing

Prescribing Considerations: Tapering

- Abrupt discontinuation is not advised.
- All tapers should be undertaken on a voluntary basis. Tapering of benzodiazepines is a collaborative process.
- Rate of tapers are not universal, since withdrawal symptoms can vary between individuals. Therefore, taper regimens should tailored and/or adjusted on an individual basis
- Generally, tapers are done very slowly over the course of several weeks to a year or more. Note that discontinuation approaches from long term use of alcohol and benzodiazepines are fundamentally different.
- Due to the long taper timeframe, nearly all benzodiazepine tapers can be undertaken in the outpatient setting, except when there are significant medical or psychiatric comorbidities and/or when starting doses of benzodiazepines are extremely high (e.g., >100mg daily diazepam
- Emergence of psychiatric symptoms during benzodiazepine tapering (anxiety, mood symptoms, psychosis) may require psychiatric consultation and adjunctive psychopharmacologic interventions.

Prescribing Considerations: Tapering

- **Tapering Goal(s):**
  - In some individuals, tapering to complete discontinuation is desired and safe
  - In other individuals tapering to a lower, safer, dosing amount is desired and safe whereas discontinuation may not.
  - Determination of tapering targets may change over the course of treatment based on individual factors, such as emergence of medical or psychiatric instability or lack thereof despite initial fears of their inevitable emergence.
  - In short, ongoing risk-benefit analyses of treatment goals are an important part of the client-provider collaboration.

Prescribing Considerations: Tapering

- **General principles**:
  - Taper rates vary from 50% a week to 10% every few weeks, and rate is largely driven by individual client factors.
  - In the case of use of multiple benzodiazepines, consolidating taper to one benzodiazepine is commonly undertaken (typically a long half-life benzodiazepine)
  - Consider taper for anyone on a multiple daily dose of a BZD > 2 weeks
  - Taper should be *scheduled* dosing and not PRN
  - Never taper more than one agent at the same time
  - Set clear goals with the patient
  - Increase frequency of visits
    - Monitor for objective signs/symptoms of withdrawal
      - BP/HR/Temp > 100, tremor, sweating

Prescribing Considerations: Tapering

- **Before starting**:
  - A team-based approach will be most effective in efforts to taper a patient from BZD
  - When in doubt consult behavioral health and/or psychiatry
  - It is essential to build a stable relationship with your patient and plan together the parameters of the taper *before* starting.
  - Evaluate and treat any co-occurring conditions
  - Obtain complete drug and alcohol history, UDS and last 12 months of CURES data
  - Review recent medical notes (ER visits) and coordinate care with other providers to ensure no other potential sources of BZDs or other controlled substances.
  - Have patient sign the treatment agreement.

Prescribing Considerations: Tapering

- **Taper approach #1**: Use the same benzodiazepine that the client is using and set taper schedule
- **Taper approach #2**: Gradually switch individual to long-acting benzodiazepine (e.g., diazepam)
- **Taper consideration #3**: In some instances, cross titration to longer acting benzodiazepines is unsuccessful. In particular, longer acting benzodiazepines may not completely cover alprazolam withdrawal. This may necessitate a taper using alprazolam—approach #1 above

- +/- **Adjunctive medications**

Example 1: "Rapid" Benzodiazepine Taper

Starting dose **lorazepam 2 mg BID** (4 mg total daily dose)—SRCH

TIMELINE	GOAL	NEXT DOSE	DOSING EXAMPLES
Week 1	Total dose reduction 25%	3 mg/day	2mg qam/1mg qhs 1mg qam/2mg qhs 1mg TID
Week 2/3	Total dose reduction 50%	2 mg/day	1mg BID Various TID combos (i.e. 0.5/0.5/1)
Week 3/4	Hold dose x 1mon	2 mg/day	Same or adjust per patient preference
Week 5	Current dose reduction by ~25% at 1-2 week interval	1.5 mg/day	0.5mg qam/1mg qhs 0.5/0.5/0.5
Week 6/7		1.25 mg/day	0.25mg qam/0.5mg qhs 0.25/0.5/0.5
Week 7/8		1 mg/day	0.5 BID 0.25/0.25/0.5
Week 8/9		0.75 mg/day	0.25mg qam/0.5mg qhs 0.25 TID
Week 9/10		0.5 mg/day	0.25 BID 0.5mg qhs
Week 10/11		0.25 mg/day	0.25mg qhs
Week 12		discontinue	

Notes: Duration of time in between each step should be at least 2 weeks for chronic users, and up to 1-2 months. At lower doses, exact 25% reductions may not be possible given available pill doses; round up or down based on previous experience with patient tolerating dose reductions in earlier steps of the taper. For divided doses, engage patient in deciding which dose they want to decrease at each step.

Example 2

Withdrawal from high dose (6mg) alprazolam daily with diazepam (Valium) substitution. (6mg alprazolam is approximately equivalent to 120mg diazepam) — ASHTON METHOD

	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

Example 2

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

— ASHTON METHOD

	Morning	Midday/Afternoon	Evening/Night	Daily Diazepam Equivalent
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

Example 3: Simple withdrawal from diazepam (Valium) 40mg daily(follow this schedule to complete ***Example 2***)

	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
Stage 25 (1-2 weeks)	--	diazepam 2mg	2mg
Stage 26 (1-2 weeks)	--	diazepam 1mg	1mg

Prescribing Considerations: Adjunctive Taper Medications

- Adjunctive medications not well studied. There is limited literature supporting the following for adjunctive symptomatic benefit:
  - **antidepressants** (trazodone 25-150mg Nightly, mirtazapine 7.5-45mg Nightly, doxepin 10-150mg Nightly),
  - **mood stabilizers** (carbamazepine 200mg BID),
  - **antihistamines** (diphenhydramine 25-50mg Nightly, promethazine (25-200mg Nightly), hydroxyzine 25-75mg Nightly, doxylamine 25-50mg Nightly),
  - **melatonin**
  - **Beta blockers** (propranolol 10mg TID)
  - **Antiepileptic medications**:
    - Pregabalin 50-200mg TID
    - Gabapentin 300-600mg TID

Prescribing Considerations: Adjunctive Taper Medications

- **Flumazenil:**
  - There is a small literature on the use of flumazenil (benzodiazepine receptor antagonist) to help in the relief of **protracted withdrawal** symptoms, in particular. However, its poor PO bioavailability make administration challenging by either intravenous, subcutaneous injection

Questions

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