KAISER PERMANENTE®

NATIONAL PERMANENTE MEDICAL GROUPS
CLINICIAN PRACTICE RECOMMENDATIONS FOR
BENZODIAZEPINES & NON-BENZODIAZEPINE SEDATIVE-HYPNOTICS/Z DRUGS
(For Adults ≥ 18 Years Old)

Purpose

The purpose of these practice recommendations are:

- To reduce the number of patients who are at risk of becoming newly dependent, tolerant, or addicted to benzodiazepines (BZDs) and non-benzodiazepine sedative-hypnotics/"Z drugs" (nBZD-Zs).
- To safely monitor and taper as medically indicated patients who are already dependent on long-term, chronic BZDs or nBZD-Zs.
- To provide recommendations for limiting the use of BZDs and nBZD-Zs for treatment of anxiety, insomnia, and other disorders.
- To avoid prescription medication and/or substance combinations that place a patient at higher risk of morbidity and mortality.
- To address the use and monitoring of BZDs and nBZD-Zs for other indications and in special populations.

Key Points to Consider:

- ***These recommendations do not pertain to Palliative care, hospice, or other end of life care treatment.***
- These are PMG recommendations; however, all prescribers need to be aware of additional state and national laws and regulations involving BZDs or nBZD-Zs prescribing that may supersede these recommendations. For questions pertaining to specific jurisdictional requirements, please refer to your respective Regional compliance and/or legal resources.
- For any prescribing outside of these recommendations (which would also fall outside of the CDC recommendations), it is highly advised that the reason(s) be documented in the patient's medical record. Recommendations should not replace medical judgment and individual assessment of treatment risks and benefits.
- Our focus is to avoid the use of BZDs or nBZD-Zs by employing non-pharmacologic and alternative pharmacologic therapies first, and reserve BZDs and nBZD-Zs for only when necessary.
- Chronic daily BZDs or nBZD-Zs monotherapy should be avoided. For suspected fraud or diversion of controlled substances, contact your local Compliance Officer or Special Investigations Unit (SIU).

BENZODIAZEPINES & NON-BENZODIAZEPINE SEDATIVE-HYPNOTICS/Z DRUGS

(For Adults ≥ 18 Years Old)

Focus Area 1: Avoid New Start BZDs

Recommendation 1

1) Avoid BZD by employing non-pharmacologic and/or effective and safe pharmacologic options for anxiety related disorders, panic disorders, and insomnia.

2) Non-pharmacologic options are effective and may include:
   a. Provider education to patient on anxiety
   b. Kaiser Permanente Educational Programs
   c. CALM App
   d. myStrength App
   e. Exercise
   f. Mindful Meditation
   g. Consider reducing alcohol, caffeine and other substances that may increase anxiety
   h. If provider feels appropriate, patient can be referred for counseling, such as Cognitive Behavioral Therapy (CBT).

3) Patients with acute, severe anxiety should also be evaluated for depression and/or substance use disorder (SUD). Consider ordering a urine drug screen.

Recommendation 2

1) For a patient that presents with moderate to severe anxiety or panic attacks, initially start a SSRI, SNRI, or buspirone.

   Pharmacologic options may include:
   - SSRIs such as escitalopram, citalopram, sertraline, fluoxetine
   - SNRIs such as venlafaxine or duloxetine, or
   - Serotonergic agent for anxiety, such as buspirone
   - Propranolol and hydroxyzine can be considered in selected patients

2) SSRI and SNRI: Monitor closely in elderly patients for risk of falls, bleeding, or hyponatremia.

3) For Patients aged 65 years and over, avoid paroxetine, hydroxyzine, or TCAs.

4) If provider feels appropriate, evaluate the need for referral to Behavioral Medicine, Psychiatry, Mental Health, and/or Addiction Medicine.

Additional Recommendations/Comments

1) BZDs use may be considered for occasional, rare (intermittent/situational) anxiety such as for pre-MRI/CT scans, pre-procedure, or pre-chemotherapy, or single-event treatment of specific phobias, such as flying phobia.

2) In the rare case that a BZD is needed, set the expectation that it will only be for a brief period and not for chronic use. Use of short-acting BZDs, such as alprazolam (Xanax®), is especially hazardous, as it may cause more rapid dependence with severe withdrawal symptoms.

3) All BZDs can promote addictive behavior, delirium and agitation, risk for falls or injury, increased risk for dementia, and difficulty with tapering and discontinuing.

4) If other therapies are not effective and BZDs are being considered, they are generally reserved for situational, time limited, severe anxiety symptoms where functioning is compromised.

5) In rare circumstances, such as visible, acute, severe anxiety or debilitating panic attacks, consider:
   - Use of Propranolol and hydroxyzine in selected patients as a PRN.
   - A one-time small supply of a concurrent BZD for a brief period at the time of initiation of treatment with SSRI or SNRI i.e., prescribe a small quantity, with the smallest quantity necessary, with a maximum of up to 15 tabs/caps or less of a low dose and rapidly taper off the BZD within the first one or two weeks.
   - Avoid starting BZDs in patients who are concurrently using alcohol, any illicit drugs, Tetrahydrocannabinol (THC), any opioids, or other sedating drugs such as zolpidem (Ambien®).

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Focus Area 2: For Patients Already Prescribed BZD and nBZDs-Zs

Recommendation 1

1) BZDs and nBZD-Zs are not recommended for long-term use due to the risks of physical and psychological dependence, tolerance, potential for severe withdrawal symptoms, and persistent adverse side effects.
   - Abruptly stopping BZDs can lead to seizures and death.

2) Discuss significant risks of BZDs and nBZD-Zs and treatment options with patients to encourage them to taper BZDs and nBZD-Zs.
   - Address patients on BZDs or nBZD-Zs and use tapering recommendations.
   - Create a treatment care plan to help patients with tapering and discontinuation.
   - For most patients in primary care settings even a minimal intervention, such as a letter with self-help information from the treating physician or a single brief consultation, can be effective in reducing or stopping BZD use. (KPWA)

Recommendation 2

1) Tapering:
   - Consider starting an SSRI or SNRI before taper and provide education on non-pharmacologic therapy interventions such as behavioral therapies and other available resources to help manage symptoms. (McMaster)

2) Gradual Tapering General Guide:
   - Provide anticipatory guidance on the possibility of transient rebound anxiety. This anxiety is usually temporary, and rarely a reason to stop the taper.
   - Tapering schedules should be individualized. The duration of time the patient has been on BZDs can help determine the tapering plan depending upon risk of severe harm, patient's clinical need, and/or on a physician's clinical judgment.
   - Taper 10% a week if the patient has been on BZDs for several months or less, or 10% every 2 to 4 weeks if the patient has been on BZDs longer.
     - Slower taper by 5% may be needed if patient has symptoms of rebound anxiety and/or insomnia especially when at <20% original dose.

   If you are having trouble tapering the BZD, consider contacting Psychiatry.

Additional Recommendations/Comments

1) Consider consultation with an Addiction Medicine specialist if you believe the patient may have a Substance Use Disorder (not just physical dependence), especially if there is continued escalation of dose.

2) Consider consultation with behavioral/mental health for patients who have any of the following:
   - A concurrent significant psychiatric disorder
   - History of Substance Use Disorder
   - Concurrent use of prescription stimulants or opioids
   - A history of drug withdrawal seizures
   - Suicidal thoughts

3) Along with gradual tapering, non-pharmacologic options are recommended. When developing gradual taper care plan also consider counseling, including cognitive behavioral therapy, if available. This can be part of the therapy plan, to help the patient cope with rebound anxiety, assist with the withdrawal process, and improve the likelihood of long-term successful discontinuation.

4) Set the expectation of revisiting the topic at face-to-face visits, with a minimum expectation that this be discussed at least annually, possibly more frequently when there are changes in the patient's clinical situation.
   - If clinical decision is to continue the chronic use of BZD, then strongly consider conducting regular checks with UDS (urine drug screen) a minimum of every 12 months.
   - PDMP (prescription monitoring program) should be checked on an ongoing basis.

Kaiser Permanente National Mediation Committee. Approved 3/2021

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Focus Area 3: Acute Insomnia

Recommendation 1	Recommendation 2	Additional recommendations/Comments

Medication treatment for insomnia is not first line and is riskier and less effective than first line behavioral treatment.
 	
There is effective evidence-based treatment for insomnia, including:
• Provider education to patient on insomnia
  ○ Sleep Hygiene education
• Kaiser Permanente Educational Programs
• CALM App (includes many calming music options, sleep stories, guided meditation selections for focus, relaxation, and sleep)
• myStrength App
• Light therapy
• CBT-I App
• Exercise
• Mindful Meditation
• As applicable, reduce alcohol, caffeine and other substances that may increase insomnia, including prescription and non-prescription medication.
	Additional adjunctive pharmacologic treatment can be considered if no response to behavioral treatment and may include:
	30-60 minutes before sleep
	• Patients under 65:
	  ○ OTC Melatonin 3-6 mg HS PRN
	  ○ Trazodone 25-150 mg HS PRN (if no cardiac or other contraindications, titrate slowly- see Focus Area 3, additional recommendations/ comments)
	  ○ Doxepin 5-10 mg HS PRN, (Oral liquid, capsules, or tablets)
	  ○ Mirtazapine 7.5-15 mg HS PRN
	• Patients age 65 or older:
	  ○ OTC Melatonin 3-6 mg HS PRN
	  ○ OTC Acetaminophen ER 650 mg (8 hour)-QHS
	  ▪ Avoid Acetaminophen plus Diphenhydramine (Tylenol PM)
	  ▪ Most beneficial in patients who may be having some aches and pains affecting their sleep
	  ○ Trazodone 25-50mg HS PRN
	  ○ Mirtazapine 7.5-15 mg HS PRN
	  ○ Doxepin 5 mg HS PRN (oral liquid)
		Do not continue BZDs or nBZD-Zs insomnia medication continuously for longer than 2 weeks, not for chronic use.
		• Set the expectation with the patient that the medication will not be prescribed for chronic use.
		
		In rare circumstances of acute, severe, and debilitating insomnia, not responsive to behavioral treatment, a one-time small supply less than or equal to 15 pills of zolpidem 5 mg at bedtime for a brief period while the patient's evidence-based behavioral insomnia treatment is being adjusted, with no refills is recommended.
		• Physical dependence rapidly occurs within 2 weeks of continuous daily use.
		• Avoid in patients taking opioids and other sedative-hypnotics or substances with sedative effects such as alcohol, due to an increased risk of respiratory depression.
		• Avoid in Patients aged 65 years and over, due to increased adverse effects including fall risks and cognitive impacts.

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Focus Area 4: Chronic Insomnia		

Recommendation 1
 	
There is no indication for BZDs or nBZD-Zs for chronic insomnia. Patients presenting with chronic insomnia should not be treated with these drugs even for occasional prn use.
• Consider non-medication therapies and other medication alternatives (as mentioned in Focus Area 3: Acute Insomnia).
  ○ CBT-I Cognitive Behavioral therapy is the recommended primary treatment for chronic insomnia (continually assessing for improvement in insomnia and severity).
  ○ If CBT-I alone is inadequate, consider use of other medication (e.g. melatonin, trazodone).
• nBZD-Zs drug effectiveness commonly diminishes after 6 weeks of treatment.
• Also consider underlying conditions that may be causing the symptom of insomnia and address those root cause conditions or circumstances.
• For patients that are already taking BZD, do not abruptly stop, initiate a slow taper.
• Patients are at an increased risk of physical dependency and therefore are also at a higher risk of physical withdrawal when stopping therapy.
	Recommendation 2
	
	<u>Tapering</u>
	• nBZD-Zs should be discontinued similarly to BZDs (as mentioned in Focus Areas 2: For Patients Already Prescribed BZD and nBZD-Zs, Recommendation #2)
	• Alternatively, nBZD-Zs can be tapered by decreasing the number of days per week the patient takes a medication. For example, take 6 nights a week for 1-2 weeks, then 5 nights a week for 1-2 weeks and so on.
	  ○ Tapering schedules should be individualized.
		Additional recommendations/Comments
		
		For melatonin titration: start with 3 mg, escalate weekly if needed to 6 mg, max of 10 mg, at least 60-90 minutes before sleep.
		• Use with caution in geriatric patients with dementia who exhibit irregular sleep-wake disorder due to detrimental effects on daytime mood functioning.
		
		For Trazodone Titration: Consider low dose trazodone: start with 25 mg nightly (if no cardiac or other contradictions). Titrate slowly by 25 mg at night every 3-4 days if needed up to 150 mg nightly, 30 minutes before bedtime.
		In the adults 65 years and older, titrate slower, with lower doses up to 100 mg/day due to the increased risk of orthostatic hypotension and possible falls.

Focus Area 5: BZDs and nBZD-Z-drugs Combination with Other Drugs that Affect the CNS

- BZDs should not be used in combination with any substance with sedative hypnotic effects, such as alcohol, illicit drugs, opioids, or other nBZD-Zs such as zolpidem (Ambien®) that may place a patient at higher risk of morbidity and mortality due to CNS and respiratory depression.

- Concurrent use of BZDs and stimulant drugs (whether prescription or illicit), can hide symptoms of benzodiazepine overdose, may increase the risk of overdose and may cause dysrhythmias and possible heart failure.

- Concurrent use of BZDs and Tetrahydrocannabinol (THC) may place a patient at higher risk of morbidity and mortality due to combined cognitive impacts.

- **BZDs & Opioids:**
  - Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. (FDA)
  - For established patients presenting on chronic BZD and/or nBZD-Zs, if the patient is also on an opioid, the combination is not recommended due to a 20% to 60% higher risk of respiratory depression/overdose. It is recommended that either the sedative-hypnotics or the opioid be tapered off.
  - While the patient is being slowly tapered off either medication, patient and/or caregiver education on the risks of overdose and the use of naloxone should be strongly considered and a prescription for naloxone nasal spray, (Narcan®), should be offered due to the higher risk of respiratory depression/overdose when these drugs are combined.

Focus Area 6: Possible Alternative Uses of BZDs

Conditions where BZDs may be an appropriate treatment (although there may be more preferred treatment options with less risk and stronger level of evidence):

- Alcohol withdrawal
- Acute and chronic vertigo
- Specific phobias (e.g. fear of flying)
- Burning mouth syndrome
- Non-REM and REM Sleep Behavior Disorders
- Tourette's/Tic's
- Anticipatory chemotherapy induced nausea and vomiting
- Seizures
- Tinnitus

Other rare neurologic indications (e.g., Catatonia)

- Muscle spasticity syndromes

Refer to the prescribing information for the contraindications, warnings, and precautions.

References:

1. 2019 PMG National Clinician Practice Recommendations for Opioid Prescribing. Oakland: Permanente Medical Group;
2. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. Journal of the American Geriatrics Society. 2019;67(4):674–94.
3. Busse J. 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain [Internet]. The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain. McMaster University Michael G. DeGroote National Pain Centre; [cited 2021Mar9]. Available from: https://nationalpaincentre.mcmaster.ca/guidelines.html
4. Center for Drug Evaluation and Research. FDA expands Boxed Warning to improve safe use of benzodiazepine drug [Internet]. U.S. Food and Drug Administration. FDA; [cited 2021Mar9]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-requiring-boxed-warning-updated-improve-safe-use-benzodiazepine-drug-class
5. Cho J, Spence MM, Niu F, Hui RL, Gray P, Steinberg S. Risk of Overdose with Exposure to Prescription Opioids, Benzodiazepines, and Non-benzodiazepine Sedative-Hypnotics in Adults: a Retrospective Cohort Study. Journal of General Internal Medicine. 2020;35(3):696–703.
6. Coronavirus Anxiety Workbook: The Wellness Society: Self-Help, Therapy and Coaching Tools [Internet]. The Wellness Society | Self-Help, Therapy and Coaching Tools. The Wellness Society (Jamma International); 2020 [cited 2021Mar9]. Available from: https://thewellnesssociety.org/free-coronavirus-anxiety-workbook/
7. Day C. Benzodiazepines in Combination with Opioid Pain Relievers or Alcohol: Greater Risk of More Serious ED Visit Outcomes. 2014 Dec 18. In: The CBHSQ Report. Rockville (MD): Substance Abuse and Mental Health Services Administration (US); 2013–. PMID: 27631051.
8. Guina J, Merrill B. Benzodiazepines I: Upping the Care on Downers: The Evidence of Risks, Benefits and Alternatives. Journal of Clinical Medicine. 2018;7(2):17.
9. Guina J, Merrill B. Benzodiazepines II: Waking Up on Sedatives: Providing Optimal Care When Inheriting Benzodiazepine Prescriptions in Transfer Patients. Journal of Clinical Medicine. 2018;7(2):20.
10. Guina J, Rossetter SR, DeRhodes BJ, Nahhas RW, Welton RS. Benzodiazepines for PTSD. Journal of Psychiatric Practice. 2015;21(4):281–303.
11. Hassinger AB, Bletnisky N, Dudekula R, El-Solh AA. Selecting a pharmacotherapy regimen for patients with chronic insomnia. Expert Opin Pharmacother. 2020 Jun;21(9):1035-1043. doi: 10.1080/14656566.2020.1743265. Epub 2020 Mar 23. PMID: 32202451; PMCID: PMC7432988.
12. Insomnia: Relaxation techniques and sleeping habits [Internet]. InformedHealth.org [Internet]. U.S. National Library of Medicine; 2017 [cited 2021Mar9]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279320/
13. Jaffer KY, Chang T, Vanle B, Dang J, Steiner AJ, Loera N, Abdelmesseh M, Danovitch I, Ishak WW. Trazodone for Insomnia: A Systematic Review. Innov Clin Neurosci. 2017 Aug 1;14(7-8):24-34. PMID: 29552421; PMCID: PMC5842888.
14. McCleery J, Cohen DA, Sharpley AL. Pharmacotherapies for sleep disturbances in dementia. Cochrane Database of Systematic Reviews. 2016;
15. Ooms S, Ju Y-E. Treatment of Sleep Disorders in Dementia. Current Treatment Options in Neurology. 2016;18(9).
16. Papillon-Ferland (Pro) L, Mallet (Con) L. Should Melatonin Be Used as a Sleeping Aid for Elderly People? The Canadian Journal of Hospital Pharmacy. 2019;72(4).
17. Rague JM. Association Between Concurrent Use of Prescription Opioids and Benzodiazepines and Overdose: Retrospective Analysis. The Journal of Emergency Medicine. 2017;53(2):278–9.
18. Richardson K, Loke YK, Fox C, Maidment I, Howard R, Steel N, et al. Adverse effects of Z-drugs for sleep disturbance in people living with dementia: a population-based cohort study. BMC Medicine. 2020;18(1).
19. Riemersma-van der Lek RF. Effect of Bright Light and Melatonin on Cognitive and Noncognitive Function in Elderly Residents of Group Care Facilities. JAMA. 2008;299(22):2642.
20. Rosoff DB, Smith GD, Lohoff FW. Prescription Opioid Use and Risk for Major Depressive Disorder and Anxiety and Stress-Related Disorders. JAMA Psychiatry. 2021;78(2):151.
21. Tip Sheet: Alternatives for Medications Listed in the AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults [Internet]. Tip Sheet: Alternatives for Medications Listed in the AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults | HealthInAging.org. Health In Aging Foundation; 2019 [cited 2021Mar9]. Available from: https://www.healthinaging.org/tools-and-tips/tip-sheet-alternatives-medications-listed-ags-beers-criteriar-potentially
22. Tori ME, Larochelle MR, Naimi TS. Alcohol or Benzodiazepine Co-involvement With Opioid Overdose Deaths in the United States, 1999-2017. JAMA Network Open. 2020;3(4).