



Prescribing Guidelines for Pennsylvania



SAFE PRESCRIBING OF BENZODIAZEPINES FOR ACUTE TREATMENT OF ANXIETY AND INSOMNIA

Anxiety is commonly encountered in clinical practice, either as an acute isolated symptom associated with major life events or comorbid with another condition, e.g., depression. Anxiety may also be the core symptom of a psychiatric disorder, including panic disorder, phobias and generalized anxiety disorder. The prevalence of anxiety disorders in the U.S. is approximately 4 percent.

Though benzodiazepines are effective in the short-term treatment of severe anxiety and panic disorders, evidence shows that continuing them beyond four to six weeks will likely result in loss of efficacy and the development of tolerance and dependence and, consequently, increase the risk of development of a

benzodiazepine substance use disorder. The risk of dependence increases with dose and duration of therapy.

While anxiety disorders are amenable to short-term treatment with benzodiazepines, they are **not** first-line treatments for anxiety disorders and are **not** effective for the long-term treatment of these disorders. Rather, there are other much more effective treatment options, including evidence-based psychotherapies, e.g., cognitive behavioral therapy (CBT), other non-pharmacological interventions, and medication management using serotonin-specific reuptake inhibitors (SSRIs) or



serotonin-norepinephrine reuptake inhibitors, (SNRIs).

Similarly, insomnia, either as a symptom of another disorder, or as the core symptom of a sleep disorder, may have a lifetime prevalence as high as 40 percent. Benzodiazepines can be effective in the short-term treatment of severe insomnia, i.e., for one to two weeks, but there is **no** evidence supporting the long-term use of benzodiazepines for the treatment of insomnia.

Beyond acute situational insomnia, persistent insomnia is best treated by addressing the underlying cause, such as poor sleep hygiene, poorly controlled pain or depression.

These guidelines address the use of benzodiazepines for the treatment of anxiety and insomnia. They are intended to help health care providers improve patient outcomes when caring for these patients and to supplement, but not replace, the individual provider’s clinical judgement.

BACKGROUND.....

Prescriptions for benzodiazepine medications filled in the United States increased by 320 percent from 1996-2013. In Pennsylvania, there are 46 prescriptions for benzodiazepines per 100 adults, ranking Pennsylvania’s prescribing frequency as the 13th highest in the nation. Over this same time interval, overdose deaths associated with benzodiazepines increased over 500 percent. A portion of this increase in mortality is likely attributable to the higher benzodiazepine dose per prescription observed, as well as the marked increase of opioid prescribing over this same period. The presence of benzodiazepines in opioid overdose deaths increased from 18 percent of opioid overdose deaths in 2004 to 31 percent in 2011.

Benzodiazepines are one of the most frequently cited types of medications found to be present in deaths associated with opioid use.

It is therefore imperative that physicians and other prescribers approach the prescribing of benzodiazepines for anxiety and insomnia with much greater deliberation and caution.

It is recommended that providers review associated Pennsylvania State Guidelines related to the use of opioids in different patient populations, including the use of opioids to treat chronic pain, the use of opioids to treat pain in the emergency department, the use of opioids in dental practice, geriatrics and the use of opioids in obstetric and gynecologic care, which may provide insight into treatment options for these populations.

Most Commonly Dispensed Benzodiazepines in US

<u>Medication</u>	<u># of prescriptions in 2011</u>
alprazolam (Xanax)	49 million
lorazepam (Ativan)	28 million
clonazepam (Klonopin)	27 million
diazepam (Valium)	15 million
temazepam (Restoril)	8.5 million

Source: Drug Enforcement Administration bulletin, January 2013

GUIDELINES.....

1. **Before initiating benzodiazepine therapy**, perform a thorough medical history, including personal and family history of substance use disorder and a thorough assessment of physical health, with special attention to hepatic, renal and pulmonary



disease. Practitioners should take particular note of patients with or at risk of sleep apnea, as the use of benzodiazepines in this patient population increases the risk of adverse events. Likewise, prescribers should obtain accurate information regarding other current medications, especially the use of other centrally-acting sedating medications, including opioids.

The use of benzodiazepines with opioids at least doubles the risk of respiratory arrest and death and should be avoided. The U.S. Food and Drug Administration now requires black boxed warnings – the FDA’s strongest warning – for concurrent use of prescription opioids and benzodiazepines. In the rare instance that patients require both an opioid prescription and a benzodiazepine prescription, they should be counseled about the risk of respiratory arrest and death and co-prescribed naloxone.

2. When there is a history of past substance use disorder, extreme caution should be exercised before prescribing benzodiazepines, given the increased potential for dependence or misuse.

- a) For patients with suspected current substance use, benzodiazepines are usually contraindicated.
- b) If benzodiazepines are prescribed to patients with past history of substance use disorder or active substance use disorder, prescribing should be associated with frequent and careful patient monitoring that includes documentation of treatment benefit and assessment for potential harm, including regular urine drug screens.
- c) Providers should understand how to interpret the results of urine drug screens and have an established process for responding to abnormal results. This process should include a referral for evaluation and treatment of substance use disorder.
- d) When a referral is made, the prescriber should conduct and document ongoing

coordination of care with the addiction treatment provider.

3. When initiating benzodiazepine treatment, the prescriber should discuss and document the risks and potential benefits associated with treatment (including education about the risk of developing dependence and/or tolerance) and the intended duration of treatment.

4. Providers are encouraged to use formalized written treatment agreements or contracts, which both educate patients about the risks of benzodiazepines use and clarify the expectations of the patients.

Expectations included in such contracts counsel patients that they should:

- a) Tell other providers that they are taking this medicine;
- b) Keep the medication in a secure place, preferably locked;
- c) Not share the medication with others; and
- d) Properly dispose of any medication no longer needed at a prescription take-back box.

Sample Patient Agreement Forms:

<https://www.drugabuse.gov/sites/default/files/files/SamplePatientAgreementForms.pdf>

5. Practitioners must access and should document their review of data available through the Prescription Drug Monitoring Program (PA PDMP AWA^Rx^E) database prior to the initial prescription and throughout treatment.

6. Evidence supports short-term benzodiazepine use as best practice. It is strongly recommended that the prescriptions provided to patients reflect and endorse this practice, i.e., a 10-day supply to relieve situational insomnia rather than 30 days with refills.



Benzodiazepine	Onset of Action	Peak Onset (hours)	Half-life Parent (hours)	Half-life Metabolite (hours)	Comparative Oral Dose
Long acting					
Chlordiazepoxide (Librium®)	Int. (po)	2-4(po)	5-30	3-100	10mg
Diazepam (Valium®)	Rapid (po, IV)	1(po)	20-50	3-100	5mg
Flurazepam (Dalmane®)	Rapid	0.5-2	Inactive	47-100	30mg
Intermediate acting					
Alprazolam (Xanax®)	Int.	0.7-1.6	6-20	-	0.5mg
Clonazepam (Rivotril®)	Int.	1-4	18-39	-	0.25mg
Lorazepam (Ativan®)	Int. (po) Rapid (sl, IV)	1-1.5 (po)	10-20	-	1mg
Oxazepam (Serax®)	Slow	2-3	3-21	-	15mg
Temazepam (Restoril®)	Slow	0.75-1.5	10-20	-	30mg
Short acting					
Midazolam (Versed®)	Most rapid IV	0.5-1 (IV)	1-4	-	-
Triazolam (Halcion®)	Int.	0.75-2	1.6-5.5	-	0.5mg

7. Intermediate to long-acting benzodiazepines, e.g., clonazepam (Klonopin®), are preferred in the short-term treatment of anxiety, whereas shorter acting agents, e.g., temazepam, are preferred to facilitate sleep. Low to moderate doses should suffice for most of the clinical situations commonly encountered.

8. **When initiating benzodiazepine treatment to provide symptom relief in the early phase of treatment of depression or an anxiety disorder**, it is essential to educate the patient about evidence-based, non-pharmacological treatments available for that disorder and to facilitate appropriate referrals, e.g., for cognitive behavioral therapy (CBT); or to simultaneously initiate the intended first-line treatment, e.g., SSRIs or SNRIs.

9. **Caution should be used in prescribing benzodiazepines to address the insomnia and/or overwhelming emotions seen in acute grief**, as they

may suppress and prolong the grieving process. Sleep hygiene education is essential. Similarly, longer-term use of benzodiazepines to relieve acute anxiety reactions encountered in PTSD can interfere with the necessary exposure to and cognitive processing of the trauma that is essential for definitive and lasting symptom relief. Benzodiazepines should not be used for patients with PTSD due to their proven lack of efficacy.

10. **Extreme caution should be used prescribing benzodiazepines for the elderly**, due to the increased risk of adverse reactions such as confusion, ataxia and falls. If no alternative treatment is effective or available, dosing should be ultra-conservative, and intermediate-acting drugs such as lorazepam or oxazepam are recommended. Long acting drugs such as diazepam or chlordiazepoxide should be avoided.



11. **Extreme caution should also be used during pregnancy or lactation** and specialist consultation sought for pregnant or breast feeding patients taking benzodiazepines.

12. **It is important to keep in mind that benzodiazepine use can worsen the course of several conditions, including** 1) depression and impulse control disorders on the behavioral health side; 2) hypoxia associated with asthma, sleep apnea, COPD, CHF and other cardiopulmonary disorders on the physical health side; and 3) fibromyalgia and chronic fatigue syndrome at the interface.

13. **For some patients, e.g., those who are intolerant of/or non-responsive to alternative pharmacotherapy, long-term use of benzodiazepines may be clinically warranted.** Carefully selected patients with anxiety disorders can be maintained on low dose regimens for years without adverse effects. It is known that abrupt discontinuation of such regimens can lead to severe withdrawal symptoms.

- a) Patients receiving chronic benzodiazepines require regular periodic monitoring that includes a determination of whether the benefits of treatment continue to outweigh the risks and if a slow benzodiazepine taper is indicated.
- b) Providers should consider specialty input regarding the appropriateness for chronic use of benzodiazepines and for guidance when benzodiazepine medications need to be tapered and discontinued.

14. **Practitioners must note the FDA’s black box warning of benzodiazepine prescribing and opioid prescribing, including those receiving medication assisted treatment (MAT) for substance use disorder.** While the co-prescription of benzodiazepines and methadone have become too common, with research indicating that at least one in three patients receiving methadone are also using benzodiazepines, patients treated with methadone or

buprenorphine and benzodiazepine are at extreme risk of overdose.

Practitioners are urged to weigh the considerable evidence demonstrating the substantial risk of concomitant prescription of benzodiazepines and opioids -- whether for pain management or as medication assisted treatment of addiction -- before prescribing either agent in the presence of the other.

In the rare instance that, despite the black box warning, a patient is prescribed Methadone or Buprenorphine and a benzodiazepine, they should be counseled about the increased risk for respiratory arrest and death and co-prescribed naloxone.

RESOURCES.....

Dose Reduction Plans <http://benzo.org.uk/manual/>

Sample Patient Agreement Form
<https://www.drugabuse.gov/sites/default/files/files/SamplePatientAgreementForms.pdf>

Screening, Brief Intervention, and Referral to Treatment (SBIRT) tool
<http://www.samhsa.gov/sbirt>

The New York City Department of Health and Mental Hygiene: Judicious Prescribing of Benzodiazepines
<https://www1.nyc.gov/assets/doh/downloads/pdf/chi/chi-35-2.pdf>

SAMHSA, The DAWN Report, December 18, 2014
Benzodiazepines in Combination with Opioid Pain Relievers or Alcohol: Greater Risk of More Serious ED Visit Outcomes
<http://www.samhsa.gov/data/sites/default/files/DAWN-SR192-BenzoCombos-2014/DAWN-SR192-BenzoCombos-2014.pdf>



National Center for PTSD – Use of Benzodiazepines for PTSD in Veterans Affairs - <http://www.ptsd.va.gov/professional/treatment/overview/benzo-ptsd-va.asp>

Risks, management, and monitoring of combination opioid, benzodiazepines, and/or alcohol use. *Postgrad Med.* 2013 Jul; 125(4):115-30. <https://www.ncbi.nlm.nih.gov/pubmed/23933900>

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Jones CM, McAninch JK. Emergency department visits and overdose deaths from combined use of opioids and benzodiazepines. *Am J Prev Med.* 2015; 49(4): 493 - 50

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