Judicious Prescribing of Benzodiazepines for Anxiety and Insomnia

- Benzodiazepines increase the risk of fatal overdose when taken in combination with opioid analgesics, alcohol, or other central nervous system depressants.
- If benzodiazepines are indicated, prescribe the lowest effective dose for the shortest duration—no more than 2 to 4 weeks.*
- Avoid co-prescribing benzodiazepines and opioid analgesics because of the risk of fatal respiratory depression.

*B The guidance in this document is not intended for end-of-life care.

Benzodiazepines increase the risk of fatal overdose when taken in combination with opioid analgesics, alcohol, or other central nervous system (CNS) depressants, and such combined use is a significant public health problem nationally and in North Carolina. A prospective observational cohort study conducted in North Carolina found the rates of overdose death among patients co-dispensed opioid analgesics and benzodiazepines were 10 times higher (7.0 per 10,000 person-years; 95% confidence interval (CI): 6.3-7.8) than among patients dispensed opioid analgesics alone (0.7 per 10,000 person-years; 95% CI: 0.6-0.9) in conjunction with a black box warning on combining opioids and benzodiazepines, the FDA released guidance for providers and consumers regarding the risk of benzodiazepines on opioid overdose.

While benzodiazepines are commonly prescribed for anxiety and insomnia, they are not considered first-line treatment for either condition (Box 1). Guidelines recommend that benzodiazepines be used only for symptomatic relief of severe anxiety and short-term treatment of severe insomnia, while waiting for the full effect of other treatment modalities. Despite these limited indications, benzodiazepines are often prescribed more broadly and as long-term treatment, and this overuse contributes to risk of misuse and overdose.

You can reduce the risk of benzodiazepine-involved overdose by providing appropriate first-line treatment for anxiety and insomnia, prescribing benzodiazepines judiciously only when clinically indicated, and tapering patients off long-term benzodiazepine treatment.
BENZODIAZEPINES

- Benzodiazepines bind to GABA receptors and depress the central nervous system.
- They are prescribed for their sedative-hypnotic, antianxiety, muscle relaxant, and anticonvulsant effects.

BOX 1. MYTHS AND FACTS ABOUT BENZODIAZEPINES AND Z-DRUGS

Myth: Benzodiazepines are first-line treatment for anxiety. 
Facts: Benzodiazepines
- May be used for 2 to 4 weeks to treat severe symptoms of anxiety disorders, ideally while waiting for the full effect of other treatment options (Boxes 2 and 3).
- Diminish in effectiveness beyond 4-6 weeks.

Myth: Benzodiazepines are first-line treatment for insomnia.  
Facts: Benzodiazepines
- May provide short-term (1 to 2 weeks) symptomatic relief for severe insomnia while other treatment modalities are being implemented.
- May result in rebound insomnia once stopped.
- Do not appear to be effective for chronic insomnia or late-night insomnia experienced more commonly by older adults.

Myth: Low-dose benzodiazepines are not addictive.  
Facts:
- Benzodiazepine use can result in physical dependence at any dose with prolonged use.
- May be misused to prevent perceived or anticipated withdrawal rather than for their originally intended purpose.

Myth: Z-drugs (eg, zolpidem, zaleplon) are safer than benzodiazepines.  
Facts: Z-drugs
- Bind to GABA receptors, similar to benzodiazepines.
- Are not recommended for long-term use.
- Offer no safety benefit compared with benzodiazepines, especially in older adults.
- Increase risk for falls in older adults.

PROVIDE APPROPRIATE FIRST-LINE TREATMENT

Assess for underlying causes of anxiety and insomnia and consider safe, effective nonbenzodiazepine treatments when indicated (Boxes 2 and 3).

PRESCRIBE BENZODIAZEPINES JUDICIOUSLY

If short-term benzodiazepine treatment is indicated, fully assess your patient, prescribe the lowest effective dose for the shortest duration and talk with your patient about the benzodiazepine prescription.

Step 1: Fully Assess Your Patient

- Obtain a comprehensive medical history, including any medical comorbidities and mental health conditions, and perform a physical examination.
- Screen for substance use as part of routine care (Resources for Providers: Screening and Monitoring Tools).
- Review all current medications for potential interactions (Table 1) and consult with your patient’s other prescribers.
- Check the Prescription Monitoring Program (Box 4), as required before prescribing any schedule IV drug.
- Avoid co-prescribing benzodiazepines and opioids because of the risk of fatal respiratory depression.

Step 2: Prescribe the Lowest Effective Dose for the Shortest Duration

- Begin treatment with the lowest recommended dose and adjust as needed based on the patient’s response (see Table 2 for information).

BOX 2. NONBENZODIAZEPINE TREATMENTS FOR ANXIETY

Nonpharmacologic
- Cognitive behavioral therapy
- Relaxation techniques
- Yoga, meditation
- Exercise

Long-term pharmacologic
- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin-norepinephrine reuptake inhibitors (SNRIs)

BOX 3. NONBENZODIAZEPINE TREATMENTS FOR INSOMNIA

Nonpharmacologic
- Cognitive behavioral therapy
- Good sleep hygiene
  - Maintaining a regular sleep schedule
  - Avoiding daytime napping
  - Developing a calming bedtime routine, which may include taking a bath or reading a book
  - Avoiding screen time before bed
  - Keeping your bedroom dark, quiet, and at a comfortable, cool temperature
  - Limiting alcohol, caffeine, and tobacco at night
- Regular exercise—except heavy exercise within several hours of bedtime
- Relaxation techniques
- Melatonin
TABLE 1. INTERACTIONS BETWEEN BENZODIAZEPINES AND SELECT COMMON MEDICATIONS²,¹²,¹⁹,²¹-²³

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Medication Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased serum benzodiazepine levels (CYP450 inhibition)</td>
<td>Antifungals</td>
<td>Ketoconazoleitraconazole</td>
</tr>
<tr>
<td></td>
<td>Macrolides</td>
<td>Clarithromycin erythromycin</td>
</tr>
<tr>
<td></td>
<td>SSRIs</td>
<td>Fluoxetine paroxetine</td>
</tr>
<tr>
<td></td>
<td>Histamine-2 blockers</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Increased sedative effects of benzodiazepines</td>
<td>Opioids</td>
<td>Oxycodone</td>
</tr>
<tr>
<td></td>
<td>Antipsychotics</td>
<td>Chlorpromazine clozapine</td>
</tr>
<tr>
<td></td>
<td>Barbiturates</td>
<td>Phenobarbital secobarbital</td>
</tr>
<tr>
<td></td>
<td>Sedating antihistamines</td>
<td>Diphenhydramine hydroxyzine</td>
</tr>
</tbody>
</table>

- Use phased dispensing (prescribing small amounts at regular intervals) where possible.¹²
- Prescribe for a maximum of 4 weeks.⁷,¹²

Step 3: Talk to Your Patients About Their Benzodiazepine Prescription

Educate patients about the benefits and risks of benzodiazepine treatment (Box ⁵,⁷,⁹,¹³,¹⁵), and remain alert to signs and symptoms of physical dependence, withdrawal, substance use disorder, and benzodiazepine misuse²,¹⁰,¹¹ (Box ⁶,²⁰,⁴¹).

BOX 4. CHECKING THE PRESCRIPTION MONITORING PROGRAM⁵,⁸,¹⁰,¹²,²⁴

The North Carolina Controlled Substance Reporting System (CSRS) provides quick, confidential, 24/7 access to your patients’ controlled substance prescription history.

1. Consult CSRS to determine whether your patient recently filled a prescription for an opioid analgesic, benzodiazepine, or other controlled substance.

2. If the patient has recently filled multiple prescriptions written by different providers and/or filled at different pharmacies:
   - Discuss your concerns with your patient, explaining the risk for overdose when benzodiazepines are used with other agents (especially opioid analgesics and other CNS depressants).
   - Communicate and coordinate with your patient’s other controlled substance prescribers.
   - Avoid abruptly discontinuing benzodiazepines.⁵,⁹,¹⁰,¹²,²⁴
     - Withdrawal can be severe, causing hallucinations, seizures, and in rare cases has been life-threatening (see page 16).

- A taper schedule is strongly recommended and clinically appropriate versus refusing continuation of this medication (Resources for Providers: Dose Reduction Plans).
- Consider that your patient might be misusing controlled substances and/or have a substance use disorder
  - If needed, explain that effective treatments for substance use disorder are available, and treat the patient yourself or refer for treatment (Resources for Providers: Treatment for Substance Use Disorder).
  - For opioid use disorder, discuss and arrange for medication-assisted treatment (e.g., buprenorphine or methadone) (Resources for Providers: Treatment for Substance Use Disorder).

See Resources for more information about the North Carolina Controlled Substance Reporting System (CSRS).
SPECIAL POPULATIONS

Older adults

Use caution when prescribing benzodiazepines for patients aged 65 and older. Older adults are particularly vulnerable to the adverse effects of benzodiazepines. (Box 7)

BOX 5. WHAT TO TELL PATIENTS ABOUT BENZODIAZEPINE TREATMENT

- You’ll be taking this medicine for a short time—no more than 4 weeks. If your symptoms don’t improve in a few weeks, we’ll reevaluate the treatment plan.
- Get your prescriptions for benzodiazepines and other controlled substances only from me.
- Fill your prescription at only one pharmacy.
- Make sure to tell other providers that you’re taking this medicine. Some other medications can have a serious interaction with this one.
- Keep this medication in a secure place, preferably locked.
- Do not share your medication with others.
- Take the medication exactly as directed.
- Dispose of the medicine safely. To find a permanent disposal site/event near you, visit https://apps.deadiversion.usdoj.gov/pubdispsearch/spring/main?execution=e151. If you cannot locate a disposal site near you, then mix the medication with an unpalatable substance like coffee grounds or kitty litter and place in a sealed container before discarding with your trash.
- There are some risks when taking this medicine:
  - Overdose: Avoid alcohol, opioids, and sedatives; they increase risk of overdose. Some over-the-counter medicines, such as antihistamines, also increase risk.
  - Tolerance: When you need more medication to get the same effect, do not increase the dose, even if you think the medicine has stopped working.
  - Physical dependence: If you develop physical dependence, stopping the drug may make you miss it or feel sick (withdrawal). You may get a fast heartbeat, insomnia, anxiety, shaky hands, nausea, have hallucinations, or just feel agitated.
  - Mood or behavior changes, including depression, anxiety, or irritability.
  - Substance use disorder (SUD): Some patients who become physically dependent on or misuse the medicine can develop a SUD.
- Seek help right away if you think you may be developing tolerance or dependence or if you experience side effects—especially ones that are new or concern you.
- Your provider and pharmacy check the North Carolina Controlled Substances Registry for your safety.

BOX 6. PHYSICAL DEPENDENCE, WITHDRAWAL, SUBSTANCE USE DISORDER, AND MISUSE

Physical Dependence
- Physiologic adaptation to a substance requiring the person to take more of the substance to achieve a certain effect.
- Can occur with the chronic use of many drugs—including many prescription drugs, even if taken as instructed.
- Causes drug-specific withdrawal symptoms if drug use is abruptly ceased.
- Benzodiazepine withdrawal syndrome symptoms include:
  - Autonomic hyperactivity (e.g., sweating, tachycardia)
  - Hand tremor
  - Insomnia
  - Nausea or vomiting
  - Transient visual, tactile, or auditory hallucinations or illusions
  - Psychomotor agitation
  - Anxiety
  - Grand mal seizures

Substance Use Disorder
- Maladaptive pattern of use leading to significant impairment or distress. See DSM-5 diagnostic criteria (Resources for Providers: Screening and Monitoring Tools).

Benzodiazepine Misuse
- Using someone else’s benzodiazepines or using benzodiazepines in a manner other than prescribed.
- May or may not be associated with physical dependence.
- Signs may include pattern of early refills; prescription problems such as lost, spilled, or stolen medications; and escalating drug use in the absence of a physician’s direction.

BOX 7. BENZODIAZEPINES IN OLDER ADULTS

- Benzodiazepine treatment in patients aged 65 and older can increase risk for falls and hip fractures:
  - Possible cognitive impairment
  - Negative interactions with other medications
  - Daytime fatigue
  - Confusion and delirium
- Initiate treatment at one-half the standard adult starting dose.
- Monitor response to treatment and minimize dosage and/or frequency to avoid adverse effects.

In older adults, benzodiazepines should never be used as first-line treatment for insomnia, agitation, or delirium, and long-acting benzodiazepines should not be used for any indication.
Pregnant women

Benzodiazepines should be avoided during pregnancy because of the risk of adverse outcomes for the newborn. Refer pregnant women on benzodiazepines to the perinatal substance use specialist 800-688-4243 for the NC Perinatal Opioid Exposure Project.

BOX 8. BENZODIAZEPINES DURING PREGNANCY AND LACTATION

- Benzodiazepine use during pregnancy is associated with risks to the newborn:
  - respiratory depression
  - poor temperature regulation
  - hypotonicity
  - neonatal abstinence syndrome
- For patients planning a pregnancy, gradually discontinue benzodiazepine treatment and consider other options.
- If postpartum benzodiazepine treatment is being considered, explain that benzodiazepine metabolites can be found in breast milk.

DISCONTINUING BENZODIAZEPINE TREATMENT

Avoid abrupt discontinuation of benzodiazepines because it can lead to severe and potentially life-threatening withdrawal symptoms, especially among patients who have taken benzodiazepines for a prolonged period. Take the following measures to taper the dosage safely:

- Determine and agree on a gradual dose reduction plan with your patient (Resources for Providers: Dose Reduction Plans).
- Set realistic goals with the patient, based on the dosage and duration of benzodiazepine use.
- Closely monitor the patient for signs of withdrawal and adjust the taper schedule as clinically indicated.
- Consider counseling or cognitive behavioral therapy for patients who have a substance use disorder or for whom withdrawal might cause substantial anxiety.

In the Empower study, a consumer-targeted written knowledge transfer tool aimed at empowering older adults to act as drivers of benzodiazepine de-prescription resulted in a 27% reduction of inappropriate benzodiazepine use at 6-month follow-up (number needed to treat (NNT) = 4). See the tool under Resources for Providers, under Dose Reduction Plans.

GUIDELINES FOR BENZODIAZEPINE USE IN OPIOID TREATMENT PROGRAMS (OTPs)

Benzodiazepine use among patients in opioid agonist medication assisted therapy is linked to poorer outcomes; the combination with opioid agonists poses significant risks for morbidity and mortality.

There are few published articles that offer useful guidance for management of benzodiazepines in OTPs. As a result, treatment protocols and clinical practice vary. In spite of the gap in the literature, care should be taken with patients admitted to opioid agonist treatment with either licit or illicit benzodiazepine use. Treatment of opioid use disorder with medications should not be discouraged or delayed, but the risks of ongoing benzodiazepine use should be taken seriously and interventions guided accordingly.

The American Association for the Treatment of Opioid Dependence published guidelines to offer guidance instead of restrictive procedures to assist programs in treating patients in OTPs who use benzodiazepines. See document link under Provider Resources, Guidelines for Benzodiazepine Use in Opioid Treatment Programs.

LONG-TERM BENZODIAZEPINE TREATMENT

Long-term benzodiazepine treatment—considered here as daily or near-daily use for more than 4 weeks—should generally be avoided. If you do prescribe long-term benzodiazepine treatment, take the following steps to minimize health risks:

- Develop a treatment plan with your patient.
- Prescribe small quantities at a time.
- Schedule regular follow-up appointments to assess the need for continued treatment.
- Regularly review the treatment plan and offer a benzodiazepine withdrawal plan at regular intervals.
- Consider monitoring with a urine drug test.
- Consider consulting a psychiatrist.

SUMMARY

Benzodiazepines used with opioids, alcohol, and other CNS depressants can lead to fatal overdose. Reduce the risk of preventable overdose deaths by using non-benzodiazepine treatments, prescribing benzodiazepines judiciously only when clinically indicated, and tapering patients off long-term benzodiazepine treatment.

HOW TO PRESCRIBE BENZODIAZEPINES JUDICIOUSLY

- Provide appropriate first-line treatment for anxiety and insomnia.
- If benzodiazepines are clinically indicated:
  - fully assess your patient, prescribe the lowest effective dose for the shortest duration—no more than 2 to 4 weeks
  - talk to your patient about the benefits and risks of benzodiazepine treatment
  - avoid co-prescribing with opioids or other CNS depressants due to the risk of fatal respiratory depression
# RESOURCES FOR PROVIDERS

**NC Controlled Substance Reporting System**
- Registration and FAQs: [https://www.ncdhhs.gov/divisions/mhddas/ncdcu/csr](https://www.ncdhhs.gov/divisions/mhddas/ncdcu/csr)
- To assign delegates to check on behalf of the provider
  1. Open [ncsrss.hidinc.com/ncsignup.html](https://ncsrss.hidinc.com/ncsignup.html), where a login window will be displayed
  2. Enter newacct in the User Name field.
  3. Enter welcome in the Password field.
  4. Follow the instructions on the screen to complete your registration.

**Screening and Monitoring Tools**
- National Institute on Drug Abuse Drug Screening Tool: [www.drugabuse.gov/nmassist](http://www.drugabuse.gov/nmassist)

**Guidelines for Benzodiazepine Use in Opioid Treatment Programs**

**Treatment Agreement Forms**

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### Treatment Agreement Forms (continued)


### Dose Reduction Plans

### Treatment for Substance Use Disorder
- Substance Abuse and Mental Health Services Administration. Find Help & Treatment: [www.samhsa.gov/treatment/index.aspx](http://www.samhsa.gov/treatment/index.aspx)
- Alliance Behavioral Healthcare HELP AND INFORMATION AVAILABLE 24/7: (800) 510-9132 [https://www.alliancebhc.org/](https://www.alliancebhc.org/)

Governors Institute: Substance Abuse Resources
[http://www.sa4docs.org/](http://www.sa4docs.org/)
RESOURCES FOR PATIENTS

Benzodiazepine Information

Benzodiazepines and PTSD

Healthy Sleep Tips
- Harvard University. Twelve Simple Tips to Improve Your Sleep: healthysleep.med.harvard.edu/healthy/getting/overcoming/tips

Tips for Managing Anxiety
- Anxiety and Depression Association of America. Tips to Manage Anxiety and Stress: www.adaa.org/tips-manage-anxiety-and-stress

Medication Take-Back Programs
- To search for the closest controlled substance public disposal location https://apps.deadiversion.usdoj.gov/pubdispsearch/spring?execution=e1s1

Treatment for Substance Use Disorder
- Substance Abuse and Mental Health Services Administration: www.samhsa.gov/treatment/index.aspx
- North Carolina: Find Help & Treatment: https://www.ncdhhs.gov/providers/lme-mco-directory


Alliance graciously acknowledges the approval of the New York City Department of Health and Mental Hygiene (through Peggy Millstone) for allowing use of their document *Judicious Prescribing of Benzodiazepines* (*New York City Department of Health and Mental Hygiene. Judicious prescribing of benzodiazepines. City Health Information. 2016;35(2):13-20; http://www1.nyc.gov/assets/doh/downloads/pdf/chi/chi-35-2.pdf*), upon which this Alliance document was based.