

Guidelines for the Use of Benzodiazepines in the State of New Mexico 2/19/2018

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Introduction:

Benzodiazepines (BZD) are indicated for a variety of uses due to sedative, hypnotic, anxiolytic, anticonvulsant, muscle relaxant, and amnesic actions. BZD are indicated for alcohol withdrawal, seizures, anxiety disorders, panic, agitation, and insomnia. BZDs have been widely prescribed since the 1960s, and are known to be associated with physical dependence and addiction. The more recently created and related “Z” drugs (i.e. zolpidem, zaleplon and eszopiclone) are now in use for insomnia. BZDs are thought to be relatively safe, but not in combination with other drugs, such as opioids, in individuals with substance use disorders, or in the elderly. Despite the hazards and despite the lack of clinical evidence for certain indications or long-term use, they are widely and perhaps excessively prescribed.

It has become increasingly apparent that benzodiazepines play a significant role in overdoses. The risk of overdose death increases as a patient concurrently uses benzodiazepines with other CNS-depressants, particularly opioids and alcohol. A black box warning was added to prescribing information by the FDA in 2016, warning against the use of benzodiazepines with opioids, recommending using alternatives, but if used, to monitor for respiratory depression and to limit quantities. The Center for Disease Control in their guidelines for opioid use recommends avoiding use of benzodiazepines with opioids.

This is occurring in the context of benzodiazepines being amongst the most widely prescribed psychotropic medications, including for long-term use (greater than 6 weeks of use), despite the risks and lack of treatment guidelines of clinical evidence of long-term efficacy. Alprazolam is the most widely prescribed psychotropic medication in the US, with 48 million prescriptions dispensed in 2013 (Grohol 2016). Benzodiazepines are controlled substances that can cause both physical and psychological dependence, and can be abused. Discontinuing benzodiazepines can often be challenging, and require expert support.

As New Mexico as a state continues to work towards decreasing drug overdose deaths and encouraging the proper use of potentially dangerous medications, it was felt that offering recommendations on the proper use of benzodiazepines could aid in that effort and provide guidance for prescribers.

The goal of this document is to provide recommendations on the appropriate use of these drug, including evidence-based clinical indications and duration of use, enhance understanding of the risk of these drugs especially in the context of combination therapy with other sedatives, and to provide advice on how to identify and manage aberrant use, including how to safely discontinue these medications when indicated.

Pharmacology of Benzodiazepines and Z-Drugs:

Benzodiazepines enhance the action of gamma-aminobutyric acid (GABA) on GABA receptors causing anxiolytic and sedative effects. Different forms all have the same effect on these receptors, but differ in rate of absorption, speed in crossing the blood-brain barrier, rate of elimination and active and inactive metabolites. Based on these pharmacologic characteristics, BZDs are categorized by duration of activity, which influences frequency or dosing.

Commonly prescribed BZDs are divided as follows:

- Short-acting: alprazolam, midazolam and triazolam.
- Intermediate-acting: oxazepam, lorazepam, and temazepam.
- Long-acting: diazepam, clonazepam, clorazepate, chlordiazepoxide, and flurazepam.

Other possible uses for benzodiazepines:

For alcohol/sedative withdrawal, catatonia, acute mania, single-dose treatment of phobias, such as flying phobia, sedation for office procedures and seizures.

Z-drugs (e.g., zaleplon, zolpidem, and eszopiclone) also enhance GABA transmission but only affect a subunit of the receptor that influences sedation. These drugs therefore are used as sleep-inducing agents. Of note, these medications have risks (Brandt and Leong 2017) and can be abused (Hajak et al 2003).

Prescribing Guidance for BZDs and Z-Drugs:

The following is a description of recommendations derived from a variety of treatment guidelines concerning the use of BZDs (Kaiser Permanente 2014, State of Maine 2018). As with all guidelines, providers should rely on individual clinical judgment for individual patients.

Before initiating BZD therapy:

1. Alternative, non-BZD, medications should in most cases be offered as first-line medication, for example (Stein and Craske 2017):
 - a. Antidepressant medications (e.g., SSRIs, SNRIs, tricyclic antidepressants)
 - b. Psychotherapy (e.g., cognitive behavioral therapy, which can be highly effective and obviate the need for any medications)
 - c. Serotonergic agents for anxiety (buspirone)
 - d. Medications for restless legs (e.g., pramipexole, ropinirole, gabapentin)
 - e. Adjunctive symptomatic medications (hydroxyzine, clonidine, propranolol)
2. The NM Pharmacy Monitoring Program (PMP) must be reviewed before writing a new prescription for a benzodiazepine if for more than 4 days, and then every three months for ongoing prescriptions. Refer to your healthcare licensing board for specific requirements regarding PMP utilization.
3. The provider will counsel the patient on the risks of these medications, such as sedation and dependence. Discuss strategy for taper as more than 6 weeks of therapy is rarely indicated. Ensure that the patient understands these risks.
4. As with opioid prescribing, providers should consider using treatment contracts and periodic urine toxicology tests.
5. All sedative medication should only be prescribed by only one provider, or, if a behavioral health provider is prescribing BZDs and a primary care provider is prescribing an opioid, there should be close coordination between the two providers. Encourage the patient to use one pharmacy.

Patients aged 65 years and over:

Both benzodiazepines and Z-drugs are considered “high-risk medications in the elderly” and are listed on the American Geriatrics Society Beers Criteria list, such that BZD and Z-drugs should be particularly avoided in the elderly (Campanelli 2012).

Individuals aged 65 and older are especially vulnerable to the adverse effects of hypnotic drugs, as their metabolic rates decline with age. Patients in this age group are more susceptible to CNS depression and cognitive impairment, may develop confusion and ataxia leading to falls and hip fractures, are at risk of drug interaction with other medications, and may be at risk of permanent cognitive impairment when using high doses of benzodiazepines (e.g., diazepam 30 mg or equivalent) on a regular basis.

If thought to be absolutely necessary, half of normal doses should be considered, using benzodiazepines that do not need a fully functioning liver for metabolism (e.g., lorazepam, oxazepam or temazepam). (Stahl 2014, Sheehan 2017, Kaiser Permanente 2014)

Evidenced-based Indications for behavioral disorders:

Four behavioral health conditions/disorders have clinical evidence to support benzodiazepines use: Panic Disorder, Generalized Anxiety Disorder, Social Anxiety Disorder and insomnia, but only if used for short durations, usually less than 2-4 weeks, and as second-line treatments as psychotherapy or antidepressants, in particular serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), are generally recommended as first line. Some providers will co-prescribe a BZD with an SSRI, to allow for immediate relief while titrating the SSRI and awaiting it taking effect. (Guina and Merrill 2018 A)

One practice guideline (NICE 2011) recommends using BZDs only as a short-term measure during crisis. The British National Formulary is quoted as advising that “benzodiazepines are indicated for the short term relief (2 to 4 weeks only) of anxiety that is severe, disabling or subjecting the individual to unacceptable distress, alone or in association with insomnia or short term psychosomatic, organic or psychotic illness”. (Quoted in Lader 2012)

There is no evidence or indication to use a BZD for Post-traumatic Stress Disorder, despite BZDs being commonly prescribed for PTSD. In fact, BZDs can increase the incidence of developing PTSD and interfere with effective treatment. (Guina and Merrill 2018 A) Many treatment guidelines, including the Department of Defense, recommend against the use of BZDs in the treatment of PTSD. The frequent overlap of substance use disorders in individuals with PTSD create increased risk in the use of these drugs. (US Department of Veterans Affairs 2014)

For insomnia, due to the development of tolerance, only short-term use of either a BZD or Z-drug is effective (Guina and Merrill 2018 A).

Long-term use:

Benzodiazepines and Z-drugs are **not recommended** for long-term use (longer than 6 weeks), apart from in exceptional circumstances (e.g., for terminally ill patients). There is no evidence to support the long-term use of these drugs for insomnia or any mental health indication. Physical dependence can occur with over 12 weeks of use, especially with higher doses and short-acting forms (Guina and Merrill 2018).

Multiple Benzodiazepine Concurrent use:

There is no clinical evidence nor treatment guideline that supports using more than one form of a benzodiazepine at a time.

Avoid Benzodiazepine or use with great caution in the following situations (Stahl 2014):

1. Active or history of substance abuse
2. Pregnancy or risk of pregnancy
3. Treatment with opioids for chronic pain or opioid use disorder.
4. Medical and mental health problems that may be aggravated with benzodiazepines, such as fibromyalgia, traumatic brain injury, developmental disability, chronic fatigue syndrome, somatization disorders, depression, bipolar disorders (except for urgent sedation in acute mania), attention deficit hyperactivity disorder, kleptomania, and other impulse disorders.
5. Chronic BZD therapy is not recommended in the treatment of Borderline Personality Disorder (Gunderson JG and Links P, 2014).
6. Cardiopulmonary disorders such as asthma, sleep apnea, chronic obstructive pulmonary disease, congestive heart failure, and other cardiopulmonary disorders, since benzodiazepines may worsen hypoxia and hypoventilation

Adverse effects of both benzodiazepines and Z-drugs:

1. Dependence: Potent BZDs with short or intermediate half-lives (e.g., alprazolam, lorazepam) appear to carry the highest risk of causing problems with dependence. Psychological or physical dependence can develop over a few weeks or months and is more likely to develop with long-term use or high doses, and in patients with a history of anxiety problems (Park 2018)
2. Tolerance to the hypnotic effects which may develop after only a few days of regular use (Lader 2012).
3. Daytime somnolence and impaired driving (hence risk when driving or operating machinery) (Lader 2012, Brandt and Leong 2017).
4. Depression and increased anxiety (Guina and Merrill 1018A)
5. Slowness of mental processing and body movements (including increased risk of dementia and falls in elderly) (Brandt and Leong 2017).
6. Increased risk of overdose when combined with sedative drugs, such as opioids or alcohol (Rose et al 2018, Guina and Merrill 2018A)
7. Increased association between benzodiazepine use and overall mortality (Weich 2014)

Withdrawal Symptoms:

Abrupt cessation of a BZD can cause altered CNS activity (tremor, seizures or delirium) particularly for physically dependent individuals on higher doses. Common symptoms over time, even with a tapering dose, can include anxiety, restlessness, irritability, insomnia, agitation, muscle tension, weakness, aches and pains, blurred vision and racing heart. Less commonly withdrawal symptoms include nausea, sweating, runny nose, hypersensitivity to stimuli, and tremor. Rarely, with the elderly or with use of high-

dose and/or high-potency BZDs, psychosis, seizures, hallucinations, paranoid delusions and tinnitus can occur. The duration of symptoms can be variable but usually last less than two weeks. (Sheehan 2017).

Again, offering a slow taper as tolerated by the patient can minimize these symptoms. While no medications offer full and consistent relief from BZD withdrawal symptoms, some medications may offer some comfort including, carbamazepine, propranolol, clonidine and analgesics (Guina and Merrill 2018B). Education, support and psychotherapy during and after the taper is completed are very helpful, including helping patients not relapse on BZDs, say with another provider (Guina and Merrill 2018B).

It may be helpful in more complex situations to refer patients to a psychiatric or addiction medicine specialist for assistance in managing both the discontinuation of the medication and treatment of any underlying behavioral health issues.

Use of BZDs and Z-drugs in patients on methadone or buprenorphine for treatment of opioid use disorder:

Patients with opioid use disorder frequently abuse BZDs to enhance the euphoria of opioids or attempt to alleviate withdrawal from opioids. Also, many patients are prescribed BZDs often inappropriately, in effort to treat anxiety symptoms or even the substance use disorder. Those with BZD use are at higher likelihood of continuing opioid abuse and failing to stay in methadone treatment. One study (Chen et al 2011) found 47% of those interviewed in a methadone treatment program had a history of BZD use, with 39.8% without a prescription. They concluded that most methadone programs do not address co-occurring anxiety problems and that methadone treatment may trigger or worsen BZD misuse. Another review found that worldwide, 18% to 50% of those in methadone treatment programs were dependent on BZDs despite the significant risks for morbidity and mortality (Williams 2014).

While a less significant issue, BZDs in combination with buprenorphine have been associated with deaths due to respiratory depression, warranting caution when these drugs are combined (Nielsen S et al 2007)

Therefore, while BZD use (common in polysubstance dependence) should not prevent a patient with an opioid use disorder being offered methadone or buprenorphine treatment (FDA 2016), extreme caution should be used and the guidelines issued by the American Association for the Treatment of Opioid Dependence (2018) should followed.

Key points include regular checking of the PMP (also required by your healthcare licensing board), close communication between the treatment program and BZD and Z-drug prescribers, education on the risks, efforts to decrease and replace BZDs with safer treatments, development of safety plans and addressing BZD misuse when it occurs. Note – methadone dispensed from an Opioid Treatment Program (OTP) is not reported to the PMP; therefore, will not be discoverable on the patient's PMP report.

Management of Patients on Chronic Benzodiazepines and Z-Drugs:

Essentially all treatment guidelines concerning the use of BZDs recommend their being used for no more than 6 weeks and some recommend as little as 4 weeks; it is recommended that an effort be made to decrease and discontinue BZD use after that period due to the significant risks of these drugs especially in older patients (Pottie 2018).

However, approaching the issue of discontinuing long-term BZDs usage should be done with care. Continuing a potentially harmful and/or ineffective treatment is not recommended but discontinuation should only be done after a careful assessment occurs and if at all possible, with the patient's agreement. To do so without patient engagement risks withdrawal symptoms, getting "fired" by the patient who then gets inadequate or no care, or the patient turning to illegal sources (Guina and Merrill 2018b).

The following is a recommended approach, especially when a provider "inherits" a patient on long-term BZD treatment per Guina and Merrill (2018b):

1. Conduct a proper assessment to include an accurate diagnosis as to the presence of a primary behavioral diagnosis versus a BZD-induced disorder. Review treatment history including if appropriate evidence-based first or second line treatments such as SSRI's or psychotherapies were tried.
2. Then assess effectiveness with a focus on functioning, not just degree of symptomatology. Many patients are on high dose BZDs yet still will not leave their house. Assessing the effectiveness of the treatment (in the absence of obvious harms) should be a critical determinate if the medication should be continued or not.
3. Assess harms from the medication. Is the medication being misused, used concurrently with illicit drugs or alcohol, causing actual or risk of drug-drug interactions (for example, with opioids), or causing cognitive impairment or falls?

If benefits clearly outweigh risks and discontinuing BZDs would appear to cause harm and decreased functioning, ongoing careful monitoring should occur to include patient education about risks, regular follow-up appointments, monitoring of the PMP and periodic urine toxicology testing. This should also occur if the provider is in the process of working with a patient who is neither being helped nor harmed by the medications but is in the process of being counselled around stopping the medications and trying alternative treatments. Note that in using toxicology testing, the provider should become familiar with the lab performing the toxicology screening to determine which BZDs are identified and be aware of false positives (e.g. sertraline can appear as a BZD in some screens) and false negatives.

Discontinuation:

For patients that agree with discontinuing long-term BZD use, and for those who are resistant but are clearly at immediate risk, there are several approaches. Of note, many patients are fearful of cutting back and stopping BZDs. Many patients will benefit from repeated education, and perhaps counseling for support along the way. There are cognitive behavioral therapy manuals and therapists who can assist in this process.

Tapering BZDs:

1. Based on assessment, attempt to have appropriate replacement treatment in place for any primary behavioral health diagnoses.
2. Provide as needed, or refer for, supportive psychotherapy during taper process.
3. Provide education and a clear plan for the taper.
4. Many studies and guidelines recommend reduction of 25% every 2-3 weeks, with if needed, a slower decrease (12.5%) for last two weeks (Pottie et al 2018).
5. Many patients benefit by being offered a “rescue” dose, one dose per day to carry with them to use at their discretion. This seems to provide re-assurance and a sense of control. Most tend not to use that medication.
6. For higher-potency/short-acting BZDs (e.g. alprazolam) a slower taper may be needed, perhaps as slow as 0.25 mg decrease in the daily dose per week (Stahl 2014). While lacking clear research support (Ait-Daoud et al 2018), many experts suggest switching to a lower-potency/long-acting BZD (clonazepam or diazepam) at an equivalent dose (see Table 1), and then tapering. It is suggested that this may attenuate the withdrawal symptoms and allow for a longer taper using smaller doses near the end point (Kaiser Permanente 2014). Some practitioners have had success switching to the long-acting form of alprazolam (Xanax XR) to ease withdrawal (Sussman J and Klee B 2005).
7. Discontinuation of Z-drugs is less well studied than discontinuation of benzodiazepines, but given that they work similarly, the same approach for tapering benzodiazepines is recommended for tapering Z-drugs (Kaiser Permanente 2014).

Table 1. Diazepam Milligram Equivalent (DME)

	Trade Name	Half-life (hours)	Dose equivalent to 5 mg diazepam ¹
Benzodiazepines			
Alprazolam	Xanax	12–15	0.25–0.5 mg
Chlordiazepoxide	Librium	5–30	15 mg
Clonazepam	Klonopin	18–50	0.25–0.5 mg
Diazepam	Valium	20–80	5 mg
Lorazepam	Ativan	10–20	0.5–1 mg
Temazepam	Restoril	3.5–18.5	10 mg
Triazolam	Halcion	1.5–5.5	0.25 mg
Z-drugs			
Eszopiclone	Lunesta	6–9	2 mg
Zaleplon	Sonata	1	10 mg
Zolpidem	Ambien	1.4–4.5	10 mg
¹ Approximate equivalencies vary depending upon the resource referenced.			

Assessing Aberrant Drug-Related Behavior:

BZDs are often misused, abused and diverted in particular by individuals prone to substance use disorders. Identifying those individuals can be a challenge, but the following behaviors provide clues that should raise suspicion and be explored with the patient (SAMHSA 2011).

1. Being more interested in BZDs (especially short-acting) than in other medications or in any other aspect of treatment.
2. Taking doses larger than those prescribed or increasing dosage without consulting the clinician.
3. Insisting that higher doses are needed.
4. Resisting urine drug screens or referrals to specialists and other aspects of treatment.
5. Resisting changes to non-BZD therapy.
6. Repeatedly losing medications or prescriptions, or seeking early refills.
7. Making multiple phone calls about prescriptions.
8. Attempting unscheduled visits, typically after office hours or when the clinician is unavailable.
9. Appearing sedated.
10. Misusing alcohol or using illicit drugs.
11. Showing deteriorating functioning and beginning to experience adverse consequences from medications (e.g., problems at home or on the job).
12. Injecting (having track marks) or snorting oral formulations.
13. Obtaining medications illegally (e.g. street dealers, family members, the Internet (unlicensed pharmacies), forged prescriptions).

A more precipitous taper may be indicated in situations when there is abuse of these medications due to the risk of harm. Any patient thought to be abusing their medication should be counseled and assessed for a substance use disorder and offered appropriate treatment.

In Summary

Benzodiazepines have a long history, and at one point were safer alternatives than the medications previously in use, such as barbiturates and meprobamate. While relatively safe, they are readily abused by patients prone to substance abuse and can be fatal when combined with other sedating substances such as opioids and alcohol. There are other significant risks, especially in the elderly. While this class of medications remain an important tool, other as effective and safer treatment options are available. When appropriate, BZDs should be considered as second-line medications for appropriate psychiatric disorders and used for a limited time period.

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