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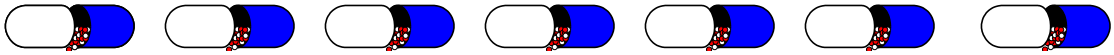

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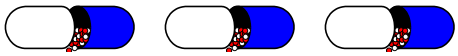

Issues and Options for Benzodiazepine Use

Introduction

The first FDA approved benzodiazepine (BZD), chlordiazepoxide (Librium), entered the U.S. market in 1960. These agents rapidly replaced barbiturates for treating anxiety and insomnia due to their relative safety, and became the most commonly prescribed drugs in the world.

Utilized for many clinical situations *(see Table 1),* four BZDs - alprazolam (Xanax), clonazepam (Klonopin), diazepam (Valium) and lorazepam (Ativan) are among the top 100 prescribed medications. BZDs cause significantly less respiratory depression than barbiturates and consequently, are rarely lethal in an overdose. However, used chronically, BZDs can be addicting, and many prescribers have questions and concerns about liability for abuse and dependence.

These agents are often taken in combination with other drugs of abuse by patients with addiction disorders. In such patients, alternatives to BZDs may be preferable. The most commonly used and FDA-approved alternative approach for the treatment of anxiety involves serontonin-selective reuptake inhibitors that are also approved as antidepressant agents, with buspirone providing another approved alternative. Off-label use of anticonvulsants, antihypertensive agents and antipsychotic agents has also been explored in clinical practice, but there is limited safety and efficacy data to support these unapproved uses.
This newsletter will discuss appropriate use of BZDs for treatment of insomnia and anxiety and how to minimize dependence risks for these agents.

Table 1: Clinical Uses of BZDs

- Anxiety disorders
  - Acute anxiety
  - Generalized anxiety disorder
  - Panic disorder
  - Phobias (social, simple)
  - Post-traumatic stress disorder
  - Obsessive-compulsive disorder
- Insomnia
- Anxiety associated with medical illness
  - Cardiovascular
  - Gastrointestinal
  - Somatoform disorder
- Convulsive disorders
- Acute status epilepticus
  - Neonatal seizures or febrile convulsions
  - Preeclampsia
  - Tetanus
- Adjunct to other anticonvulsants
- Amnestic (before surgery or procedure)
- Spastic disorders and other types of acute muscle spasm
  - Cerebral palsy
  - Multiple sclerosis
  - Paraplegia secondary to spinal trauma
- Involuntary movement disorders
  - Restless leg syndrome
  - Akathisia associated with neuroleptic use
  - Choreiform disorders
  - Myoclonus
- Detoxification from alcohol and other substances
- Agitation or anxiety associated with other psychiatric conditions
  - Acute mania
  - Psychotic illness
  - Anxiety associated with depression
  - Impulse control disorders
  - Catatonia or mutism
- Other adjunctive uses
  - Surgery
  - Dentistry
  - Diagnostic studies, such as computed tomography, magnetic resonance imaging and endoscopy
  - Cardioversion
  - Chemotherapy

Toxicity and Drug Interactions

When used alone, BZDs carry an extremely low risk of acute toxicity. However, BZDs are often used with other types of medications, including other drugs with abuse potential, and these drugs can enhance the toxic effects of BZDs. BZDs potentiate other central nervous system depressants, including other hypnotics, sedating antidepressants, neuroleptics, anticonvulsants, antihistamines and alcohol. Fatal overdoses in addicted patients often involve the combination of BZDs and alcohol, with or without opiates.

In addition, pharmacokinetic drug interactions may occur. Hepatic biotransformation is the primary route of metabolism for BZDs. Some active metabolites are formed which affect duration of action. Oxazepam and lorazepam have inactive metabolites, which contribute to their short half-lives and durations.

BZDs that are metabolized by the cytochrome P-450 (CYP-450) enzyme system should be carefully monitored when used concomitantly with drugs that inhibit the CYP-450 system. For example, selective serotonin reuptake inhibitors (SSRIs) may increase diazepam blood levels leading to increased sedative-hypnotic effects or other side effects.

Side Effects/Adverse Drug Events

- Side effects most commonly seen with BZD therapy involve dose-dependent CNS depression such as drowsiness, fatigue, confusion, dizziness, ataxia, and vertigo.
- Other side effects include memory impairment, behavioral changes, nausea, headache, and respiratory depression.

Anxiety

Among the medications utilized in the management of anxiety disorders, BZDs have accumulated the most safety and efficacy information to date. BZDs generally produce nearly immediate effects, and therefore can potentially be utilized for short-term, intermittent, "as-needed" use. However, intermittent, “as needed” use can also positively reinforce the ongoing use of BZDs, when clinicians may be trying to encourage the management of anxiety through other pharmacological (see below) and non-pharmacological approaches. In addition, intermittent use of short-acting BZDs can lead to rising and falling plasma levels, with the latter providing an additional trigger for anxiety states in some patients. Although many patients *can* use BZDs judiciously, clinicians should maintain vigilance for overuse or inappropriate use. In general, clinicians should aim for short-term use of regularly scheduled doses in appropriately evaluated and diagnosed individuals.

Alternatives for Treatment of Anxiety

Problems with BZD dependence, tolerance, withdrawal, rebound and abuse limit long-term BZD use. An understanding of toxicity and side effects of BZDs, abuse patterns, and alternative anxiolytic and hypnotic agents help clinicians with appropriate pharmacologic management.

A growing body of literature now supports the anxiolytic efficacy of numerous other agents; particularly certain antidepressant medications (e.g., SSRIs) *(see Table 2)*. Antidepressants, anticonvulsants, buspirone (Buspar), and certain antihypertensive agents may be effective in subsets of patients with anxiety, though it must be stressed that these ***other agents are not FDA approved*** for the treatment of anxiety, and the current medical literature should *always* be consulted prior to initiating alternative agents.

To choose an appropriate alternative to a BZD, physicians should be able to delineate whether an anxiety disorder exists in a particular patient and whether this is related to a co-morbid medical (e.g., hypoxia) or psychiatric condition. Patients should be encouraged to understand that the onset of action of antidepressants, buspirone and anticonvulsants is not as immediate as that of BZDs. Therapy may require patience and, because of side effects, a low dosage may be required initially.

The use of some of the listed alternatives does not imply FDA approval of these products in treatment of anxiety, and thus may *not* be appropriate for many patients. In all cases, the risks and benefits of a specific approach should be considered in the context of the individual patient. Overall, SSRIs have become the front-line alternative to BZDs in a variety of conditions, based on a favorable risk-benefit profile.

Table 2: Efficacy of Pharmacologic Agents in the Treatment of Anxiety Disorders

Disorder	BZDs	SSRIs	TCAs	ACVs*	Bu	AHTs‡
Anxiety with co-morbid depression		++				
Acute anxiety	++					+
Generalized anxiety disorder	++	+	++	±	++	
Panic disorder	++	++	++	+		
Social phobia	+	++	+		+	
Post-traumatic stress disorder	±	+	+	+	+	
Obsessive-compulsive disorder		++	+		+	

BZDs = benzodiazepines;
SSRIs = selective serotonin reuptake inhibitors;
TCAs = tricyclic antidepressants;
ACVs = anticonvulsants;
Bu = Buspirone (Buspar);
AHTs = antihypertensives.

++ = proven efficacy in numerous controlled trials;
+ = reported efficacy in open trials or in patients with comorbid depression;
± = equivocal efficacy, anecdotal reports or adjunctive use;
= no good clinical evidence of efficacy.
*--Anticonvulsants include valproic acid (Depakene) and gabapentin (Neurontin).
‡--Antihypertensives include beta blockers and clonidine (Catapres).

Insomnia

Insomnia is described as difficulty in falling asleep, frequently awakening in the night, or early morning awakening. The DSM-IV criteria define insomnia as being "associated with complaints about the quantity, quality, or timing of sleep at least 3 times a week for at least 1 month." As insomnia is a symptom of a problem rather than an isolated disease, and numerous medical and psychiatric conditions predispose individuals to insomnia, these should be considered and treated before hypnotic therapy is begun. Insomnia is often associated with substance-use disorders, early abstinence or protracted withdrawal. Other causes include stress, tension, pain, arthritis, diabetes, diet, caffeine, and nocturia.

Management of insomnia includes educational, behavioral, and often pharmacological interventions. Behavioral interventions include educating about relaxation strategies and behaviors that can disrupt sleep. Also important are attention to sleep hygiene techniques, such as maintaining a regular sleep-wake cycle, avoiding daytime naps, avoiding caffeine or heavy meals at night, and engaging in gentle exercise well before bedtime or utilizing other relaxation techniques.

Zolpidem (Ambien), an imidazopyridine, is a hypnotic agent with a chemical structure unrelated to BZDs.[34] Unlike the BZDs, zolpidem does not interfere with sleep stages 3 and 4, nor does it decrease rapid-eye-movement (REM) sleep. Tolerance and withdrawal symptoms do not appear as readily with this agent as with BZDs. However, zolpidem is classified as a schedule IV controlled substance (like BZDs), and synergistic effects with BZDs and alcohol have been observed, as have problems with abuse and dependence. Problems with vivid dreams, nightmares and rebound insomnia have also been reported.

Non-BZD pharmacotherapy for the management of insomnia includes the sedating antidepressant trazodone (Desyrel), tertiary tricyclic antidepressants such as amitriptyline (Elavil) and doxepin (Sinequan), and newer antidepressant agents such as mirtazapine (Remeron).

Table 3: Management of Insomnia

Non-pharmacological	Non-BZD Pharmacotherapy	BZD[1] Pharmacotherapy
Management of : ▪ Stress ▪ Tension ▪ Pain ▪ Comorbid disease states ▪ Nocturia ▪ Diet Behavioral education: ▪ Relaxation strategies ▪ Behaviors that disrupt sleep ▪ Practice good sleep hygiene Hypnosis	Non-benzodiazepines: ▪ zolpidem[2] ▪ zaleplon[2] Antidepressants ▪ TCAs ▪ Trazodone Barbiturates ▪ few indications for use Over the counter agents (usually containing diphenhydramine)	Short half-life ▪ More likely to be rebound insomnia after discontinuation Long half-life ▪ May cause residual daytime sedative effects and impaired psychomotor and mental performance during continued therapy

[1.] BZDs are generally preferred for short-term mgmt of insomnia due to established efficacy and relative safety.
[2.] Ambien (zolpidem) and Sonata (zaleplon) may be preferred in some patients due to rapid onset, short duration of action, and safety profile. Postmarketing data include reports of abuse, dependence, and withdrawal

There is little information available in the form of specific goals for treatment of insomnia and anxiety. It is difficult to put time frames on the treatment of these diseases because the outcomes of treatment are largely determined by individual patient characteristics.

Table 4: Benzodiazepine Treatment of Insomnia

Type of Insomnia	Treatment
Transient insomnia • Lasting several days related to minor stress	• Short elimination half-life BZD • Low dose • 1-3 nights
Short-term insomnia • Lasting several weeks due to stress of daily activities	• BZD used with strategies to improve sleep hygiene • Limit to a few weeks • Reevaluate therapy if lasting more than 2-3 weeks
Long-term insomnia • Lasting for a prolonged time due to an underlying condition	• Treat underlying conditions first • Aim to gradually discontinue after several months

Classification / Half-Life

Based on half-life, BZDs can be classified several ways. One method divides them into three categories: short-acting, intermediate-acting, and long-acting.

Short-acting:
- Can be used for sleep latency and nocturnal awakenings
- Half-lives of less than 6 hours

Intermediate-acting:
- Effective for sleep latency, nocturnal awakenings, and improving total sleep time
- Half-lives of 6 to 24 hours

Long-acting:
- Effective for nocturnal awakenings, improving total sleep time, and treating associated daytime anxiety
- Long half-lives of more than 24 hours, mostly due to active metabolites

There is little evidence for persistent benefits of either short or long acting BZDs on sleep parameters beyond 4 weeks of therapy, without repeated dose escalation. Adverse effects can persist beyond 4 weeks.

Special Population Considerations - Elderly

The aging process, including physiological changes, psychomotor slowing, cognitive dysfunction, and paradoxical disinhibition amplification; health problems, and social stressors, make prescription drug use more likely and more risky in the elderly.

- Misuse by the elderly population is often attributed to misunderstanding directions for appropriate use.
- The elderly may have a greater response to BZD therapy due to comorbid disease states, polypharmacy (drug interactions), changes in diet and activity, or pharmacokinetic and pharmacodynamic changes such as decreased clearance, alteration in protein binding, and increased drug sensitivity.
- With normal dosing, the elderly are more at risk for dependence, withdrawal, prolonged sedation, and cognitive and psychomotor impairment, which put them at greater risk for falls, fractures, and motor vehicle crashes.

- Longer acting drugs are more likely to accumulate than the short-acting drugs and are more likely to cause residual sedation, decreased attention, and decreased cognitive function.
- Agents with short half-lives or with no active metabolites are better choices for use in the elderly (examples include lorazepam, oxazepam, temazepam), but adverse events similar to those associated with longer half-life agents are still reported.
- Cognitive impairment is common, although memory impairment appears to be reversible when BZDs are discontinued.

Dependence and Abuse

Physical dependence (or "physiological dependence") refers to biochemical, physiological, and behavioral consequences of repeated exposure to a drug resulting in tolerance, and a withdrawal reaction when the drug is discontinued. This usually occurs in patients who have received excessive doses for an extended period of time, but it can occasionally occur with therapeutic dosages received for relatively short periods.

BZD therapy can give rise to physiologic and psychological dependence based on the drug's dosage, duration of therapy and potency. Dependency will develop sooner (one to two months) in a patient who is taking a high dosage of a high-potency agent such as alprazolam than in a patient who is receiving a relatively low dosage of a long-acting, low-potency agent such as chlordiazepoxide. With physiologic dependence, withdrawal symptoms emerge with rapid dose reduction or abrupt discontinuation.

- **TABLE 5: Potency and Half-Life of Various Benzodiazepines**

High-potency benzodiazepines	Low-potency benzodiazepines
Drugs with a short half-life	*Drugs with a short half-life*
Alprazolam (Xanax)	Oxazepam (Serax)
Lorazepam (Ativan)	Temazepam (Restoril)
Triazolam (Halcion)	
	Drugs with a long half-life
Drugs with a long half-life	Chlordiazepoxide (Librium)
Clonazepam (Klonopin)	Clorazepate (Tranxene)
	Diazepam (Valium)
	Flurazepam (Dalmane)

- **Tolerance** is the need for increasing amounts of a substance to achieve intoxication or desired effect, or a diminishing effect with continued use of the same amount of the substance. Tolerance to all actions of BZDs can develop, although at variable rates and to different degrees. Tolerance develops to the *sedative* effects of BZDs during long-term treatment, but tolerance to the *anxiolytic* effects is less common. Tolerance to the *hypnotic* effects tends to develop rapidly, which may be beneficial in daytime anxiolysis but makes long-term management of insomnia difficult.

  Patients typically notice relief of insomnia initially, followed by a gradual loss of efficacy. Tolerance to the anxiolytic effect seems to develop more slowly than does tolerance to the hypnotic effects, but there is little evidence to indicate that BZDs retain their efficacy after four to six months of regular use. BZD therapy is often continued to suppress withdrawal states, which usually mimic symptoms of anxiety. Dosage escalation often maintains the cycle of tolerance and dependence, and patients may have difficulty discontinuing drug therapy.

- **Withdrawal** reactions consist of a group of predictable physical signs and symptoms that occur after the abrupt discontinuation of, or rapid decrease in dosage. Signs and symptoms of the reaction are a more extreme form of the original symptoms that were being treated, such as anxiety or insomnia, and possibly signs that were not present prior to use. *Discontinuing BZDs suddenly in physically dependent patients may produce severe and life-threatening withdrawal*.

  Short-Term Withdrawal Symptoms
  Withdrawal effects from therapeutic dosages of BZDs are mainly anxiety symptoms. In addition, autonomic instability (i.e., increased heart rate and blood pressure level, tremulousness, diaphoresis), insomnia and sensory hypersensitivity are common. The most serious acute withdrawal symptoms are seizures and delirium tremens, which most commonly occur with abrupt discontinuation. The time frame for emergence of acute withdrawal symptoms corresponds to the half-life of the particular agent used.

  Some elements of withdrawal are believed to occur in a majority of patients who have taken therapeutic dosages of BZDs for more than a few months, although the severity of withdrawal symptoms generally depends on the amount of the original dosage, the rate at which the dosage is tapered, the selection of patients and the definition of withdrawal symptoms.

  Protracted Withdrawal
  A protracted abstinence syndrome has been observed by addictionologists familiar with BZD addiction. Symptoms include prolonged (for several months) anxiety, depression and insomnia. In addition, physical symptoms related to gastrointestinal, neurologic and musculoskeletal effects may occur. This abstinence phenomenon may develop despite long, slow, tapering of the dosage and is hypothesized to result from chronic neuroadaptation.

Psychological Dependence

- Psychologically, long-term use of BZDs may lead to overreliance on the need for the agent, loss of self-confidence and varying degrees of drug-seeking behavior. Patients may be reluctant to discontinue the drug because of misplaced fears or anticipatory anxiety.

- Psychological dependence can occur with or without physiological dependence (tolerance and withdrawal). The symptoms of psychological dependence are:
  - Taking larger doses than intended
  - Unsuccessful attempts to cut down
  - Spending too much time obtaining, or recovering from use
  - Giving up important activities to use
  - Continued use in spite of recurrent problems

- Using multiple physicians to get prescriptions, or taking the drug for reasons other than those for which it was prescribed are other inappropriate drug-taking behaviors associated with psychological dependence.

- Psychological dependence does *not* develop in most patients

Benzodiazepine Abuse

Abuse is defined as use that causes any of the following: failure to fulfill role obligations at work, home or school, recurrent use in physically hazardous circumstances, legal problems or social impairment.

BZDs are rarely the preferred or sole drug of abuse. An estimated 80 percent of BZD abuse is part of polydrug abuse, most commonly with opioids. A two-year treatment outcome study by the National Institute on Drug Abuse found that 15 percent of heroin users also used BZDs daily for more than one year, and 73 percent used BZDs more often than weekly. Studies indicate that from 5 percent to as many as 90 percent of methadone users are also regular users of BZDs. Studies also indicate that 3 to 41 percent of alcoholics report that they abused BZDs at some time, often to modulate intoxication or withdrawal effects.

Most addiction medicine specialists believe that BZDs are relatively contraindicated in patients with current alcohol or drug abuse problems. However, in a review in the American Journal on Addictions in 2001, authors Posternak and Mueller conclude that although most BZD abusers concurrently abuse other substances, there is little evidence to indicate that a *history* of substance abuse,(e.g. those in *active recovery*), is a major risk factor for future BZD abuse or dependence. They state that the position that BZDs are contraindicated in former substance abusers appears to lack empirical justification.

BZDs have multiple uses for polydrug addicts: they are used to enhance euphoriant effects of opioids (such as to "boost" methadone doses), to alleviate withdrawal or abstinence syndromes (such as between heroin "fixes"), to temper cocaine highs, to augment alcohol synergistically and to modulate withdrawal states.

Most/Least Common Agents of Abuse

As potential drugs of abuse, short-acting BZDs seem to be preferred among addicts because of the rapidity of their onset of action. In general, mood-altering substances are most highly reinforcing in patients with chemical dependence if the agent has a rapid onset of action, a high potency, a brief duration of action, high purity and water solubility (for intravenous use) or high volatility (ability to vaporize if smoked). Data suggest that highly lipophilic BZDs (i.e., those that cross the blood-brain barrier more rapidly), such as diazepam, and agents with a short half-life and high potency, such as lorazepam or alprazolam, are the most reinforcing BZDs and, therefore, ones most likely to be abused.

Clonazepam is a high-potency BZD with a long half-life. It is widely prescribed for a variety of psychiatric and neurologic conditions. Although clonazepam is perceived as "safe," addiction medicine specialists have found that it is frequently abused as a street drug. Oxazepam (Serax), clorazepate (Tranxene) and chlordiazepoxide have similarly been considered to have lower reinforcing effects than other BZDs, but there is limited evidence to support differences in abuse potential across the BZD class.

APPENDIX I - TAPER SCHEDULES

Much discomfort of BZD withdrawal is lessened by implementing a gradual taper. Regardless of taper schedule, several principles should be kept in mind while discontinuing BZDs.

1. Modify taper as needed if relapse, rebound, and/or withdrawal occurs.

2. Tapering does not eliminate withdrawal symptoms, but can prevent severe withdrawal.

3. Patients should be educated about the withdrawal symptoms that may occur.

4. Some form of psychological support, either simple encouragement or formal cognitive and behavioral therapies, should be implemented, and any underlying psychiatric conditions treated.

Suggested Taper Schedules

1. Convert drug into an equivalent dose of diazepam and then reduce the diazepam dose by 2 mg weekly over a period of 2 to 6 months.

OR

2. Perform first 50% reduction quickly and second 50% reduction gradually.

- Start with a 25% reduction of initial daily dose per week until 50% of dose is reached.

- The dose can then be decreased by 12.5% of initial dose every 4 to 7 days.

- If more prolonged taper is needed, the dose can be decreased by 6.25% every 4 to 7 days.

OR

3. Discontinuation schedule based on half-life, daily dose, and duration of use.

- Low doses of long or short half-life BZDs taken for more than 1 month can be decreased by 20% of initial dose per week for 4 weeks.

- High doses of long half-life BZDs taken for more than 1 month should be reduced by 60% of initial total daily dose.
  - This total daily dose should be divided and given every 6 hours on day one.
  - Decrease the dose by 10% daily until the taper is complete.

- High doses of short half-life BZDs taken for more than 1 month can be switched to an equivalent dose of diazepam or another long-acting BZD and then follow the taper as outlined above.
  - Switching from short-acting to longer-acting BZDs will produce a gradual decrease in drug concentration and decrease the chance of withdrawal symptoms.

APPENDIX II - CONSIDERATIONS FOR BENZODIAZEPINE (BZD) USE

Over-prescribing and/or inappropriate prescribing of hypnotic and anxiolytic BZDs is a common problem that leads to increased risks of patient dependence. General careful **prescribing practices that can be followed to avoid BZD dependence include:**

- Use BZDs only for anxiety or insomnia that seriously disrupts the patient's lifestyle, not for minor complaints.
- Non-drug alternative treatment strategies should be utilized, such as lifestyle changes, counseling, and eliminating underlying causes.
- Warn patients of tolerance, dependence potential, and difficulty of withdrawal if treatment is prolonged.
- Limit the supply of medication provided.
- Specify on the prescription that the drug should be taken "when needed," and make sure the patient understands that daily dosing is not required to see beneficial effects.
- Use the smallest dose possible.
- Review the need for continued medication regularly and discontinue as soon as possible.
- Withdraw BZD-dependent patients slowly.

Patient education topics which should be covered to maximize BZD therapy:

- The cause and symptoms of the disease state
- Treatment options
- How to monitor for symptoms and side effects
- Follow-up regimen
- Warning signs of relapse, tolerance, and dependence
- Length of treatment

Criteria to evaluate patients for the need of long-term treatment:

- Justifiable continued use of BZDs
- Benefit from treatment
- BZD use within reasonable limits
- Stable use over time
- Patient avoidance of other prescription or nonprescription substances
- Side effects or impairment from BZD use
- Appropriate BZD use confirmed by a family member who can monitor the patient

Prepared by:
UMKC Drug Information Center
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