



Pharmacist Toolkit: Benzodiazepine Taper

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This toolkit is intended to highlight both the evidence base available as well as strategies of clinical decision making used by expert clinicians. The content reflects the views and practice of the authors as substantiated with evidence-based facts as well as opinion and experience.

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Table of Contents

Overview	2
Populations at Risk for Complications	2
Screening and Diagnosis	2
Severity of Dependence Scale (SDS)	3
Benzodiazepine Withdrawal	3
Common Acute Benzodiazepine Withdrawal Symptoms	4
Common Protracted Benzodiazepine Withdrawal Symptoms	4
Benzodiazepine Withdrawal Scales.....	5
Treatment	5
Special Populations	6
Elderly	6
Hepatic impairment	7
Renal impairment.....	7
Pregnancy.....	7
Breastfeeding	7
Co-occurring Mental Health Disorders	7
Co-occurring Substance Use	8
Harm Reduction	9
Clinical Pearls	9
Strategies to overcome barriers to tapering.....	9
Strategies to prevent inappropriate use	9
Best practices when tapering.....	9
Special Note-Authors' Experience	10
References	10

Overview

Long-term use of benzodiazepines has been known to produce complications related to discontinuation, withdrawal symptoms, increased risk of accidental overdose when combined with other central nervous system depressants, persistence of benzodiazepine related side-effects, physical dependence, and benzodiazepines use disorders.¹⁻³ There were nearly 272,000 emergency department encounters within the United States involving nonmedical use of benzodiazepines in 2008. In many of these visits (40%), benzodiazepines were used in conjunction with alcohol.⁴ The number of nonmedical benzodiazepine emergency department visits increased to 426,000 in 2011. The use of alcohol was present in 24.2% of these visits.⁵

From 1996 to 2013, the number of adults that obtained a prescription for a benzodiazepine increased by 67%. The amount of benzodiazepines dispensed more than tripled during that same time period, from 1.1-kg to 3.6-kg lorazepam-equivalents per 100,000 adults. Based on information from the National Institute on Drug Abuse, the number of overdose deaths involving a benzodiazepine increased from 1135 in 1999 to 8791 in 2015. Three quarters of the deaths involving a benzodiazepine also involved an opioid.⁵⁻⁹ Because of concerns regarding patient safety, several guidelines and expert consensus statements have cautioned against chronic benzodiazepine use, especially in the elderly and other at-risk populations.⁶⁻¹⁰ Though benzodiazepines remain first-line treatments for acute alcohol withdrawal and may be used acutely as anticonvulsants, they should generally be avoided for anxiety disorders, panic disorder, and insomnia. Other effective treatment options with superior safety profiles should be used when possible for these conditions. If a benzodiazepine is used, it should be limited to 2-4 weeks.

Populations at Risk for Complications

There are several populations at greater risk for complications from long-term benzodiazepine treatment that should be considered for tapering. In elderly patients, the use of benzodiazepines increases risk of serious adverse effects including impaired cognitive functioning, complications with mobility, impaired driving ability, and falls.¹¹⁻¹⁴ Another at-risk patient population are individuals prescribed concomitant opioids and benzodiazepines. The combination increases the risk of overdose and death, and is the most common present combination in both intentional and unintentional overdose-related deaths.¹⁵ Relative contraindications to the co-prescribing of benzodiazepines and opioids include active misuse, or current or past substance use disorders involving benzodiazepines, opioids, alcohol, and/or other central nervous system depressants. Other special populations at risk for complications from benzodiazepines include those with unstable psychiatric illness, diagnosis of posttraumatic stress disorder, and medical comorbidities such as morbid obesity, sleep-disordered breathing, chronic obstructive pulmonary disease, traumatic brain injury, and hepatic or renal dysfunction.¹⁶⁻¹⁹ Furthermore, in nine out of eleven studies, a positive association was found between long-term benzodiazepine use and dementia. Though causality has not been proven, the available data suggest a causal link and several mechanisms have been implicated.²⁰

Screening and Diagnosis

Many of the at-risk populations described above meet criteria for being diagnosed with Sedative, Hypnotic and Anxiolytic Use Disorder. This new diagnosis requires at least 2 of the following criteria occurring within a 12-month period. The disorder is mild if 2 to 3 criteria are met, moderate if 4 to 5 criteria are present, and severe with 6 or more criteria present.

DSM-5 Diagnosis for Sedative, Hypnotic and Anxiolytic Use Disorder:²¹

- Continuing to use a barbiturate, benzodiazepine or other sedative-hypnotic, despite negative personal consequences.
- Repeated inability to carry out major functions at work, school or home on account of use.
- Recurrent use in physically hazardous situations.
- Continued use despite recurrent or persistent social or interpersonal problems caused or made worse by use.
- Tolerance, as manifested by needing a markedly increased dose to achieve intoxication or desired effect, or by markedly diminished effect with continued use of the same amount.
- Withdrawal with the characteristic syndrome or use of the drug to avoid withdrawal.
- Using more of the drug or using for a longer period than intended.
- Persistent desire to cut down use or unsuccessful attempts to control use.
- Spending a lot of time obtaining or using the substance or recovering from use.

- Stopping or reducing important occupational, social or recreational activities due to use.
- Craving or strong desire to use.

Severity of Dependence Scale (SDS)

The [Severity of Dependence Scale \(SDS\)](#) was created to provide a short and easily administered self-report scale to measure the degree of dependence for different types of drugs.²² The SDS contains five items related to the psychological components of dependence. A score above six is indicative of dependence.

Benzodiazepine Withdrawal

When a benzodiazepine is regularly used for 8 weeks or more, the agent should be gradually tapered rather than abruptly stopped because of the potential to precipitate withdrawal. High dose and long-term use are associated with a greater chance of developing benzodiazepine withdrawal. Withdrawal symptoms may include anxiety, depersonalization, depression, hypersensitivity to sensory stimuli, perceptual distortions, and weight/appetite changes. During this time, the symptoms of pre-existing psychiatric conditions may recur, potentially to a greater severity than they did during pre-treatment and may continue for a prolonged period of time.^{23,24} Epileptic seizures and other neuropsychiatric symptoms (psychosis, delirium) may also occur, though are much less common.²⁵ Benzodiazepine withdrawal can be divided into the acute and protracted withdrawal phase.

Acute benzodiazepine withdrawal syndrome, from a pharmacological perspective, may persist from 5 to 28 days, though generally peaks after approximately 14 days. After this time, most symptoms should return to the extent that they were present prior to discontinuation.²⁶⁻³² Benzodiazepine withdrawal syndrome includes symptoms common to most anxiety disorders, but also includes some symptoms more specific to benzodiazepine withdrawal. The acute withdrawal phase may develop into a protracted phase.

During the protracted withdrawal phase, many patients and clinicians have observed that symptoms of withdrawal may continue for extended periods of time. It has been reported that benzodiazepine withdrawal symptoms of anxiety, sensory hypersensitivity, depression, muscle spasms, paresthesia and tinnitus can persist 6 to 12 months after discontinuation.^{26,33-40} It can also be difficult for patients and providers to determine the extent of their symptoms prior to the taper. It is not uncommon for patients to describe benzodiazepine withdrawal symptoms and severe anxiety even while currently using a benzodiazepine.^{38,41} While these symptoms may return to pre-discontinuation levels weeks after the period of peak withdrawal, many symptoms may continue to decrease in the months thereafter. For some patients these symptoms may all together disappear or be less than they were prior to the discontinuing the benzodiazepine. It is not uncommon for patients to report an improvement in anxiety, mood, and cognition.^{36,38,41} In these circumstances, symptoms gradually decline but never fully disappear, or episodically reappear. The most common “protracted withdrawal” symptoms are anxiety, cognitive impairment, depression, gastrointestinal disturbances, insomnia, and various sensory and motor phenomena.^{33,38}

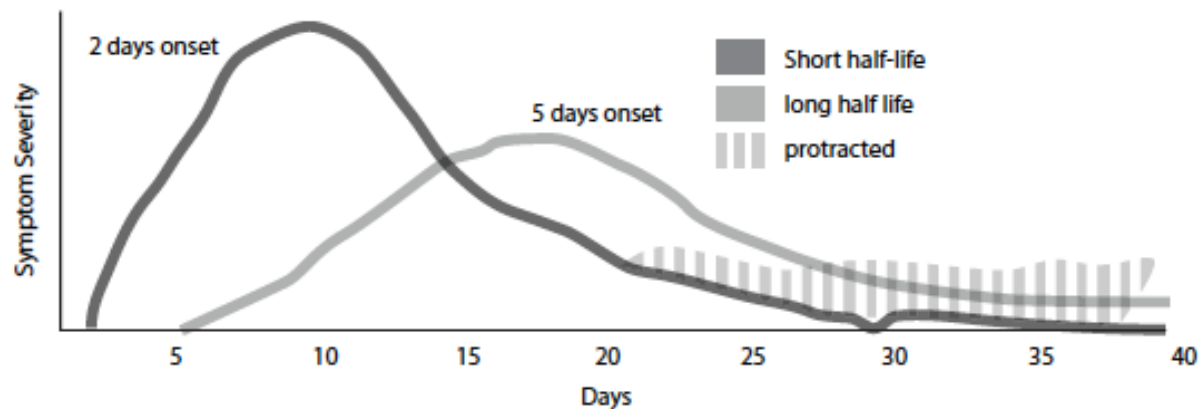
Common Acute Benzodiazepine Withdrawal Symptoms⁴²

Symptoms common to all anxiety states	Symptoms relatively specific to benzodiazepine withdrawal
Anxiety, panic attacks, agoraphobia	Perceptual disturbances, sense of movement
Insomnia, nightmares	Depersonalization
Depression, dysphoria	Hallucinations (visual, auditory), misperceptions
Excitability, jumpiness, restlessness	Distortion of body image
Poor memory and concentration	Tingling, numbness, altered sensation
Dizziness, light-headedness	Formication
Weakness, "jelly legs"	Sensory hypersensitivity (light, sound, taste, smell)
Tremor	Muscle twitches, jerks, fasciculation
Muscle pain, stiffness (limbs, back, neck, jaw, head)	Tinnitus
Sweating, night sweats	*Confusion, delirium
Palpitations	*Fits
	*Psychotic symptoms
*Usually confined to rapid withdrawal from high doses of benzodiazepines	

Common Protracted Benzodiazepine Withdrawal Symptoms⁴²

Symptoms	Usual course
Anxiety	Gradually diminishing over a year
Insomnia	Gradually diminishing over 6 to 12 months
Depression	A few months: responds to antidepressants
Cognitive impairment	Gradually improving but may last a year or more and occasionally incomplete
Perceptual symptoms tinnitus paresthesia - tingling, numbness, pain usually in limbs, extremities	Gradually receding, but may last at least a year and occasionally persist indefinitely
Motor symptoms muscle pain, weakness, tension, painful tremor, shaking attacks, jerks, blepharospasm	Gradually receding, but may last at least a year and occasionally persist indefinitely
Gastrointestinal symptoms	Gradually receding, but may last at least a year and occasionally persist indefinitely

The benzodiazepine withdrawal syndrome



Time course for short-acting and long-acting benzodiazepine withdrawal.

Used with Permission: *Benzodiazepine Toolkit. Reconnexion 2018*⁴³

Benzodiazepine Withdrawal Scales

Two scales have been developed to assess benzodiazepine withdrawal but have not yet been well-validated, despite initially being published around 1990.

The [Clinical Institute Withdrawal Assessment - Benzodiazepines \(CIWA-B\)](#) is a 22-item questionnaire used to assess withdrawal symptoms in patients tapering off or discontinuing benzodiazepines.⁴² Scores from 1 to 80 estimate the severity of withdrawal.

The [Benzodiazepine Withdrawal Symptom Questionnaire \(BWSQ\)](#) is a 20-item questionnaire which includes symptoms of benzodiazepine withdrawal that are rated as “no”, “yes-moderate” or “yes-severe” and scored as 0, 1 or 2 points, respectively.³⁵ Scores from 0 to 40 estimate the severity of withdrawal.

Treatment

For most patients, a gradual taper over several months can be implemented to discontinue benzodiazepine therapy.

The goals for a successful taper are to decrease withdrawal effects and manage rebound symptoms as well as recurrence of underlying symptoms that were being managed by the benzodiazepine.

Many practitioners continue to follow recommendations suggesting conversion from shorter- to longer-acting agents in order to decrease potential withdrawal symptoms. Data on whether this practice increases the rate of successful taper is lacking, but switching to an alternative agent may be helpful for some patients.⁴⁶

Equivalent doses of benzodiazepines are included in the table below. Of note, high doses of alprazolam may not have complete cross-tolerance with other agents, so a gradual switch to a longer-acting agent, such as clonazepam, may be necessary.

Approximate Benzodiazepine Dose Equivalents⁴⁷

Benzodiazepine	Approximate Dosage Equivalents	Elimination Half-Life (may include active metabolites)
Alprazolam	1 mg	12-15 hours
Chlordiazepoxide	25 mg	>100 hours
Clonazepam	1 mg	20-50 hours
Diazepam	10 mg	>100 hours
Lorazepam	2 mg	10-20 hours
Temazepam	15 mg	10-20 hours

In general, outpatient benzodiazepine tapers should occur at a rate of approximately a 25% dose reduction every week. As the end of the taper nears, this rate may need to be decreased even further to 25% every 2 weeks if the patient is experiencing withdrawal or rebound symptoms. Longer tapers can also be considered for patients who are apprehensive about discontinuing the medication or who have failed taper attempts in the past. Slower tapers may also need to be considered for patients on high doses of benzodiazepines or those who have been taking the medication consistently for many years. These tapers can include a dose decrease of 10-25% every two to four weeks and last up to six months. Doses should be scheduled instead of “as needed.” Follow-up visits should be scheduled every 1-4 weeks, depending on the patient’s response to the taper.

The EMPOWER trial was conducted to compare the effect of a direct-to-consumer educational intervention to usual care in long-term benzodiazepine users aged 65 years and older recruited from 30 community pharmacies.⁴⁸ The intervention arm of the study received an 8-page packet educating the patients on the risk of benzodiazepine use, presenting peer success stories and alternate treatment options, describing tapering protocols and encouraging patients to discuss tapering with their physician. The [EMPOWER brochure](#) includes a sample tapering protocol that can be used to assist patients in discontinuing benzodiazepine therapy. The direct-to-consumer approach in this study led to 27% of the intervention group discontinuing their benzodiazepine at the six month follow-up, compared with 5% of the control group.

Several medications have been evaluated to assist with benzodiazepine tapering and withdrawal symptoms. Hydroxyzine, carbamazepine and pregabalin have all shown some benefit on withdrawal symptoms based on limited data.⁴⁹⁻⁵² However, there are no strong recommendations for use of any particular medication to increase the success rates of benzodiazepine tapers.

Among anticonvulsants studied (carbamazepine, valproate, gabapentin, pregabalin, tiagabine, oxcarbazepine, and topiramate), only carbamazepine and pregabalin demonstrated efficacy in reducing benzodiazepine withdrawal syndrome symptoms.⁵³ The utility of other agents, while mechanistically sensible, is questionable because of inconclusive results and small study samples. The potential benefit of using an anticonvulsant agent instead of directly tapering the benzodiazepine would be if the safety concerns for using benzodiazepine to complete the taper were too great. For example, a patient who has not demonstrated the ability to use the taper as directed or is found to be diverting benzodiazepines would be considered a safety concern.

The addition of psychotherapy when tapering benzodiazepines can lead to increased successful tapers and future abstinence rates. Cognitive behavioral therapy (CBT) for anxiety and insomnia have been shown to be beneficial for discontinuing benzodiazepine therapy in patients not already receiving specialty mental health services.^{54,55}

Special Populations

Elderly

- Older adults may be more susceptible to adverse effects of benzodiazepines such as sedation and balance problems leading to falls.
- Reducing the dose of a shorter-acting agent before converting to a longer-acting agent may be prudent secondary to the possibility of decreased metabolism in elderly patients.

Hepatic impairment

- Most benzodiazepines are primarily metabolized via hepatic CYP-mediated oxidation. These agents may have prolonged duration of effect in patients with marked liver impairment.
- Benzodiazepines with active metabolites, such as diazepam, clonazepam, and midazolam, may be most concerning in these patients.
- Lorazepam, oxazepam, and temazepam are mostly metabolized by conjugation and do not have active metabolites, which makes them the preferred agents in patients with hepatic impairment and the elderly.
- When choosing an agent to use for a benzodiazepine taper in this population, lorazepam may be the best option.

Renal impairment

- Most benzodiazepines do not need to be adjusted for renal impairment.
- Lorazepam should not be used in patients who have renal failure.

Pregnancy⁵⁶

- Benzodiazepines were previously FDA category D drugs before changes were made to the nomenclature of their rating system. There are concerns with cleft lip/palate and urogenital and neurological malformations. However, recent studies have not shown an increased risk for these complications.
- Recommend patients taper benzodiazepines in pregnancy. More rapid tapers over a period of a month can be employed, if tolerated.
- Minimize use as much as possible; use only as needed. Try to avoid use during the first trimester. Weigh the benefit vs. the risk of continued use. If a benzodiazepine is needed, consider an agent with a short half-life. Also use the medication sparingly and intermittently.
- Consider switching to an antidepressant which may be safer in pregnancy. Avoid paroxetine.
- Avoid use near the time of delivery to prevent withdrawal symptoms in the newborn.

Breastfeeding⁵⁶

- All benzodiazepines can cross into the breast milk, however the long-term effects on infants are unknown. Babies may experience side effects such as sedation, respiratory depression, difficulty breastfeeding, and hypotonia (“floppy baby syndrome”).
- If necessary, use an agent with a shorter half-life. Infants may not have developed the mechanism to metabolize benzodiazepines which leads to a longer half-life.

Co-occurring Mental Health Disorders

Benzodiazepines do have a role in the treatment of anxiety, panic, and sleep disorders. If it is decided that use of a benzodiazepine is appropriate, treatment should be limited to two to four weeks.

Patients currently taking long-term benzodiazepines to treat a mental health condition may be more safely and appropriately treated with alternative therapies.

Anxiety⁵⁷

- Selective serotonin reuptake inhibitors (SSRIs) or serotonin/norepinephrine reuptake inhibitors (SNRIs)
- Buspirone
- Hydroxyzine
- Pregabalin
- CBT
- Exposure therapy
- Benzodiazepines should generally be reserved for patients who continue to have severe symptoms of anxiety despite trials of several other appropriate treatments. Risk vs. benefit of benzodiazepine use should be carefully considered in these situations.

Insomnia

- Psychological/behavioral therapy⁵⁸
 - Cognitive Behavioral Therapy for Insomnia (CBT-I)
 - Stimulus control therapy
 - Relaxation therapy
- Sedating antidepressants (trazodone, mirtazapine, amitriptyline, doxepin)⁵⁷
- Antihistamines (hydroxyzine, diphenhydramine)
- Ramelteon or melatonin

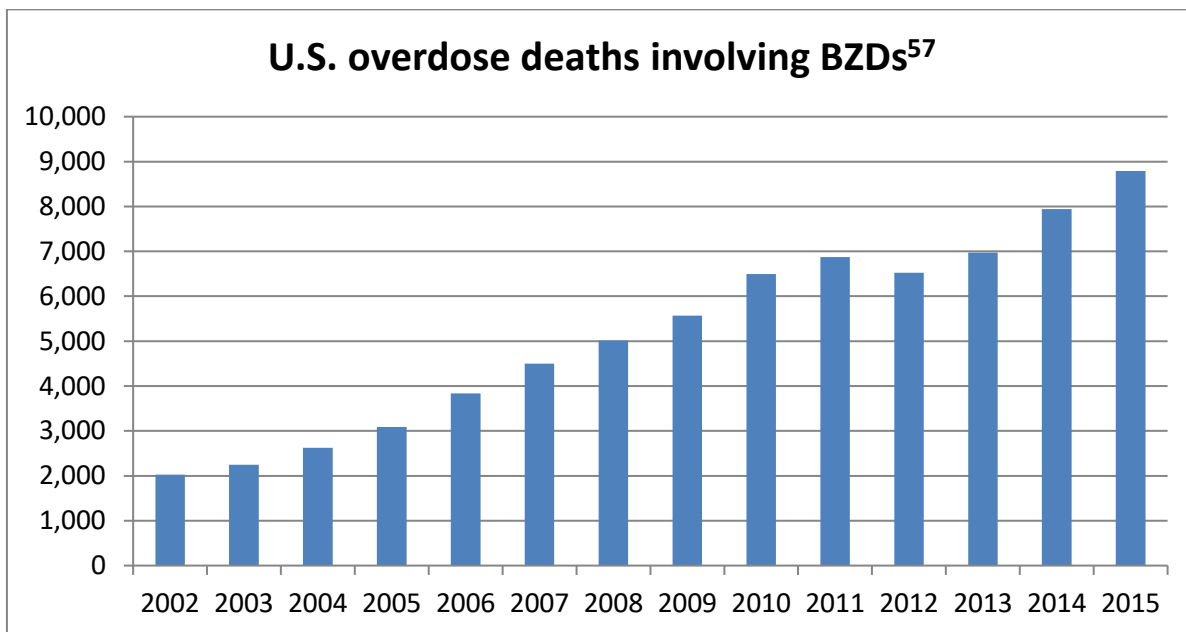
Post-Traumatic Stress Disorder (PTSD)⁵⁹

- Psychological/behavioral therapy⁵⁸
 - Cognitive Behavioral Therapy for Insomnia (CBT-I)
 - Stimulus control therapy
 - Relaxation therapy
- Sedating antidepressants (trazodone, mirtazapine, amitriptyline, doxepin)⁵⁷
- Antihistamines (hydroxyzine, diphenhydramine)
- Ramelteon or melatonin

Co-occurring Substance Use

Patients with co-occurring substance use are at a greater risk for adverse outcomes and possible overdose with benzodiazepine use because of the additive sedative and respiratory depressant effects with many of the substances commonly misused.

After opioids, benzodiazepines are the drug class most commonly involved in intentional and unintentional overdose deaths. There was a 4.3-fold increase in the total number of deaths involving benzodiazepines from 2002 to 2015.⁶⁰ Opioids play a role in approximately 75% of deaths involving benzodiazepines.



In 2016 the Food and Drug Administration added a black box warning cautioning against the concomitant use of benzodiazepines and opioids.

For patients with a primary substance use disorder, inpatient admission with a rapid taper over 2 to 3 weeks can be considered.

Harm Reduction

- If complete discontinuation is not possible, taper the benzodiazepine to the lowest dose possible and encourage only as needed or intermittent use
- Caution patients to avoid mixing benzodiazepines with other depressant drugs or alcohol.
- Advise patients to never take other people's prescribed medications.
- Advise patients to avoid driving or other dangerous activities after taking benzodiazepines.

Clinical Pearls

Strategies to Overcome Barriers to Tapering

- **Barrier:** Fear of return of symptoms (anxiety, insomnia)
 - **Strategy:** Slow taper to avoid withdrawal symptoms
 - **Strategy:** Provide education advising that anxiety and insomnia can be part of withdrawal but will improve with time
 - **Strategy:** If anxiety or insomnia truly remain, treat appropriately with alternative agents or psychotherapy
- **Barrier:** Sense of safety because of long-term use without adverse effects
 - **Strategy:** Highlight potential negative outcomes, including:
 - Cognitive impairment/dementia
 - Balance problems/falls
 - Motor vehicle accidents
 - Unintentional overdoses can occur even when dose has been stable

Strategies to Prevent Inappropriate Use

- **Strategy:** Clearly explain risks vs. benefits prior to initiation
- **Strategy:** Inform patient of plan for short-term or intermittent, as needed use
- **Strategy:** Avoid use in patients with risk factors for adverse outcomes, including:
 - Current, recent, or recurrent substance use disorder
 - Current opioid use
 - Elderly patients
 - Diagnosis of sleep apnea or COPD

Best Practices when Tapering

- Provide patient with clear written instructions for taper
 - Discuss how prescription will be written, quantity provided and appropriate refill date
 - Consider having patient sign a treatment agreement including information on consequences related to early refill requests, prescriptions from other providers, or misuse of other substances
- Although it is not absolutely necessary, converting to a long-acting agent for the duration of the taper may mitigate withdrawal symptoms compared with short-acting agents
- Staying at a dose for longer than expected is acceptable, but do not increase the dose once a taper has started
- Avoid "as needed" use of benzodiazepines during the taper
- Provide seven to fourteen day supply of medication

- Obtain urine drug testing prior to starting taper and periodically thereafter
 - Repeat urine drug testing if noticeable changes in behavior are noted, the patient misses follow-up appointments or requests early refills
 - Monitor for use of other substances to replace benzodiazepine or manage withdrawal symptoms
 - Monitor Gamma-Glutamyl Transferase (GGT) for alcohol use
 - Use of the urine drug testing to monitor adherence with benzodiazepine prescription or use of non-prescribed benzodiazepines is limited⁶¹
 - Alprazolam, lorazepam and clonazepam may not be detected by the urine drug testing
 - Cutoff concentrations may be too high to detect usual doses of more potent benzodiazepines such as alprazolam, triazolam and clonazepam
 - Short-acting agents may only be detected in urine for 1 to 3 days
 - False-positive results may be caused by sertraline, efavirenz or oxaprozin

Special Note-Author's Experience

The fear of coping without a benzodiazepine plays a major role for many patients when tapering. Unresolved issues that long-term drug use has masked often return and are painful. Tolerating painful feelings and the associated anxiety that have been numbed for a significant period of time is a challenge. Such patients have been conditioned to use benzodiazepines for coping with these feelings and anxiety and may find the normal range of feelings to be overwhelming. It is often a major component of their resistance to taper. Providing a safe place to talk about this experience is essential. Consider recommending psychotherapy, particularly to those patients that have significant anxiety and/or mood changes. Watch carefully for other substance use during this time as well.

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