Benzodiazepine Dependence and Withdrawal: Identification and Medical Management

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Abstract: Background: Primary care physicians prescribe benzodiazepines for the treatment of anxiety. Although most patients use the benzodiazepines appropriately, some patients experience benzodiazepine abuse, addiction, or physical dependence, each of which is a distinct syndrome. Benzodiazepine dependence, which relates to the development of tolerance and an abstinence syndrome, can be produced by three disparate benzodiazepine use patterns. These distinct benzodiazepine use patterns can in turn create distinct withdrawal syndromes. High-dose benzodiazepine use between 1 and 6 months can produce an acute sedative-hypnotic withdrawal syndrome. In contrast, low-dose therapeutic range benzodiazepine use longer than 6 months can produce a prolonged, subacute low-dose benzodiazepine withdrawal syndrome. Daily, high-dose benzodiazepine use for more than 6 months can cause a combination of an acute high-dose benzodiazepine withdrawal and a prolonged, subacute low-dose withdrawal syndrome. In addition, patients may experience syndrome reemergence.

Methods: A literature search was conducted using the medical subject headings benzodiazepines, substance abuse, substance dependence, substance withdrawal syndrome, and benzodiazepines adverse effects. The years 1970 to the present were reviewed.

Results and Conclusions: Medical management for acute benzodiazepine withdrawal includes the graded reduction of the current benzodiazepine dosage, substitution of a long-acting benzodiazepine, and phenobarbital substitution. However, the medical management of benzodiazepine dependence does not constitute treatment of benzodiazepine addiction. Primary care physicians can accept complete, moderate, or limited medical responsibility regarding patients with substance use disorders. However, all physicians should provide diagnostic and referral services. (J Am Board Fam Pract 1992; 5:167-76.)

The benzodiazepines have proved to be clinically effective and generally safe pharmacotherapeutic tools for primary care physicians. Although there is some debate over the magnitude of inappropriate benzodiazepine use, investigators generally find their use appropriate to the medical and psychiatric conditions for which they are prescribed. Nevertheless, these drugs are psychoactive and mood altering; subject to misuse and abuse, they can be agents of addiction.

Different responses to the benzodiazepines often reflect the presence of two separate, but occasionally overlapping, groups of patients. The group that takes benzodiazepines for medically prescribed and appropriate reasons does not generally experience dosage escalation or drug-related dysfunction. A second group abuses benzodiazepines, usually in a polydrug use pattern, and experiences drug-related dysfunction.

The majority of patients take benzodiazepines as prescribed and the majority of physicians appropriately prescribe them. Even so, both physicians and patients can contribute to the inappropriate use of the benzodiazepines.

Benzodiazepine abuse, addiction, and physical dependence are distinct clinical phenomena. Benzodiazepine abuse is defined as benzodiazepine use that causes impairment and dysfunction in the patient's social, occupational, emotional, psychological, or physical well-being. The impairment and dysfunction range from mild to severe and often are self-limiting. Benzodiazepine addiction is a chronic, progressive, pathological process with biopsychosocial components that...
generally include (1) a compulsion to use a benzodiazepine, (2) a loss of control over benzodiazepine use (or over drug-induced behavior), and (3) the continued use of the drug despite adverse consequences. In contrast, benzodiazepine dependence relates to the development of physical tolerance and withdrawal.

Benzodiazepine abuse and addiction occur most often among patients who have a history of alcoholism or other drug abuse or addiction, usually in a polydrug pattern. Also, individuals without a history of addiction, but with a first-degree relative who has a history of addiction, have been found to be at higher risk for addiction, creating a compelling argument for physicians to obtain routinely a substance use history before prescribing benzodiazepines.

Benzodiazepines can be misprescribed in terms of (1) appropriateness of specific drug to specific indications, (2) length of time, and (3) dosage. Furthermore, physicians' prescribing decisions might be based on nonclinical or inaccurate information—for example, shift a patient from diazepam to alprazolam in the mistaken belief that alprazolam would be the less addicting drug. Similarly, a physician might suddenly discontinue prescribing benzodiazepine for all patients to avoid a benzodiazepine-related lawsuit, thus precipitating patients into abrupt withdrawal syndromes.

**Benzodiazepine Dependence**

Whatever the circumstances, some patients have taken benzodiazepines for many months or years; some have taken benzodiazepines at doses that exceed therapeutic range; and some have experienced a full spectrum of addiction symptoms with therapeutic dosage of benzodiazepines. For all of these patients, benzodiazepine dependence problems are a likely sequelae.

Benzodiazepine dependence occurs when there is adaptation to these drugs at the cellular and tissue level, which would be followed by a withdrawal syndrome upon cessation of the drug. The biological alterations include receptor site changes in response to benzodiazepine use and withdrawal. For some patients the distress related to benzodiazepine dependence and withdrawal is so severe that it becomes debilitating and their symptoms can be confusing to the treating physician.

It is clinically useful to classify benzodiazepine dependence into separate, but overlapping, phenomena that relate both to benzodiazepine use patterns and eventual withdrawal syndromes.

First, high-dose benzodiazepine use longer than 1 month but less than 6 months can cause a classic acute, sedative-hypnotic-type withdrawal syndrome, similar in quality to an acute alcohol withdrawal.

Second, low-dose, therapeutic-range daily benzodiazepine use for more than 6 months can produce a prolonged, subacute low-dose benzodiazepine withdrawal syndrome. This syndrome is characterized by the symptoms of withdrawal anxiety and insomnia and possibly a prolonged period of bursts of anxiety and insomnia. In rare patients, primarily the elderly, low-dose withdrawal can have severe sequelae, including seizure and psychosis most commonly seen with high-dose withdrawal.

Third, daily, high-dose benzodiazepine use more than 6 months can produce not only the acute high-dose benzodiazepine withdrawal syndrome but also a prolonged, low-dose withdrawal syndrome.

Benzodiazepine dependence is often a sign of benzodiazepine abuse or addiction; however, dependency alone is not a sufficient criterion for diagnosing either abuse or addiction. Further abuse and addiction history must be obtained for such diagnoses.

Whereas the medical management of benzodiazepine dependence is an important step in the treatment of benzodiazepine addiction, it does not constitute treatment of the underlying addictive disease. Medical management of benzodiazepine dependence should be understood as the management of physical sequelae of a larger addiction process in which the primary care physician can play an important role.

When patients have taken benzodiazepines at higher doses and for longer periods of time than recommended, they should be assessed for abuse, dependence, or addiction not only to benzodiazepines but also to alcohol and other drugs. Physical dependence can occur within or outside a pattern of polydrug abuse, and a majority of patients have a personal or family history of alcoholism.

A patient with uncomplicated benzodiazepine dependence and tolerance usually can be detoxi-
fied on an outpatient basis by his or her primary care physician. In contrast, the patient who exhibits signs and symptoms of addiction (which may include benzodiazepine use) would benefit from a multidisciplinary team approach at a chemical dependency treatment program that offers medical, psychiatric, psychological, nursing, counseling, education, and self-help elements. Benzodiazepine abstinence can be enhanced greatly by a combination of inpatient treatment followed by close medical and psychosocial follow-up.16

In either situation, it is critical that the patient be detoxified from the benzodiazepine slowly. A tapered withdrawal should take place over a minimum of 1 month, and it could range from 4 to 12 weeks. In no instance should a physician abruptly discontinue patients' benzodiazepine use, nor should patients be allowed to quit "cold turkey" on their own, despite their possible arguments to the contrary.

**Benzodiazepine Withdrawal: Clinical Syndromes**
The primary care physician is likely to encounter the following three primary clinical syndromes that can occur upon cessation of benzodiazepine therapy: (1) acute sedative-hypnotic-type benzodiazepine withdrawal, (2) subacute prolonged benzodiazepine withdrawal, and (3) preexisting symptom reemergence.14

**Acute Sedative-Hypnotic-Type Benzodiazepine Withdrawal**
Dependence (and hence acute withdrawal) can develop to both high-dose17-19 and therapeutic-range benzodiazepine use.20-23 The benzodiazepine sedative-hypnotic-type withdrawal is the normal cluster of anxiety-related symptoms that occur following cessation of alcohol, benzodiazepines, and other sedative-hypnotics. Acute benzodiazepine withdrawal signs include anxiety, insomnia, tremors, agitation, nightmares, anorexia, and seizures; less frequently, nausea and vomiting, hallucinations, depersonalized feelings, delirium, and hypersensitivity to visual and auditory stimuli can occur. With abrupt cessation of high doses, patients can experience a psychotic episode or grand mal seizures and death.24 Figure 1 shows the sedative-hypnotic-type withdrawal syndrome, with peak liability for symptoms, including seizures, at about 5 to 7 days. Onset of symptoms occurs in 1 to 2 days for short-acting benzodiazepines and in 2 to 4 days for the long-acting benzodiazepines.25 Treatment of this phenomenon is described later in detail. In general, acute benzodiazepine withdrawal symptoms are expected to be severe if daily benzodiazepine use was high and especially if benzodiazepine use was prolonged.26

**Subacute, Prolonged Benzodiazepine Withdrawal**
In response to high-dose and even therapeutic-range benzodiazepine therapy, some patients will experience severe distress for extended periods following the acute benzodiazepine withdrawal period.27 It has been estimated that perhaps one-quarter of long-term, low-dose benzodiazepine users have problems with benzodiazepine withdrawal despite gradual reduction, and perhaps one-third of these patients experience severe and prolonged distress.1 This distress is distinct from both acute withdrawal and symptom reemergence. Figure 1 also shows the variation in intensity of low-dose withdrawal symptoms following detoxification, when the patient experiences fluctuations in anxiety symptoms every few days. These symptoms, chiefly anxiety and insomnia, as well as possible tachycardia, increased blood pressure, muscle spasms, paresthesias, and, rarely, psychosis, can occur in bursts lasting several days between periods of anxiety relief. The onset of
Anxiety Reemergence

Both the sedative-hypnotic-type withdrawal syndrome and the low-dose withdrawal syndrome need to be distinguished from reemergence of the original, underlying psychopathologic state. In many situations — such as with a new patient — the primary care physician would not be aware of the original pathologic disorder.

For the person with anxiety disorder reemergence, the symptom course will differ from the fluctuating, prolonged, subacute benzodiazepine withdrawal syndrome by remaining at a relatively stable and often clinically important level of severity. Figure 1 illustrates symptom reemergence following detoxification from benzodiazepines. These symptoms increase in severity until they establish a baseline of severity. In other words, following the acute withdrawal period, the patient does not drop to a baseline of low symptom severity or have fluctuating bursts of symptoms: the symptoms become constant and follow the normal course of the psychiatric disorder in question. In a previous article of this journal, we provided a decision tree for discriminating among depressant withdrawal-related anxiety symptoms, stimulant-induced anxiety symptoms, and anxiety disorders.

A tentative diagnosis of a psychiatric disorder can be made only after the patient has been free of all drugs for 30 days. A period of 60 to 90 drug-free days should pass before the physician can make an accurate and formal diagnosis of the psychiatric problem. After such a baseline, the physician can be confident of an accurate diagnosis and can treat using stepwise anxiety treatment. Stepwise anxiety treatment emphasizes the use of nonpharmacological tools, such as psychotherapy and stress reduction, as well as nonpsychoactive anxiolytics, such as buspirone, for the treatment of anxiety in patients who have experienced substance use disorders.

Table 1 provides a comparison of clinical syndromes related to benzodiazepine withdrawal as described above. Patients who are dependent upon therapeutic-range doses of benzodiazepines can become alarmed at the emergence of normal anxiety, variations in sleep patterns, and musculoskeletal discomfort. Such patients might attribute these normal stresses and strains as symptoms of benzodiazepine withdrawal and seek medical help. The primary care physician should be on guard for such symptom misinterpretation.

Acute Benzodiazepine Withdrawal: Medical Management

The most basic tenet that applies to the medical detoxification from benzodiazepines is that it—
Table 1. Comparison of Syndromes Related to Benzodiazepine Withdrawal.*

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Symptoms</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute sedative-hypnotic-type</td>
<td>Anxiety, insomnia, nightmares, seizures, psychosis, hyperpyrexia, death</td>
<td>Onset 1–2 days after stopping short-acting benzodiazepines; onset 2–4 days after stopping long-acting benzodiazepines</td>
</tr>
<tr>
<td>withdrawal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subacute, prolonged benzodiazepine</td>
<td>Anxiety (including somatic manifestations), insomnia, nightmares, muscle spasm, psychosis</td>
<td>Symptoms begin 1 day after stopping of benzodiazepines; can continue for weeks to months, but will improve with time</td>
</tr>
<tr>
<td>withdrawal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom reemergence</td>
<td>Variable but should be the same as symptoms prior to taking benzodiazepines</td>
<td>Symptoms emerge when benzodiazepine is stopped and will continue unabated</td>
</tr>
</tbody>
</table>


should be slow and gradual. Under no circumstances should a patient be abruptly terminated from a benzodiazepine. For patients who have developed tolerance to and dependence on benzodiazepines, there are three primary options for the gradual detoxification process: (1) graded reduction of the current benzodiazepine, (2) substitution of a long-acting benzodiazepine for the original benzodiazepine, and (3) substitution of phenobarbital for the benzodiazepine (or benzodiazepine-polydrug combination).

The selection of detoxification strategy depends upon (1) the detoxification setting, (2) the severity of the tolerance and dependence, (3) physician expertise specific to benzodiazepine dependence, and (4) the total drug combinations used by the patient.

Graded Reduction of Current Benzodiazepine
Gradually reducing the benzodiazepine dosage is primarily useful when the dependence has developed in patients who (1) take only benzodiazepines, (2) become dependent when taking doses within a therapeutic range, and (3) are being treated in primary care medical settings. The process involves a planned fixed-dosage reduction of the benzodiazepines in a flexible time frame. We recommend a dosage reduction of 10 to 15 percent each week, maintaining a divided dosage schedule. DuPont recommends a 6- to 12-week tapering period for outpatient detoxification. Faster reductions are possible but require regular physician contact and support.

Substitution of a Long-Acting Benzodiazepine
The substitution of a long- or longer-acting benzodiazepine allows for a more gradual reduction of the serum levels, thereby greatly reducing withdrawal symptoms and symptom reemergence.

A preferred long-acting benzodiazepine is chlordiazepoxide, which is an effective substitute for such short-acting agents as alprazolam or for alcohol-benzodiazepine combinations. Chlordiazepoxide has a relatively low street value when compared with other benzodiazepines, such as diazepam, and it has a more rapid onset of action than diazepam. Chlordiazepoxide and diazepam are two popular benzodiazepines used for substitution and withdrawal, and Table 2 can be used to calculate equivalency. Clonazepam has also been suggested for use in alprazolam withdrawal and may provide better protection against withdrawal seizures.

The key to success for substitution or graded withdrawal in an outpatient setting is time. For a patient who has been on a short-acting benzodiazepine for 1 to 2 months, a tapered withdrawal can take 2 to 3 weeks. If a patient has been taking benzodiazepine for months or years, a gradual reduction lasting 2 to 4 months or more will be necessary. If breakthrough anxiety or frank withdrawal symptoms occur, the physician should increase the dose until the symptoms resolve and begin an even more gradual reduction. Close, consistent follow-up and support are needed.

As the reduction proceeds, underlying suppressed or masked psychiatric symptoms may become more readily apparent. At this time, adding

Table 2. Benzodiazepine Equivalency.

<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>Dosage (mg)</th>
</tr>
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<tbody>
<tr>
<td>Chlordiazepoxide</td>
<td>25</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>2</td>
</tr>
<tr>
<td>Diazepam</td>
<td>5</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>30</td>
</tr>
<tr>
<td>Flurazepam</td>
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<tr>
<td>Lorazepam</td>
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<td>Triazolam</td>
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<tr>
<td>Chlorazepate</td>
<td>3.75</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>0.25</td>
</tr>
</tbody>
</table>
nonpsychoactive medications to the regimen is most useful.

**Phenobarbital Substitution Technique**

Smith and Wesson developed the phenobarbital substitution technique for benzodiazepine withdrawal because this technique (1) has the broadest utility for all benzodiazepines, (2) is useful for benzodiazepine-polydrug combinations, (3) is useful for polybenzodiazepine combination dependence, (4) is useful for high-dose benzodiazepine dependence, and (5) can be used for all sedative-hypnotics. Phenobarbital is cross-tolerant to all the benzodiazepines and all other sedative-hypnotics. It is long acting and effectively prevents serious sequelae of benzodiazepine withdrawal, such as withdrawal seizures and withdrawal psychosis.

Table 3 outlines the phenobarbital withdrawal conversion for benzodiazepines and other sedative-hypnotics. The phenobarbital substitution method uses propranolol for acute and subacute somatic complaints and symptoms. Note that phenobarbital is used during acute benzodiazepine withdrawal and detoxification. Propranolol (20 mg every 6 hours) is used starting at the peak times of symptom intensity through the following 2 weeks. Propranolol can be also used during periods of acute distress, such as those caused by tachycardia, increased blood pressure, and anxiety related to low-dose or prolonged withdrawal symptoms of anxiety and insomnia. Again, propranolol therapy used beyond 2 weeks is not recommended. Carbamazepine is also being used experimentally to attenuate prolonged withdrawal symptoms, although its utility for panic disorder patients withdrawing from benzodiazepines may be poor, because it lacks antipanic efficacy. Long-acting sedative-hypnotics and long half-life benzodiazepines should be used cautiously for patients with severe liver disease because of the possibility of uneven doses and escalating side effects. Consideration should be given to short half-life benzodiazepines. Similarly, propranolol is generally contraindicated for patients with history of allergy, bronchial asthma, or emphysema, as it can promote bronchospasm and block the bronchodilating effect of epinephrine.

**The Primary Care Physician and Addiction Medicine**

A fundamental principle of addiction medicine is that the management of medical and psychiatric conditions that result from a substance use disorder, such as addiction, cannot be considered to be overall treatment for that substance use disorder. Furthermore, a patient who has a substance use problem involving benzodiazepines could have preexisting anxiety disorder that needs to be treated as an additional, primary disorder.

The primary care physician should recognize that the medical management of drug-related intoxication, overdose, or withdrawal is merely the beginning of the overall treatment of any substance use disorder. Substance use disorders represent an interplay among pharmacological, environmental, and host susceptibility factors. Consequently, multidisciplinary approaches include, but are not limited to, medical management issues. All patients with a substance use disorder need a detailed history and a thorough physical examination and evaluation. Some of these patients will need serious medical intervention, while others will need primarily non-
medical support and psychosocial treatment and education.

Ideally, a chemical dependency treatment program or clinic is the best place to meet the specific needs of a patient who has a complicated addiction problem. This setting allows a multidisciplinary team of allied health care professionals to address directly substance use issues in depth through multiple interviews and assessments, specifically tailored educational tools, and a group process.

The American Medical Association has described three levels of responsibility for physicians regarding patients with substance use problems. The lowest level covers the basic responsibility for all physicians engaged in clinical activities. A middle level covers responsibilities for physicians who accept some addiction treatment chores, while the highest level covers responsibilities for physicians who engage in long-term addiction treatment. The basic concepts in these guidelines are also appropriate for psychiatric problems.

**Level I: All Physicians with Clinical Responsibility**

Not all physicians choose to provide primary treatment of substance use disorders. All physicians who treat patients, however, are responsible for making a good-faith diagnosis and at least referral of patients with substance use problems. Whatever the type of medical practice, all physicians should be able to recognize substance use disorders during the early stages of the disease, not only late-stage medical and psychiatric complications.

During patient examinations, all physicians should include a substance use history. If a substance use problem is identified, the physician should attempt to match available treatment options in the community with the patient's treatment needs and personal resources. The physician should become familiar with local medical resources for chemical dependency treatment in preparation for appropriate referrals.

**Level II: Physicians Accepting Limited Addiction Treatment Responsibility**

Some physicians accept the responsibility of providing medical care that will allow the patient to participate in a long-term treatment program. These physicians accept the responsibility of helping the patient attain a drug-free state.

At this level of responsibility, the physician should provide treatment of general medical problems, as well as treatment of substance-use sequelae, including acute withdrawal management. The physician should also assume the role of patient educator, giving patients information about their substance use diagnosis, as well as an honest appraisal of the patients' responsibilities for continued treatment and recovery. The physician should assist the patient in evaluating the available resources for treatment, at least to the point of creating a preliminary treatment and recovery plan, including the involvement of appropriate family and friends.

Although the patient will receive more intensive treatment at a chemical dependency treatment program, the physician can provide pre- and post-treatment medical management consistent with the treatment provided at that program.

**Level III: Physicians Accepting Responsibility for Long-Term Treatment of Addiction**

A physician who accepts this highest level of responsibility must acquire a higher level of expertise and training in addiction medicine. Through direct medical care or through clinical supervision, this physician is responsible for establishing supportive, therapeutic, and nonjudgmental relationships with drug-addicted and -abusing patients. Within that context, the physician is responsible for the medical management of general medical problems, acute withdrawal syndromes, and other substance-use-related sequelae, including relapse.

A physician practicing at this higher level of responsibility must keep abreast of ongoing developments in the pharmacological management of substance use problems. Except for acute withdrawal management, the physician will prescribe psychoactive medication only in the event of an obvious and severe psychiatric condition that threatens to jeopardize the patient's well-being.

This physician will actively participate in the patient's treatment and recovery plan, which includes, with the patient's participation, ongoing evaluation and updating. The physician should also involve the patient with an abstinent peer group and enlist the assistance of appropriate family and supportive friends as treatment participants.
Primary care physicians should evaluate all anxiety disorder patients for substance use problems and all substance-using patients for anxiety disorder. They can use their medical expertise to provide basic information about substance use problems and explain the types and continuum of treatment, as well as patient responsibilities for treatment and recovery. Physicians should motivate patients to accept appropriate treatment and referrals and make arrangements for specific appointments rather than merely make referral suggestions.

Primary care physicians should seek the assistance of addiction medicine and psychiatric consultants, especially in more difficult cases. Primary care physicians can train office nursing staff to become knowledgeable about substance use problems. The physician and nursing office staff can create an alliance with local resources (e.g., treatment programs, addiction counselors) and such self-help support services as Alcoholics Anonymous, Narcotics Anonymous, Cocaine Anonymous, and Al-Anon for family members of the patient with a substance use problem.

References


