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Addiction: Part I. Benzodiazepines--Side Effects, Abuse Risk and Alternatives

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Benzodiazepines are widely prescribed for a variety of conditions, particularly anxiety and insomnia. They are relatively safe and, with overdose, rarely result in death. However, used chronically, benzodiazepines can be addicting. These agents are often taken in combination with other drugs of abuse by patients with addiction disorders. In such patients, alternatives to benzodiazepines may be preferable and may include antidepressants, anticonvulsants, buspirone, antihypertensive agents and the newer neuroleptic medications. Caution must be used when prescribing benzodiazepines to patients with a current or remote history of substance abuse. (Am Fam Physician 2000; 61:2121-8.)

There is little doubt of the therapeutic efficacy of benzodiazepines in reducing anxiety, inducing sleep and quelling panic symptoms. As noted in a 1990 report by the American Psychiatric Association (APA) on benzodiazepine dependence, toxicity and abuse,[1] the anxiolytic and hypnotic efficacy of benzodiazepines has been well established by numerous placebo-controlled studies.

Benzodiazepines are widely prescribed, with four of them--alprazolam (Xanax), clonazepam (Klonopin), diazepam (Valium) and lorazepam (Ativan)--listed among the top 100 most commonly prescribed medications.[2] Benzodiazepines generally produce almost immediate effects, and thus may be prescribed for short-term, intermittent, "as-needed" use. Because many of the anxiety disorders wax and wane over time, patients with these disorders often prefer benzodiazepines because these agents can be taken intermittently,

when patients feel the need to take them, and most patients can use benzodiazepines judiciously.[1]

Benzodiazepines are also widely prescribed for other reasons, such as muscle spasticity, convulsive disorders, presurgical sedation, involuntary movement disorders, detoxification from alcohol and other substances, and anxiety associated with cardiovascular or gastrointestinal conditions[3] *(Table 1).*

According to the APA report on benzodiazepines,[1] 11 to 15 percent of the adult population has taken a benzodiazepine one or more times during the preceding year, but only 1 to 2 percent have taken benzodiazepines daily for 12 months or longer. In psychiatric treatment settings and in substance-abuse populations, however, the prevalence of benzodiazepine use, abuse and dependence is substantially higher than that in the general population.[4,5]

Because benzodiazepines are controlled substances with abuse potential, special attention must be directed toward the patient's addiction history before these agents are prescribed. An understanding of the toxicity and side effects of benzodiazepines, abuse patterns and alternative anxiolytic and hypnotic agents may help clinicians maximize treatment outcomes and reduce medicolegal liability risks.

TABLE 1
Clinical Uses of Benzodiazepines

- 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

Information from Hollister L, Muller-Oerlinghausen B, Rickels K, Shader R. Clinical uses of benzodiazepines. J Clin Psychopharmacol 1993;13(suppl 1):1-169.

Neurochemistry

Benzodiazepine receptors are ubiquitous throughout the central nervous system. Benzodiazepine receptors are linked predominantly to g amino butyric acid (GABA) receptors, which sensitize benzodiazepine receptors to the neurotransmitter GABA, the most prominent inhibitory neurotransmitter in the central nervous system. Benzodiazepines enhance the affinity of the recognition site for GABA by inducing conformational changes that make GABA binding more efficacious. Activation of the benzodiazepine-GABA-chloride ionophor complex is responsible for producing the therapeutic anxiolytic effects of benzodiazepines and for mediating many of the side effects and, possibly, dependence and withdrawal from these drugs.[6]

Similarly, other sites for drug and neurotransmitter binding are associated with the GABA receptor complex, which serves as a primary site of action of benzodiazepines, barbiturates and other sedative-hypnotics, such as alcohol.[6] Benzodiazepines and barbiturates act at separate binding sites on the receptor to potentiate the inhibitory action of GABA. They do so by allosterically altering the receptor (changing its conformation) so that it has a greater binding affinity for GABA. Ethanol modifies the receptor by altering the membrane environment so that it has increased affinity for GABA and the other sedative-hypnotic drugs. That benzodiazepines, barbiturates and ethanol all have related actions on a common receptor type, which explains their pharmacologic synergy and cross tolerance. Thus, benzodiazepines are used during alcohol detoxification.

With long-term high-dose use of benzodiazepines (or ethanol), there is an apparent decrease in the efficacy of GABA-A receptors, presumably a mechanism of tolerance.[6,7] When high-dose benzodiazepines or ethanol are abruptly discontinued, this "down-regulated" state of inhibitory transmission is unmasked, leading to characteristic withdrawal symptoms such as anxiety, insomnia, autonomic hyperactivity and, possibly, seizures.

Toxicity and Side Effects

With the introduction of chlordiazepoxide (Librium) in 1960, and because of the relative safety of benzodiazepines, these agents rapidly replaced barbiturates as sedative-hypnotics. They cause significantly less respiratory depression than barbiturates and, consequently, are rarely lethal in an overdose.

Fatal overdose with benzodiazepines is rare. When it does occur, the combination of benzodiazepines and alcohol, with or without opiates, is often the cause of death.

As a class of drugs, benzodiazepines share many clinical properties, although the different agents in this class may display different pharmacokinetic and pharmacodynamic properties *(Table 2).* Pharmacologic properties

such as potency, half-life and lipophilicity, the duration of treatment and the rate of a dosage increase or decrease have a bearing on the occurrence of side effects.[1] The development of physiologic dependence is somewhat predictable and is proportional to the total benzodiazepine exposure (dose 3 duration of treatment), although significant variability may exist among patients.

Toxicity and Drug Interactions

When used alone, benzodiazepines carry an extremely low risk of acute toxicity. However, benzodiazepines often are used with other types of medications, including other drugs with abuse potential, and these drugs can enhance the toxic effects of benzodiazepines. The latter interact synergistically with other central nervous system depressants, including other hypnotics, sedating antidepressants, neuroleptics, anticonvulsants, antihistamines and alcohol.[8] Fatal overdoses in addicted patients often involve the combination of benzodiazepines and alcohol, with or without opiates. In addition, pharmacokinetic drug interactions may occur. For instance, selective serotonin reuptake inhibitors (SSRIs) may increase diazepam blood levels,[9] and nefazadone (Serzone) may increase alprazolam levels[10] through hepatic enzyme inhibition, leading to increased sedative-hypnotic effects or side effects.

TABLE 2
Potency and Half-Life of Various Benzodiazepines

High-potency benzodiazepines

Drugs with a short half-life
- Alprazolam (Xanax)
- Lorazepam (Ativan)
- Triazolam (Halcion)

Drugs with a long half-life
- Clonazepam (Klonopin)

Low-potency benzodiazepines

Drugs with a short half-life
- Oxazepam (Serax)
- Temazepam (Restoril)

Drugs with a long half-life
- Chlordiazepoxide (Librium)
- Clorazepate (Tranxene)
- Diazepam (Valium)
- Flurazepam (Dalmane)

Psychomotor Retardation

Psychomotor slowing may be especially profound following initial administration of a benzodiazepine or with a sudden dosage increase. It also may be noted in patients, such as the elderly, who have decreased rates of metabolism or greater susceptibility to central nervous system depression.[8] Psychomotor symptoms include drowsiness, poor concentration, ataxia, dysarthria, motor incoordination, diplopia, muscle weakness, vertigo and mental confusion.[11] Studies of the psychomotor effects suggest that benzodiazepines slow reaction time and impair driving skills, increasing the risk of motor vehicle crashes in patients who are taking these agents.[12]

Memory Impairment

Benzodiazepines induce anterograde amnesia, which accounts for the beneficial effects of benzodiazepines such as midazolam (Versed) for presurgical medication. These specific amnestic effects appear to be separate from sedation.[11] Episodic memory (the remembering of recent events and the circumstances in which they occurred and their time sequences) is particularly impaired and more markedly so in heavy alcohol drinkers who also use benzodiazepines. Specific deficits in visuospatial ability and sustained attention have also been described in patients who have taken therapeutic doses of benzodiazepines regularly for longer than one year.[13]

Paradoxical Disinhibition
Increased excitement, irritability, aggression, hostility and impulsivity may occur in some patients who take benzodiazepines. This paradoxical disinhibition may, in rare cases, result in attacks of rage or violence, or other indiscretionary or antisocial behaviors.[14] Such reactions may be due to disinhibition of behavioral tendencies normally suppressed by social restraints (as can also be the case with alcohol). These reactions occur most commonly in children, in the elderly and in persons with developmental disabilities.

Depression and Emotional Blunting
An association has been noted between benzodiazepine use and depressive symptoms and, in some cases, the emergence of suicidal ideation. Some evidence indicates that higher benzodiazepine dosages are associated with an increased risk of depression and that reducing the dosage or discontinuing therapy may resolve the depressive symptoms.[15] Although the mechanism of this action is unclear, benzodiazepine-related depression might occur as a physiologic result of a reduction in central monoamine activity.

"Emotional anesthesia" may also be seen in clinical practice. This effect may be sought by drug addicts who become progressively more incapable of tolerating their emotions and life stressors.

Adverse Effects in Pregnancy
Benzodiazepines cross the placenta and are classified as class D teratogens. They may lead to the development of dependence and consequent withdrawal symptoms in the fetus.[16] Benzodiazepines are excreted in breast milk and thus are usually contraindicated in breast-feeding mothers.

Tolerance
Tolerance to all of the actions of benzodiazepines can develop, although at variable rates and to different degrees. Tolerance to the hypnotic effects tends to develop rapidly, which may be beneficial in daytime anxiolysis but makes long-term management of insomnia difficult.[17] Patients typically notice relief of insomnia initially, followed by a gradual loss of efficacy.[18] 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 benzodiazepines retain their efficacy after four to six months of regular use.[19,20] Benzodiazepine 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.

Dependence
Benzodiazepine therapy can give rise to physiologic and psychologic dependence based on the drug's dosage, duration of therapy and potency.[1] Thus, dependence will develop sooner (such as in 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. As a result of physiologic dependence, withdrawal symptoms emerge with rapid dose reduction or abrupt discontinuation of the drug.

Short-acting, high-potency agents, such as alprazolam, cause dependence sooner than longer-acting agents such as chlordiazepoxide and diazepam.

Psychologically, long-term use of benzodiazepines may lead to overreliance on the need for

the agent, loss of self-confidence and varying degrees of drug-seeking behavior.[8] Patients may be reluctant to discontinue the drug because of misplaced fears or anticipatory anxiety. Some patients combine alcohol with benzodiazepines when they are not able to acquire the desired or "needed" effects.

Short-Term Withdrawal Symptoms
Withdrawal effects from therapeutic dosages of benzodiazepines are mainly anxiety symptoms.[1,21] 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 the emergence of acute withdrawal symptoms corresponds to the half-life of the particular agent being used.

Some elements of withdrawal are believed to occur in a majority of patients who have taken therapeutic dosages of benzodiazepines 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.[1,18]

Protracted Withdrawal
A protracted abstinence syndrome has been observed by addictionologists who are familiar with benzodiazepine addiction.[22] 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, judicious tapering of the dosage and is hypothesized to result from chronic neuroadaptation.

Effects in Elderly Patients

Among the elderly, the risk of drug interactions, psychomotor slowing, cognitive dysfunction and paradoxical disinhibition may be amplified. Benzodiazepine use in the elderly is associated with an increased rate of falls that cause hip and femur fractures and an increased likelihood of motor vehicle crashes.[23,24] Cognitive impairment is common, although memory impairment may be reversible when benzodiazepines are discontinued.[25]

Cognitive deterioration associated with normal aging processes and dementia can be worsened by benzodiazepine side effects. Cortical suppression mechanisms may be disturbed in the elderly, and disinhibited behaviors may increase with benzodiazepine use. With less cognitive and social reserve in the elderly patient, the short- and long-term withdrawal symptoms and other benzodiazepine side effects may lead the patient to frequently visit or telephone the physician. The physician may feel "trapped" into arguing against the use of benzodiazepines and prescribing benzodiazepines to elderly patients. In one study,[26] this impasse was broken by referring elderly patients to inpatient detoxification, which resulted in a dramatic decrease in annual physician visits.

Benzodiazepine Abuse

Benzodiazepines are rarely the preferred or sole drug of abuse. An estimated 80 percent of benzodiazepine abuse is part of polydrug abuse, most commonly with opioids.[27] A two-year treatment outcome study by the National Institute on Drug Abuse[28] found that 15 percent of

heroin users also used benzodiazepines daily for more than one year, and 73 percent used benzodiazepines more often than weekly. Studies indicate that from 5 percent to as many as 90 percent of methadone users are also regular users of benzodiazepines. High-dose benzodiazepine abuse is especially prevalent in patients who are taking methadone.[29]

Studies indicate that 3 to 41 percent of alcoholic persons report that they abused benzodiazepines at some time, often to modulate intoxication or withdrawal effects.[4] The contemporary alcoholic is usually a multiple-drug user. As many as 80 percent of alcoholics under the age of 30 have been addicted to or use at least one other drug.[27]

Medical prescriptions constitute the primary source of supply for people who abuse benzodiazepines. Prescriptions may also have a street value, which encourages rerouting to illicit sources. Benzodiazepines have multiple uses for polydrug addicts: they are used to enhance the 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.

As potential drugs of abuse, short-acting benzodiazepines seem to be preferred among addicts because of the rapidity of their onset of action.[30] 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).[31] Data suggest that highly lipophilic benzodiazepines (for example, 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 benzodiazepines and, therefore, the ones most likely to be associated with abuse.[30]

Clonazepam is a high-potency benzodiazepine 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 also frequently abused as a street drug. On the other hand, oxazepam (Serax), clorazepate (Tranxene) and chlordiazepoxide appear to have lower reinforcing effects than other benzodiazepines.

Compared with generic formulations, trade-name prescription drugs can be worth twice as much per tablet when they are sold on the street because they are readily recognizable as the "real thing" when compared with the photographs of tablets in the *Physicians' Desk Reference.*[31] Generic pills are often unrecognizable and hence are worth less when diverted for street sale. In many U.S. cities, the street value of Xanax or Klonopin may be $5 to $10 per pill, depending on dosage strength.

Benzodiazepine Alternatives

The problems with benzodiazepine dependence, tolerance, withdrawal, rebound and abuse limit their use for long-term treatment of anxiety disorders in patients with alcohol or drug addiction. A growing body of literature now supports the anxiolytic efficacy of numerous other agents *(Table 3).* Antidepressants, anticonvulsants, buspirone (Buspar), certain antihypertensive agents and newer neuroleptics all have been shown to be effective in subsets of patients with anxiety.[32]

Most addiction medicine specialists believe that benzodiazepines are relatively

contraindicated in patients with current alcohol or drug abuse problems and in patients who are in recovery. To choose an appropriate alternative to a benzodiazepine, physicians should be able to delineate which subtype of anxiety disorder exists in a particular patient. Patients should be encouraged to understand that the onset of action of antidepressants, buspirone and anticonvulsants is not as immediate as that of benzodiazepines. Therapy may require patience and, because of side effects, a low dosage may be required initially.

TABLE 2
Efficacy of Pharmacologic Agents in the Treatment of Anxiety Disorders

Disorder	BZs	SSRIs	TCAs	ACVs*	Bu	ANs†	AHTs‡
Acute anxiety	++					+	+
Generalized anxiety disorder	++	+	++	±	++		
Panic disorder	++	++	++	+			
Social phobia	+	++	+		+		
Post-traumatic stress disorder	±	+	+	+	+	+	
Obsessive-compulsive disorder		++	+		+	±	

BZs = benzodiazepines; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants; ACVs = anticonvulsants; Bu = Buspirone (Buspar); ANs = atypical neuroleptics; 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).
†--Atypical neuroleptics include risperidone (Risperdal), olanzapine (Zyprexa) and quetiapine (Seroquel).
‡--Antihypertensives include beta blockers and clonidine (Catapres).

Insomnia
Insomnia is a common sequela of numerous medical and psychiatric conditions, and is often associated with substance-use disorders, early abstinence or protracted withdrawal. Management of insomnia includes 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 or utilizing other relaxation techniques.

Nonbenzodiazepine pharmacotherapies for the management of insomnia include the sedating antidepressant trazodone (Desyrel), tertiary tricyclic antidepressants such as amitriptyline (Elavil) and doxepin (Sinequan), and newer antidepressant agents such as nefazodone and mirtazapine (Remeron).[33]

Zolpidem (Ambien), an imidazopyridine, is a hypnotic agent with a chemical structure unrelated to benzodiazepines.[34] Unlike the benzodiazepines, 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 benzodiazepines. However, zolpidem is classified as a schedule IV controlled substance (like benzodiazepines), and synergistic effects with benzodiazepines and alcohol have been observed. Problems with vivid dreams, nightmares and rebound insomnia have also been reported.[34]

Final Comment

Although benzodiazepines are effective in a wide range of medical and psychiatric conditions, caution must be exercised with their use, particularly when these agents are prescribed to patients with an active or remote history of substance abuse or addiction. Their greatest asset is also their greatest liability: drugs that work immediately tend to be addictive. Compared with benzodiazepines, antidepressants have a longer onset of action but are the best agents for long-term treatment of anxiety disorders. Anticonvulsants, antipsychotics, antihypertensives and buspirone also are effective but have an intermediate onset of action.

Clinical judgment is based on an assessment of the risks versus the benefits of therapy. Such an approach might take into account whether substance abuse is active or remote, whether other family members or other health care professionals are actively involved in the patient's care, and how well the physician knows the patient. Physicians should also freely seek consultation from specialists such as psychiatrists and addiction medicine specialists. Education, consultation and documentation not only improve the level of clinical care but also provide necessary risk management and medicolegal liability protection.

This is Part I of a two-part article on addiction. Part II, "Identification and Management of the Drug-Seeking Patient," will appear in the next issue.

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