Drugs

BENZODIAZEPINE DEPENDENCE AND WITHDRAWAL

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INTRODUCTION

The benzodiazepines have had tremendous marketing success worldwide in the last 25 years because of their efficacy in treating various disorders. After the introduction of Librium in the early 1960's and Valium soon thereafter, this class of drugs rapidly became the most widely prescribed drugs in the United States accounting for a consumption of approximately 8000 tons in 1977. In fact, diazepam was the most widely prescribed drug in the U. S. for many years during the 1970's. During this time, most of the drugs (greater than 90%) were being prescribed by primary care and general practicing physicians for patients with anxiety, depressed mood, insomnia, muscle spasm and seizures.

However, during the late 1960's and 1970's, the medical literature and public press publicized the concern that benzodiazepines were being used and abused by a great number of people and overprescribed by the medical profession. This concern was due in part to reports of dependence and withdrawal phenomena when the drugs were stopped. Because of this publicity, there has been a significant decrease (30-40%) in the overall use of this class of drugs.

The decrease in the use of the benzodiazepines due to perceived publicized dangers has created considerable controversy in the medical literature. Many authors now feel that benzodiazepines are underutilized in a large group of people who could benefit from them (1,2) considering approximately 8% of the general U. S. population suffers from some sort of anxiety disorder (3,4). They point out that significant abuse and addiction to the benzodiazepines is rare considering the large number of persons using the drugs (5). This view has been supported by several surveys of the lay public such as that by Clinthorne, et al (6), who found that attitudes regarding the medical use of benzodiazepines were generally conservative, i.e., generally intermittent and for short periods except when severe stress was present. Their study concluded that the American public in general had reservations regarding the safety of benzodiazepines and that casual use was not common. A repeat survey in 1979 found the public to be even more conservative in that 1) beliefs about the negative consequences of benzodiazepines became more widespread, 2) changes in attitude occurred in men as well as women and among recent users as well as nonusers, and 3) people were less likely to condone the use of the benzodiazepines for mild to moderate anxiety. In this repeat survey, no change was found in people's beliefs regarding the efficacy of the drugs, their effect on problem solving or the

willingness to condone their use in those with severe impairment due to anxiety. Other surveys (4) have found that 1.6% of the population have taken anxiolytic medication daily for more than one year.

Still benzodiazepines are used significantly, medically or otherwise, by the population. In a California survey of men (aged 15-34 years) fatally injured in automobile accidents, significant levels of diazepam were detected in 1 out of 20, usually in combination with alcohol (7). Undoubtedly, this study represents a gross underestimation of this drug's use among drivers since it excluded those most likely to use benzodiazepines, i.e., older, females (8). More evidence that benzodiazepines are being used significantly by the population can be found in the data of the Drug Abuse Warning Network. In the 1982 survey by this agency (9), diazepam was the second most common drug mentioned in emergency department admissions for drug abuse across the United States, with the benzodiazepines as a group being mentioned in 24% of drug related admissions.

This review will attempt to put in perspective the abuse and withdrawal hazards of this class of drugs which has been so effective in treating the disorders for which indications exist.

DEFINITIONS

Before considering this topic, it is necessary to define several terms that are commonly used when referring to drugs with abuse or addicting potential (10).

Abuse. Self administration of any drug in a culturally disapproved manner that causes adverse consequences.

Addiction. A behavioral pattern of drug abuse, characterized by overwhelming involvement with the use of a drug (compulsive use), the securing of its supply, and a high tendency to relapse after discontinuation.

Dependence. The physiologic state of neuroadaptation produced by repeated administration of a drug, necessitating continued administration to prevent the appearance of the withdrawal or abstinence syndrome. Dependence may be psychological or physical.

Reinforcement. The tendency of a pleasure producing drug to lead to repeated self administration.

Tolerance. Tolerance has developed when, after repeated administration, a given dose of a drug produces a decreased effect or, conversely, when increasingly larger doses must be

administered to obtain the effects observed with the original dose.

Cross-tolerance and cross-dependence. The ability of one drug to suppress the manifestations of physical dependence produced by another drug and to maintain the physically dependent state.

Withdrawal. The psychological and physical reactions to abrupt cessation of a dependence producing drug.

Relapse. The reoccurrence, upon discontinuation of an effective medical treatment, of the original condition from which the patient suffered.

Rebound. The exaggerated expression of the original condition sometimes experienced by patients immediately after cessation of an effective treatment.

MECHANISM OF ACTION OF THE BENZODIAZEPINES

In recent years, it has become apparent that the action of the benzodiazepines is through stereospecific, saturable, high affinity receptors that enhance the postsynaptic inhibitory effects of the neurotransmitter gamma-aminobutyric acid (GABA) in the cerebral cortex, hypothalamus, cerebellum, midbrain and hippocampus. Binding affinity for the receptor correlates closely with potency as an anticonvulsant and anxiolytic suggesting the existence of an endogenous ligand that normally interacts with the receptor (11,12). The receptors most likely responsible for the anxiolytic effects of the benzodiazepines are in the limbic system and the neocortex. Those responsible for the muscle relaxing effects are probably in the brainstem and spinal cord.

GABA is widely present as a neurotransmitter, mostly associated with local inhibitory neurons. In fact, it is the primary inhibitory neurotransmitter in the brain. It is thought to act by inducing hyperpolarization of the neural cell through alterations in chloride flux. A model for the GABA/benzodiazepine/chloride channel complex is illustrated in figure A.

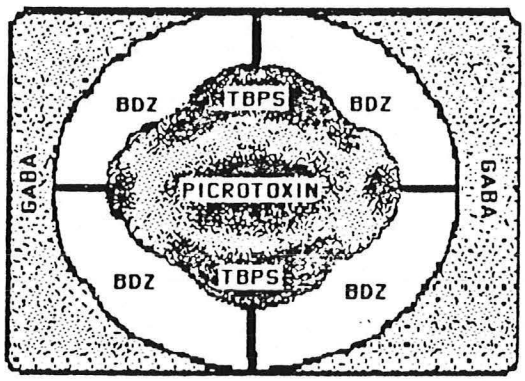
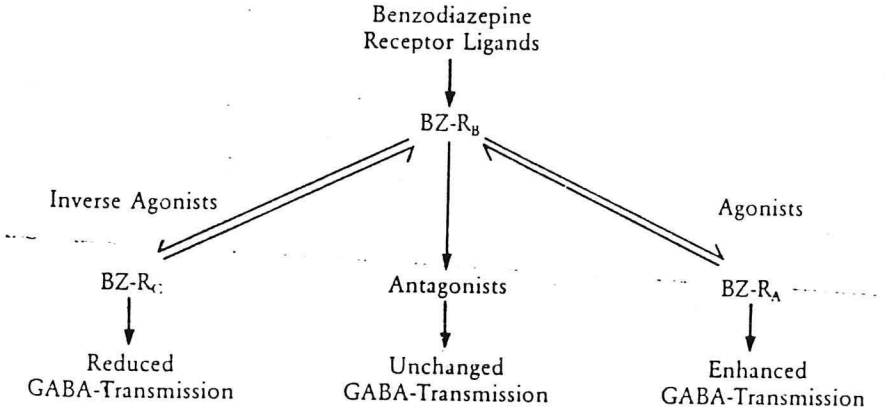


Figure A (13)

The benzodiazepine receptor is located at a site adjacent to the GABA receptor and acts as a modulator. GABA seems to affect postsynaptic inhibition by activating chloride channels resulting in a flux of chloride to occur across neuronal membranes according to the concentration gradient (11). Without GABA, benzodiazepines do not affect the chloride channel. Consequently, its role is that of a modulator.

It is felt now that at least two benzodiazepine receptor sites exist in the central nervous system (14). In addition, data indicate that binding sites can exist in at least three configurations as illustrated in figure B (below).

Without benzodiazepine receptor ligands, the binding site takes the BZ-Rb form that interacts with the GABA receptor associated chloride channel leading to an unmodified GABA induced chloride permeability. Benzodiazepine agonists convert the receptor to the BZ-Ra conformation which enhances GABA induced chloride permeability which depending on the membrane potential and the chloride equilibrium potential can produce hyperpolarization, no change in membrane potential or depolarization. Benzodiazepine antagonists bind to the BZ-Rb form and do not change GABA transmission in the natural state. They merely block any changes that could be induced by benzodiazepine agonists. Inverse agonists, such as some beta-carboline derivatives, convert the receptor to the BZ-Rc form that reduces GABA transmission and cause seizures and anxiety.



Interactions of benzodiazepine agonists, antagonists or inverse agonists with the GABA/benzodiazepine receptor complex

Figure B

The difference in benzodiazepine antagonists and inverse agonists has been demonstrated in studies such as that by Ongini, et al (15), where the effects of a beta-carboline were compared to that of a known benzodiazepine antagonist, Ro 15-1788 (an imidazobenzodiazepine). In this study, cats were given diazepam which produced typical effects such as muscle relaxation, ataxia, sedation and stimulatory behaviors. After three weeks of daily dosing, the animals were given Ro 15-1788 or the beta-carboline (figure C).

Behavioral signs of abstinence	Ro 15-1788			FG 7142		
	Control ($n=4$)	1 day of diazepam ($n=4$)	22 days of diazepam ($n=4$)	Control ($n=4$)	1 day of diazepam ($n=4$)	22 days of diazepam ($n=4$)
Tremors	0	3	4	4	4	4
Muscle twitches	0	0	4	0	0	0
Increased muscle tone	0	3	4	4	2	1
Arched back posture	0	0	4	1	1	0
Decreased motor activity	0	0	4	4	3	4
Irritability	0	0	4	2	1	0

Figure C

An acute abstinence syndrome characterized by tremor, increased muscle tone, muscle twitching and back arching was precipitated by the antagonist, Ro 15-1788, when it was given to diazepam treated animals, but no effect was seen when it was given to control animals. On the other hand, the beta-carboline did not produce an abstinence syndrome in the diazepam treated animals. Instead, it seemed to reverse the acute effects of the benzodiazepine. When given to control animals, it produced tremors, increased muscle tone and irritability, effects that are the opposite of diazepam.

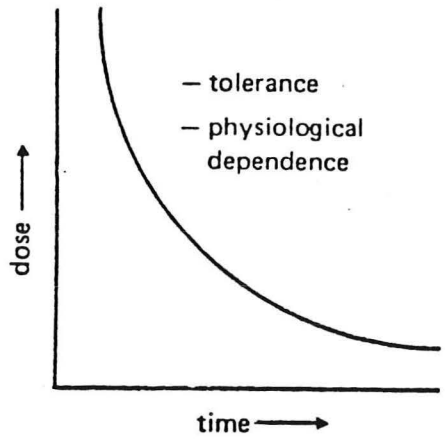
Peripheral benzodiazepine receptors have been identified in the peripheral nervous system, endocrine system, platelets, kidney, liver and lung. Their function and relation to anxiety is unknown but may be modified with anxiolytic treatment (16).

PATHOPHYSIOLOGY OF WITHDRAWAL

The occurrence of rebound insomnia or anxiety in some patients after withdrawing from benzodiazepine therapy has led some authors to believe that production of the endogenous benzodiazepine receptor ligand can be modified by benzodiazepine administration. The functional concentration of this endogenous ligand or postsynaptic GABA sensitivity (17) decreases during chronic benzodiazepine use due to feedback down-regulation. When the benzodiazepine is suddenly withdrawn, a rebound phenomenon could occur because of a lag in production or release of the ligand. This concept was studied by Scharf and Feil (18) by examining the effects of various benzodiazepines on the receptor characteristics. They found that the effects on the receptor depend on the half-life of the drug and on its receptor affinity. Withdrawal of long acting drugs, especially those with active metabolites such as flurazepam and diazepam, will result in less receptor vacancy, and consequently withdrawal, than shorter acting drugs. This occurs because the production of the endogenous ligand has more time to recover from its feedback suppression with drugs whose active metabolite concentration falls slowly. The same authors postulated that drugs with a high receptor affinity would cause more down regulation of GABA production and release than drugs with a low receptor affinity. Consequently, withdrawal of drugs with high receptor affinity would result in greater withdrawal symptoms. According to this hypothesis, the withdrawal of short-acting, high affinity drugs, such as lorazepam or clonazepam, would result in rapid benzodiazepine receptor vacancy and a decrease in normal GABA inhibitory influences leading to more severe symptoms than withdrawal of long-acting, lower affinity drugs which would give

the GABA system more time to recover its normal function before significant receptor vacancy occurs.

Another notion of benzodiazepine dependence has been reviewed by Haefely (19) arguing that benzodiazepine dependence can be thought of as a "drug-induced adaptive syndrome" or the animal's homeostatic respnse to the physiologic changes induced by the drug. Tolerance or physical dependence develops to the benzodiazepines as a function of time of administration and dose as illustrated in figure D. Low doses of a drug must be given over a longer period of time to induce tolerance or physiologic dependence whereas high doses can produce the same effect over a shorter exposure time.



Schematic diagram to illustrate that the induction of tolerance and physiological dependence is a function of drug dose and duration of drug exposure

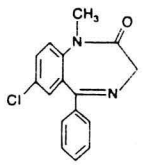
Figure D

Although the concepts of benzodiazepine dependence can be fully explained on a receptor level, there is data to suggest that conditioned tolerance to the drugs also may play a role (20). With this phenomenon, tolerance and dependence to a drug may be different in different situations. For example, if a patient is in a situation or environment where benzodiazepine use has been frequent and with specific resonses, tolerance and dependence may be greater and withdrawal more severe than in other environmental conditions.

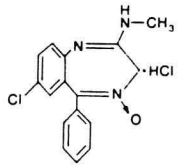
PHARMACOKINETICS OF THE BENZODIAZEPINES

The chemical structures of the benzodiazepines are very similar with minor substitutions on a basic ring structure illustrated in figure E.

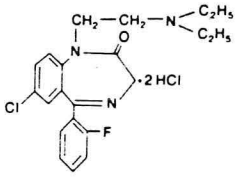
DIAZEPAM (Valium)



CHLORDIAZEPOXIDE HYDROCHLORIDE (Librium)



FLURAZEPAM HYDROCHLORIDE (Dalmane)



CLORAZEPATE DIPOTASSIUM (Tranxene)

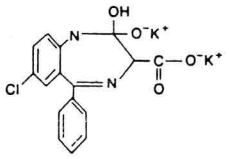
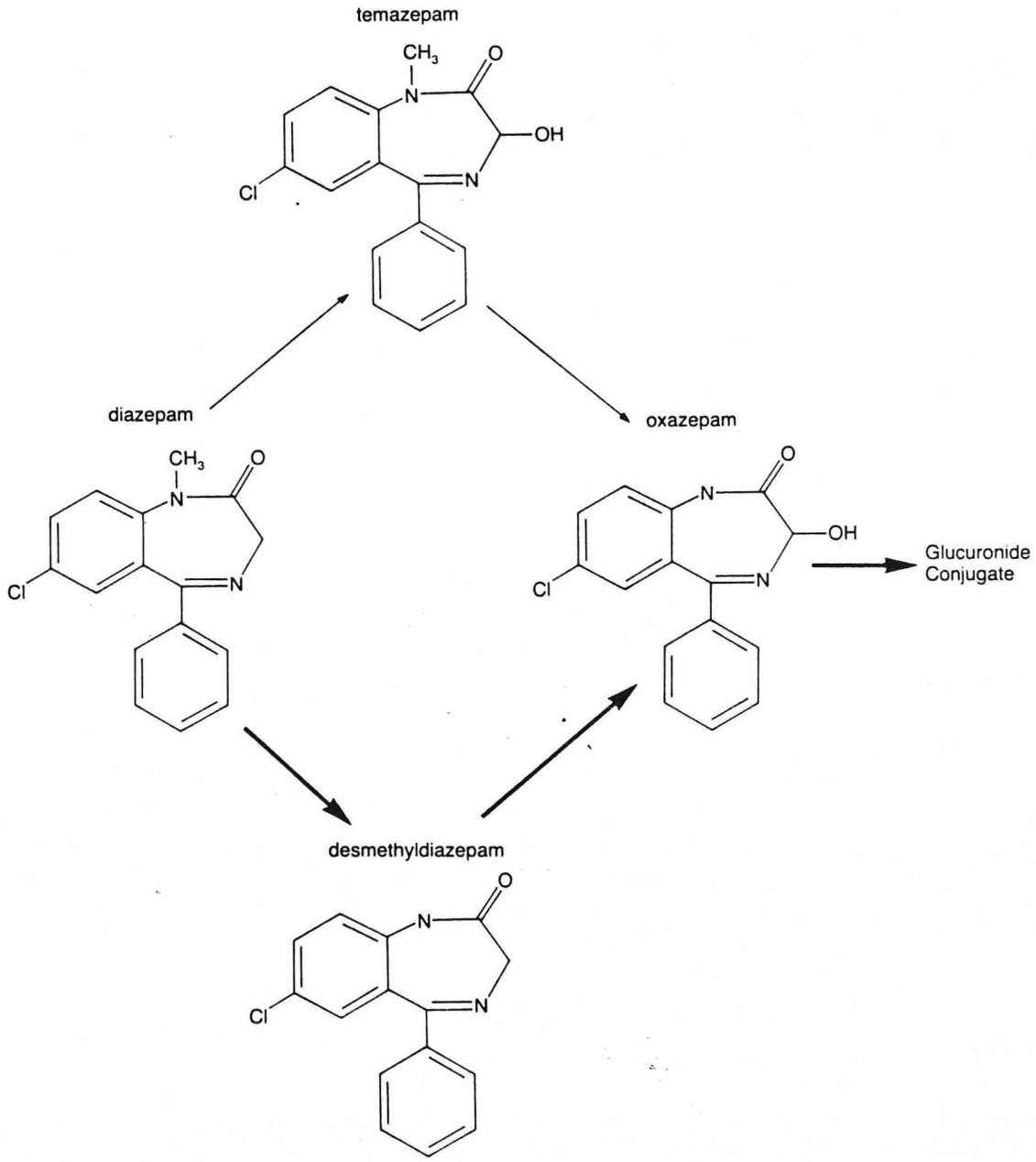


FIGURE E. (21)

Diazepam, the most commonly prescribed benzodiazepine, is rapidly absorbed from the gastrointestinal tract reaching a peak serum concentration in approximately one hour. Its half-life is long (20-100 hours) consisting of a 7-10 hour distribution phase and an elimination phase of 20- 100 hours. The drug is very lipophilic which accounts for the short duration of action after a single dose and the fact that the drug accumulates in the brain.

Benzodiazepines are highly protein bound (80-99%) making dosing difficult in patients with low serum albumin concentrations. The drugs are metabolized by desmethylation and conjugation with glucuronide as illustrated in figure F.



Diazepam metabolism. Heavy arrows indicate the major metabolic pathway.

FIGURE F. Diazepam Metabolism (21)

Desmethylation takes place slowly in the liver. Consequently, the drugs metabolized by this mechanism have a long duration of action, e.g., diazepam. On the other hand, conjugation with glucuronide usually is rapid and drugs metabolized by this means have short half-lives and durations of action.

In general, benzodiazepines are divided into three groups based on elimination half-life, i.e., ultrashort-acting, short-acting and long acting (adapted from 21,22).

Ultrashort-acting (half-life less than 10 hours)

1. Midazolam (Versed) has a half-life of 2-5 hours.

2. Temazepam (Restoril) has a half-life of 10 hours. Its O-conjugate metabolite is inactive.

3. Triazolam (Halcion) has a half-life of 2-3 hours and no active metabolites.

Short-acting or intermediate-acting (half-life of 10-24 hours)

1. Alprazolam (Xanax) has a half-life of 12-15 hours. It is metabolized to alpha-hydroxyalprazolam and benzophenone, both of which are inactive.

2. Lorazepam (Ativan) has a half-life of 10-20 hours. It is slowly absorbed orally but has rapid, reliable absorption when given intramuscularly. It is metabolized to the inactive metabolite lorazepam glucuronide.

3. Oxazepam (Serax) has a half-life of 3-21 hours and like lorazepam is slowly absorbed when taken orally, limiting its use as a hypnotic. It is metabolized to oxazepam glucuronide, an inactive metabolite.

Long-acting (half-life greater than 24 hours)

1. Chlodiazepoxide (Librium) has a half-life of 5-30 hours. Its half-life is prolonged in elderly patients. Its active metabolites, desmethychlordiazepoxide and demoxepam, have half-lives that are longer than the parent compound.

2. Chlorazepate (Tranxene) has a half-life of 36-200 hours but its pharmacologic activity is related to its active metabolite, desmethyldiazepam. Its conversion to the metabolite and absorption are dependent on gastric acidity.

3. Clonazepam (Clonopin) has a half-life of 10-50 hours. Multiple active metabolites have been found.

4. Diazepam (Valium)- see above discussion.

5. Flurazepam (Dalmane) has a half-life of 50-100 hours. It has an active metabolite, desalkylflurazepam that accumulates with multiple dosing.

6. Prazepam (Centrex) has a half-life of 26-200 hours. Its active metabolite is desmethyldiazepam and it has similar elimination kinetics as diazepam.

ABUSE POTENTIAL OF BENZODIAZEPINES

Although benzodiazepines are less toxic than barbiturates, they still have abuse potential as evidenced by their use by opiate and sedative abusers to get high and their being sold illicitly on the street. When benzodiazepine use has been studied in persons seeking treatment for drug or alcoholism dependence, it has been found to be much higher than in the population in general. Ogborne and Kapur (23) found evidence of benzodiazepine use, by urine screening, in 32% of 111 consecutive admissions to a nonmedical detoxification unit. While some of these drugs may have been prescribed by a physician, Beary and coworkers (24) have found that 76% of patients who used benzodiazepines in a drug dependence treatment center obtain the drugs illegally.

In general, it is believed that the abuse potential of the benzodiazepines is related to their peak psychoactive intensity and the rapidity of onset of subjective effects that users feel are pleasurable. However, one must separate the pleasure producing effects and other effects such as sedation which may or may not be pleasant depending on the attitude of the user. For example, Roache and Griffiths (25) found that the fast-acting drug triazolam when compared to pentobarbital had less potential for abuse; but that subjects taking tiazolam more consistently underestimated their degree of impairment, thereby making the liability of abuse higher for the benzodiazepine.

Because benzodiazepines are frequently prescribed for alcoholics undergoing acute and chronic detoxification, Jaffe, et al (26), studied the abuse potential of halazepam and diazepam in patients undergoing alcohol withdrawal. Halazepam was chosen because it has been reported to be a weaker short-term reinforcer and has less capacity to supress withdrawal symptoms when compared to diazepam, both characteristics suggesting it has less abuse potential. Equivalent anxiolytic doses of halazepam and diazepam were compared.

Differences in the euphoria produced by the drugs are presented in figure G. In general, diazepam produced significanly more euphoria than halazepam, especially in the first two hours after administration.

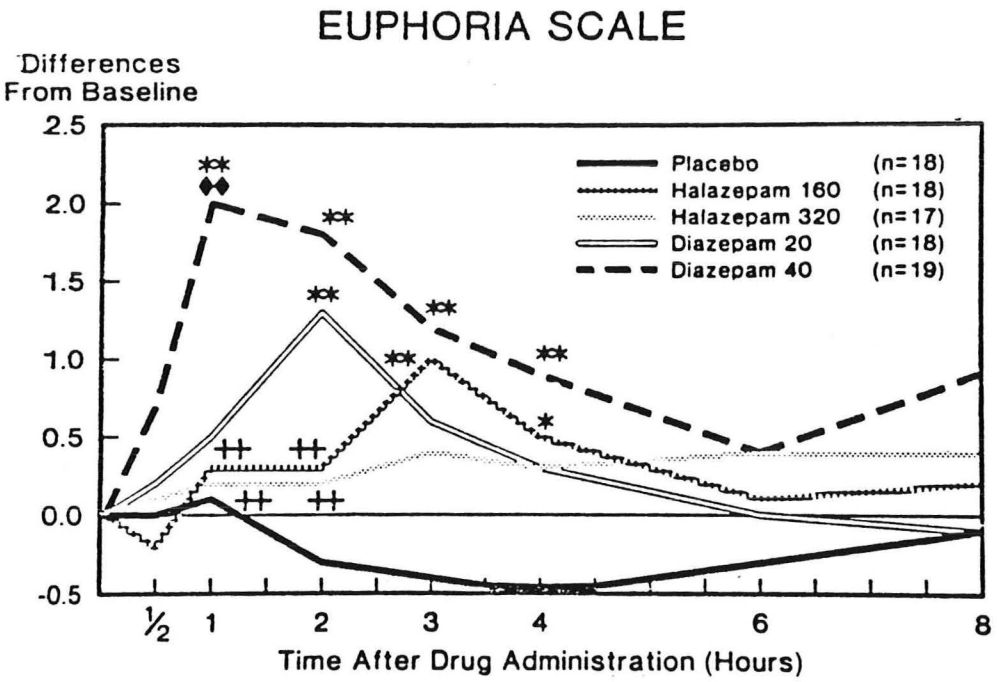


Figure G.

Figure H illustrates the differences in sedation when the two drugs are compared to placebo. Both 20 mg and 40 mg doses of diazepam induced significant sedation within one hour of ingestion. Both doses of halazepam produced significant sedation but only after two hours. The authors concluded that since diazepam produced more rapid and intense effects, its abuse potential was greater than halazepam. The fact that diazepam has more abuse potential than many of the other benzodiazepines has been documented in other studies (27).

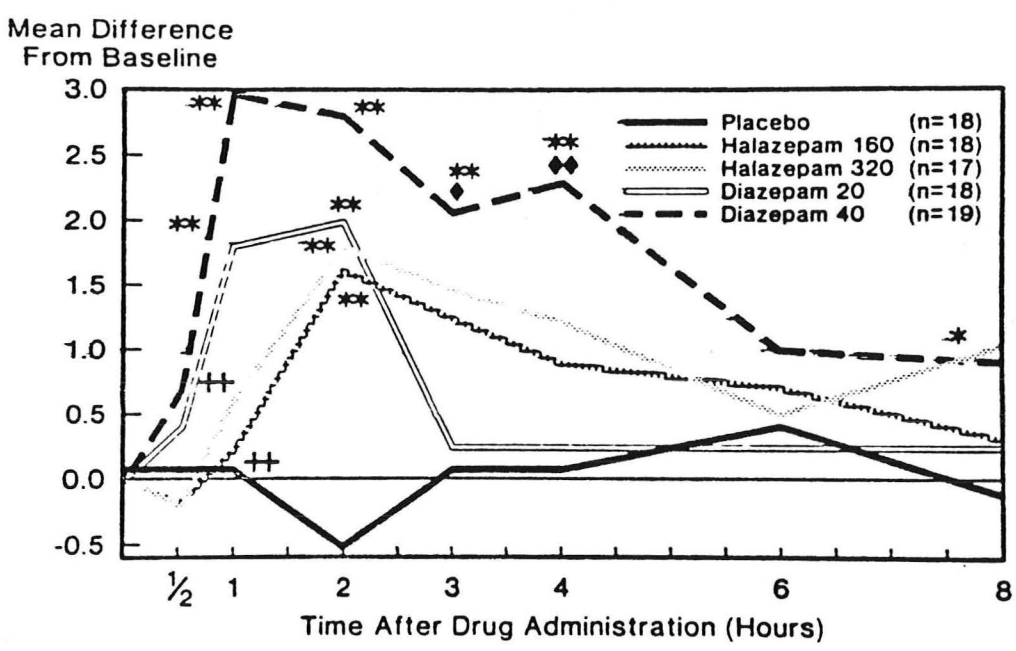


Figure H

However, a distinct preference of benzodiazepine use over other drugs of known abuse potential has been challenged. In a review of data from their studies, Uhlenhuth and coworkers (28) found that students given placebo or various doses of diazepam actually preferred placebo when compared to 5mg and 10 mg diazepam as illustrated in figure I. When given 2 mg of diazepam, the subjects had no clear preference of the drug or placebo.

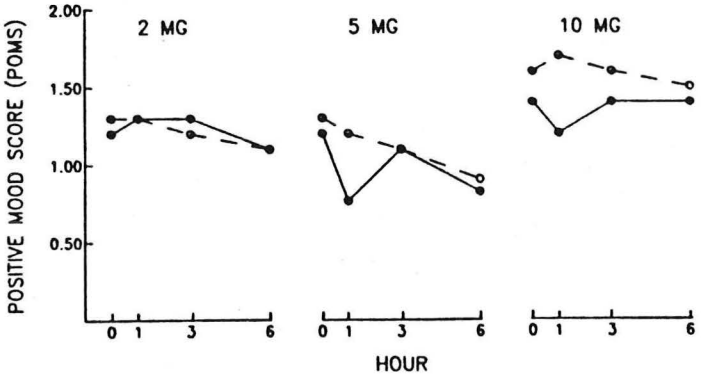


Figure I

In a comprehensive review of the literature, Dietch (5) concluded that the incidence of true benzodiazepine dependence is low. However, certain groups, i.e., polydrug abusers, alcoholics and those with borderline and antisocial personalities, are at sinificanyly higher risk.

INDICATIONS FOR USE OF BENZODIAZEPINES

The benzodiazepines are most-widely used as hypnotics, anxiolytics, muscle relaxants and anticonvulsants. The indications for the use of these drugs will not be discussed in detail but can be found below.

INDICATIONS

Anxiety	Alcohol Withdrawal	Insomnia
Chlordiazepoxide	Chlordiazepoxide	Flurazepam
Diazepam	Diazepam	Temazepam
Oxazepam	Oxazepam	Triazolam
Chlorazepate	Chlorazepate	Midazolam
Lorazepam		
Prazepam	Anticonvulsant	Preop Sedation
Alprazolam	Diazepam	Chlordiazepoxide
Halazepam	Chlorazepate	Diazepam
	Clonazepam	Lorazepam

Anxiety-Depression	Muscle Spasm
Oxazepam	Diazepam
Lorazepam	
Alprazolam	

Anxiety is the most common disorder for which the benzodiazepines are prescribed. The drugs are very effective and tolerance to the anxiolytic effects does not develop (29). Although the drugs in this group are very similar, subtle differences may give one an advantage in a particular situation. For example, prazepam may cause less drowsiness than the others because of the slow appearrance of the active metabolite, desmethyldiazepam. The decision to use one of these drugs for anxiety should not be casual. In general, they should be reserved for patients with a generalized anxiety disorder, i.e., someone with pathologic anxiety that impairs function and is not associated with panic attacks and avoidance behavior or obsessive

compulsive thinking. Most patients with situational anxiety that is not intense enough to impair function do not need medication. It should be remembered that benzodiazepines do not cure anxiety but only allow the patient some degree of functional ability. The drugs should not be used for more than 4 months without careful reconsideration of the ongoing indications for its use and risks.

Many patients with panic disorders have varying degrees of anxiety with the attacks, often leading to avoidance behavior. In general, the benzodiazepines help alleviate the anxiety but may not influence the underlying disorder, except for alprazolam which seems to have a specific anti-panic effect.

Benzodiazepines are very effective in treating short-term or intermediate-term insomnia not caused by psychiatric or medical disease.

Diazepam is the only benzodiazepine specifically indicated for use as a muscle relaxant. Much of its efficacy is probably related to its hypnotic and anxiolytic properties.

CLINICAL MANIFESTATIONS OF WITHDRAWAL

Studies describing the incidence of withdrawal are difficult to interpret because the symptoms of withdrawal from benzodiazepines are very similar to those of the anxiety for which the benzodiazepine was prescribed in the first place (Table 1). Nausea, depression, depersonalization and paresthesias are more likely to represent withdrawal.

Table 1

Clinical Manifestation of Withdrawal

Anxiety, apprehension (30)
Concentration difficulties
Dizziness
Irritability
Insomnia (31,32,33)
Fatigue
Headache
Muscle twitching, aching or weakness
Postural hypotension
Psychosis (34,35)
Tremor
Sweating

Nausea, anorexia*
Observable depression*
Depersonalization, derealization*
Increased sensory perception*
Abnormal perception or sensation of movement*
Hyperthermia*
Seizures (36,37,38,39)*
Delirium (40)*
? Neuroleptic malignant syndrome (41)

*More likely to represent withdrawal rather than an exacerbation or return of original anxiety.

The incidence of withdrawal symptoms in long-term users of benzodiazepines after discontinuation of therapy is in the range of 30-50% (42). Most of the symptoms are mild and serious consequences such as seizures are rare. The incidence of significant withdrawal in short-term users is approximately 5%. Again, most symptoms are mild such as rebound insomnia.

Rebound insomnia is common after abrupt discontinuation of short acting drugs even when used for a short period of time as illustrated in figure J where the short-acting drugs triazolam (T), midazolam (M) and lormetazepam (L) produced much more rebound insomnia than the longer acting drugs flurazepam (F) and quazepam (Q) even after only two weeks of therapy (43).

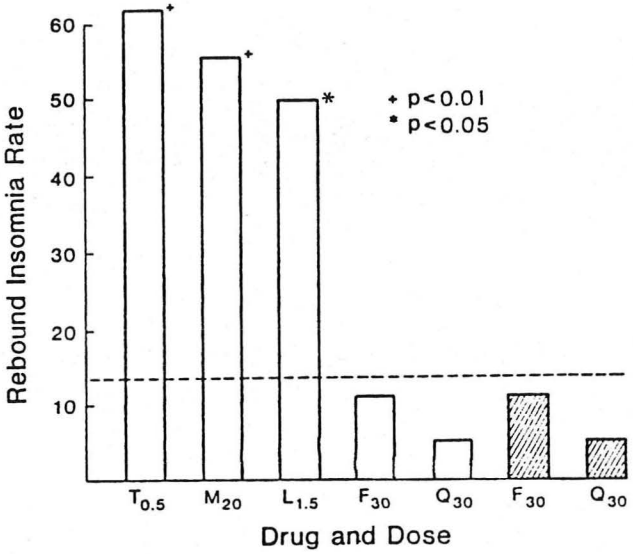


Figure J

A neonatal abstinence syndrome may be seen in children whose mothers are chronic benzodiazepine users. Clinical manifestations of this syndrome include tremors, irritability, tachypnea, hyperactivity, vigorous sucking, weight loss and vomiting. The syndrome usually develops 2-6 days after delivery but may be delayed up to 10 days due to the delayed metabolism of the drugs in some infants.

Assessing withdrawal symptoms in patients who suddenly stop or alter their benzodiazepine dose is very difficult for several reasons. First, as mentioned above, the symptoms of withdrawal are very similar to the anxiety that precipitated the drug use in the first place. Consequently, distinguishing withdrawal from a reappearance of anxiety can be difficult. Second, many patients who use and abuse benzodiazepines abuse other drugs such as alcohol, making it difficult to separate benzodiazepine withdrawal from the withdrawal seen with other drugs. For example, van Sweden (38) reported an elderly patient who presented with complex partial seizures after withdrawal from a long history of alcohol and lorazepam (20-30 mg/day) use. Although the time course of the seizures suggested benzodiazepine withdrawal as the inciting factor in that the seizures developed

five days after stopping the drugs, a contributing effect from the alcohol could not be ruled out. Finally, distinguishing withdrawal from pseudorebound or pseudowithdrawal can be very difficult since the clinical course of anxiety can be extremely variable. The concept of pseudorebound or pseudowithdrawal is illustrated in figure K (19). This occurs when the baseline for the disease or symptoms, in this case anxiety, is not constant. Consequently, if the benzodiazepine is stopped when the disease activity is at a peak, symptoms of worsening anxiety may be interpreted as withdrawal.

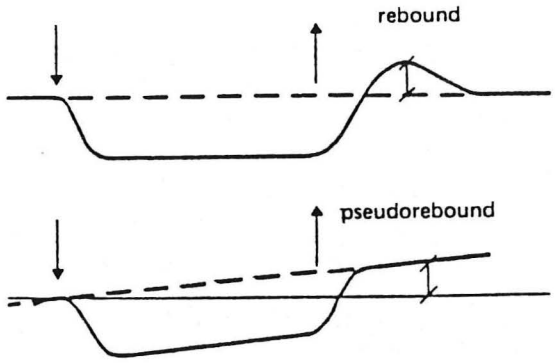


Figure K

Several factors have been identified that affect the development of benzodiazepine dependence and withdrawal.

Dose. In general, dose of the drug used has been thought to influence withdrawal symptoms in that larger doses taken over a given period of time would be more likely to cause symptoms. Certainly the model illustrated in figure D would suggest this. However, this has been difficult to prove in the existing literature. In fact, there probably is little effect of dose on withdrawal symptoms with standard therapeutic doses. With supratherapeutic doses, withdrawal incidence is dependent to some extent on the amount of drug taken per unit time.

Duration of drug use. Clearly, withdrawal is more severe in patients who have used benzodiazepines for a long period of time when compared to patients who have received short courses of therapy (29). However, there is no clear time period to predict when withdrawal symptoms will occur or how severe they will be. Although animal studies suggest that dependence can be detected

within days of beginning benzodiazepines (44), most clinical studies suggest that several months of daily use are necessary to induce significant withdrawal symptoms although minor symptoms such as rebound insomnia may occur after short-term (days) treatment. Rickels, et al (29), studied the incidence of tolerance and withdrawal in 180 chronically anxious patients treated with diazepam, 15-40 mg/day. They found that the length of drug treatment was the most important determinant of withdrawal reactions. If patients were treated continuously less than 8 months, the incidence of significant withdrawal was 5% while those who were treated for more than 8 months had a 43% incidence of withdrawal. However, no instances of life-threatening withdrawal were noted. In summary, the withdrawal syndrome is very unusual if therapeutic doses of the benzodiazepines are used for a short period of time.

Other drugs used. Patients who use other central nervous system depressants such as alcohol are more likely to suffer withdrawal symptoms upon discontinuation of their benzodiazepines. This is true with even moderate or social intake of alcohol (29,38).

Time of withdrawal. It has been thought by most authors that abrupt withdrawal of benzodiazepines causes more severe symptoms than gradual tapering of the dose (45). This has been difficult to prove and disputed by many studies probably because the longer acting drugs have a built in tapering mechanism due to the long half-life of the drugs or active metabolites.

Half-life. In general, it has been thought that the incidence, peak and intensity of withdrawal symptoms are greater with the cessation of shorter-acting when compared to longer-acting drugs (46), although this concept has been challenged by some authors (47). Usually symptoms peak within a few days of drug cessation and resolve over a two to three week period.

TREATMENT OF WITHDRAWAL

The management of a patient who is withdrawing from a benzodiazepine dependent state can be difficult. Several methods have been tried but very few well controlled studies have been done. With any of these methods, close observation and psychological support is essential if success is to be expected.

Behavioral strategies usually have been used in combination with pharmacologic therapy since such strategies do not work well

alone. Relaxation techniques are not effective, but anxiety management training can be useful as adjunctive therapy (48).

The most common and probably the most effective withdrawal technique is a gradual tapering of the benzodiazepine used or a substitute over a period of one to three weeks. Persons using short-acting drugs may develop more intense symptoms that usually respond to switching to a longer-acting drug (49). When switching to another longer-acting drug remember that even the longer-acting drug may have a short duration of action acutely because of distribution kinetics. Consequently, frequent doses should be used until a steady state has been reached (usually one or two weeks). With a drug such as diazepam, a taper consisting of a 10% reduction in dose per day will usually be tolerated (50). While tapering, if symptoms of withdrawal or anxiety appear, the dose may have to be adjusted upward and tapered more slowly (51).

Barbiturates have been used to treat benzodiazepine withdrawal because some have mild anxiolytic properties, although they are not mediated through the benzodiazepine receptor. Because of this, some authors have tried barbiturates, especially phenobarbital, for the treatment of benzodiazepine withdrawal with some success (52).

Propranolol in doses of 60-160 mg per day, orally, in three or four doses, has been shown to reduce the symptoms of diazepam withdrawal (53). As in alcohol withdrawal, beta blockers treat only the symptoms due to sympathetic overactivity and in this situation have little effect if any on the anxiety.

Clonidine has been reported to alleviate the symptoms of benzodiazepine withdrawal in several case reports. However, in a double-blind, placebo controlled study, Goodman, et al, were unable to show any benefit of clonidine in this disorder (54).

Carbamazepine seems to be effective in treating benzodiazepine withdrawal as demonstrated by Klein and coworkers (55). Doses of 600-800 mg per day can be added over about one week. The benzodiazepine is then tapered over approximately 2 weeks with close observation.

Buspirone is a new type of anxiolytic drug that has been tried in benzodiazepine withdrawal. It does not block the withdrawal syndrome (56) but may block the return of anxiety in some patients. More studies are necessary before recommendations on its use in this situation can be made.

OVERDOSE

Because of their large index of safety, overdoses with benzodiazepines alone are rarely life-threatening. Even large doses of the drugs rarely produce prolonged coma or respiratory depression. Most fatal overdoses or those requiring respiratory support involve multiple drugs, usually other sedatives or alcohol. Respiratory depression with benzodiazepines alone usually occurs after intravenous injection where its incidence is 1-2%.

Drowsiness is the most common symptom after an overdose of a pure benzodiazepine. Ataxia, dizziness, weakness, tachycardia and dysarthria are also common. Nystagmus is seen in about 10% of pure overdoses but may occur in up to 22% of those combined with alcohol (57). Paradoxical delirium may rarely occur. Seizures, hyperreflexia and hypertension are occasionally seen but usually are indicators of alcohol withdrawal in patients taking benzodiazepines. Serum levels correlate poorly with clinical presentation, probably due to extensive protein binding and lipophilicity.

Clonazepam causes more drowsiness and ataxia than the other benzodiazepines. It also may cause nystagmus, dysarthria, irritability, aggressiveness, sialorrhea and bronchorrhea.

Bailey (57) compared the clinical characteristics of 25 patients with overdoses of chlordiazepoxide alone with 23 patients who took an overdose of the drug with ethanol and found that the patients with "mixed" ingestions had significantly more depression of mental status that was correlated with the blood levels of the benzodiazepine ($p < 0.05$) but not with the blood levels of ethanol. In the patients taking the "pure' ingestions, consciousness did not correlate with blood levels of the drug.

Most patients who take an overdose of benzodiazepines with alcohol have a history of chronic alcoholism and many take benzodiazepines for the control of withdrawal symptoms. For this reason, chronic benzodiazepine use is probably contraindicated in alcoholic patients.

CONCLUSIONS

The benzodiazepines are a group of drugs that are relatively safe and very effective in treating certain disorders, especially anxiety and insomnia. The risk for significant dependence and subsequent withdrawal is small if therapeutic doses are used for

short periods of time (less than four months). When patients are started on these drugs, they should be counselled regarding risks of dependence and warned against sudden reductions in dosages. Reassessment of the need for continued treatment should be made periodically and the drug discontinued if indications for further treatment do not exist. Withdrawal of the drug after prolonged exposure to high doses should be undertaken carefully with close supervision.

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