

Should Benzodiazepines Be Prescribed To Treat Insomnia And Anxiety Related Disorders?

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INTRODUCTION

Benzodiazepines are commonly prescribed drugs used to treat insomnia and anxiety. They are often found in forms such as Xanax (alprazolam) and Valium (diazepam). For many, these drugs have proven essential for ensuring a restful night's sleep, but for others they are the cause of sleepless ones. Negative effects of benzodiazepines such as addiction, dependence, and impaired cognition plague many patients. While doctors are prone to prescribe these medications readily due to their high level of effectiveness, this practice can pose a great risk to certain populations .

Structure of Benzodiazepines

Benzodiazepines consist of a benzene ring and diazepine ring (see fig 1). Varying side chains which attach to this basic structure account for the various drugs formed from this compound. Xanax (alprazolam), Librium (chlordiazepoxide), Klonopin (clonazepam), Tranxene (clorazepate), Valium (diazepam), Paxipam (halazepam), and Ativan (lorazepam) are prescribed for long term use while ProSom (estazolam), Dalmane (flurazepam), Doral (quazepam), Restoril (temazepam), and Halcion (triazolam) are prescribed specifically for short term use.

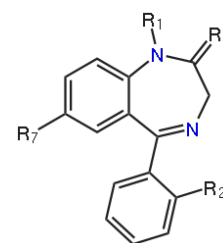


Figure 1. Structure of a Benzodiazepine Ring

Mechanism of Action

GABA is the primary inhibitory neurotransmitter of the central nervous system. GABA receptors exist in two forms, GABAA and GABAB. GABAA receptors (GABAAR) are present on neuron membranes and work as ligand-gated ion channels. When GABA binds to GABAA receptors, the flow of chloride ions into the cell increases. The influx of negatively charged chloride ions causes the cell to undergo hyperpolarization. In turn, the transmission of action potentials is less likely to occur, and neurotransmission is inhibited.

GABAA receptors are found as part of a protein complex. This complex also houses different allosteric binding sites which can indirectly affect GABAA when activated. Benzodiazepine can bind to one of the allosteric sites on this complex. When benzodiazepine binds to its receptor on the protein complex, it causes the GABAA receptor to experience a conformational change. This change locks the GABAA receptor in a form to which GABA has a higher level of affinity. This results in an even greater influx of chloride ions than would normally be triggered by the binding of GABA. In this way, benzodiazepines work as an agonist of GABAA and slow down the brain and nervous system .

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Uses of Benzodiazepines

Benzodiazepines are most often associated with the treatment of insomnia and anxiety. Insomnia is a sleeping disorder causing difficulty in sleeping or falling asleep. Anxiety often accompanies depression or other psychological disorders and is characterized by excessive stress, worry, or fear. The ability of benzodiazepines to inhibit brain activity and neurotransmission helps to promote sleep and relaxation, and induces a calming effect. Benzodiazepines are also used to treat muscle spasms, convulsive disorders, and to induce sedation prior to surgery. Further uses of benzodiazepines are listed in the tables below.

Clinical Uses of Benzodiazepines	
Anxiety disorders	Detoxification from alcohol and other substances
Acute anxiety	Agitation or anxiety associated with other psychiatric conditions
Generalized anxiety disorder	Acute mania
Panic disorder	Psychotic illness
Phobias (social, simple)	Anxiety associated with depression
Post-traumatic stress disorder	Impulse control disorders
Obsessive-compulsive disorder	Catatonia or mutism
Insomnia	Other adjunctive uses
Anxiety associated with medical illness	Surgery
Cardiovascular	Dentistry
Gastrointestinal	Diagnostic studies, such as
Somatoform disorder	computed tomography, magnetic resonance imaging and
Convulsive disorders	endoscopy
Acute status epilepticus	Cardioversion
Neonatal seizures or febrile convulsions	Chemotherapy
Preeclampsia	Information from Hollister L, Muller-Oerlinghausen B, Rickels K, Shader R.
Tetanus	Clinical uses of benzodiazepines. J Clin Psychopharmacol 1993;13(suppl 1):1-
Adjunct to other anticonvulsants	169.
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	

Table 1. Benzodiazepines are used to treat a myriad of ailments.

The Effectiveness of Benzodiazepines in the Treatment of Insomnia

Benzodiazepines have been established as an effective treatment for insomnia. In an analysis of twenty-two studies of benzodiazepines and benzodiazepine-receptor agonists, significant improvements were found in total sleep time, number of awakenings, and sleep quality of the treated patients. However, only nine of those studies contained information complete enough to allow for accurate calculation of effectiveness. The nine studies analyzed involved a total sample of 343 patients who were treated with benzodiazepines and 337 who were members of control groups. All participants fell between the ages of 18 and 65. Participants who received the medication fell asleep sooner than 71% of the control group slept longer than 76% of the control group, woke up less often than 74% of the control group, and had better sleep quality than 73% of the control group. All of the studies examined in this meta-analysis used a “placebo –control group, parallel-group design, randomized patient assignment, and double-blind assessment of outcomes.”(Nowell, et al., 1997)

An additional study was conducted on 54 patients who were prescribed benzodiazepines. The participants of the study were of sixty-five years of age or older and were at the hospital during the three day study period. Thirty one of the patients had not used benzodiazepines previously.

Half of these patients reported shorter sleep onset while taking the medication at the hospital. In other areas of sleep assessment, such as duration of sleep, number of awakenings, and sleep quality, many had an improved sleep experience in the hospital compared with their sleep at home. However, little difference in sleep improvement was observed between those who were newly introduced to benzodiazepines and those who were already using them prior to entering the hospital. This indicates that the improvement in sleep which the patients experienced could be attributed to the hospital environment or other factors rather than to the prescription of benzodiazepine medications. While the outcome of this study does not support the effectiveness of benzodiazepines, it was conducted on a relatively small group and for a short period of time. These factors limit the value of this study and its conclusions .

Risks Associated With Benzodiazepine Use

While benzodiazepines are considered to be one of the safest sedatives, their use is sometimes accompanied by side effects which can put a patient at risk. Patients most commonly found to be at risk are those who take benzodiazepines for extended periods of time, who abuse other substances, and those who are elderly.

Dependency & Withdrawal

According to the FDA fast-onset, short acting benzodiazepines should be prescribed for only five consecutive weeks in order to avoid the risk of dependency. In reality, however, they are often used for longer periods of time which can lead to complications. Millions of Americans have inadvertently become dependent on benzodiazepines as a result of receiving repeated prescriptions over time. Of the estimated 1 million users in the United Kingdom and 4 million users in the United States, 50% are thought to be dependent on benzodiazepines.

Tolerance as a result of prolonged exposure

Tolerance is defined as “a need for markedly increased amounts of the substance to achieve the clinical effect, or markedly diminished effect with continued use of the same amount of the substance.” For those who use benzodiazepines to promote sleep, tolerance can develop relatively quickly. Dependency can increase within a few short days or weeks. Many of those who use benzodiazepines to induce sleep tend to gradually increase their doses beyond recommended levels. Patients may pressure their doctors to increase their prescriptions or perhaps visit multiple doctors or clinics to obtain numerous prescriptions simultaneously. Sometimes patients may even turn to street drug dealers to obtain the doses they crave. Such practices put users at further risk of becoming dependant on the drug.

Withdrawal

Withdrawal symptoms associated with discontinued use of benzodiazepines include “restlessness, irritability, insomnia, muscle tension, weakness, aches and pains, blurred vision, and heart racing.” Many continue to take benzodiazepines in order to avoid going through a withdrawal stage. However, continuing to take the drug may cause patients to become increasingly dependent and may dull the drug’s ability to provide relief.

In cases where users are not using benzodiazepines for recreational use, the negative effects experienced upon discontinuation are usually a result of relatively low-dose benzodiazepine dependence. However, even when administered at low dosages, long term exposure can result in

dependence and negative withdrawal symptoms. With longer-acting drugs, one or two months of exposure can put a patient at risk. With shorter-acting drugs, taking the drug daily for a week can affect the patient. Short-acting benzodiazepines have also been proven to cause rebound insomnia which negatively affects the user's sleep the night after the drug is used.

Drugs which have slower elimination such as Xanax and Valium are more likely to cause side effects because metabolites accumulate in the body if the drug is used repeatedly. However, users of these drugs are less likely to suffer from withdrawal. On the other hand, drugs such as Doral and ProSom, which have shorter half-lives and elimination time, are more likely to cause withdrawal symptoms.

Long-term or high-dose exposure to benzodiazepines results in a decrease in the effectiveness of the body's natural GABAA. It is thought that continuous administration of the drug causes the body to adapt to presence of the drug. When the drug is removed, the forces to which it is normally opposed are left with no adversary. In the case of benzodiazepines which are used to treat anxiety and induce sleep, abrupt discontinuation can cause a surge in nervous activity.

While the exact mechanism responsible for benzodiazepine dependence has not been found, theories have been proposed and studies have been done which may provide an answer, at least in part. Benzodiazepines serve as an agonist of GABAA. When a drug which works as an agonist is administered chronically, it causes a decrease in the number of receptors found in the body. This is known as down regulation. The receptors are decreased by means of internalization, degradation, or recycling of the receptor. A decrease in receptors would then cause the drug to become less effective as well as decrease the body's ability to respond to its natural GABA. However, some studies have found there to be no significant decrease in the number of receptors in those chronically exposed to benzodiazepines. Therefore, other theories attribute the ineffectiveness of benzodiazepines to modification of the GABAA receptors rather than to a loss of those receptors.

Abuse By Abusers

The Abuse of Benzodiazepines by Those Who Abuse Other Substances

According to the APA, the prevalence of those individuals dependent on benzodiazepines among substance-abusers was found to be significantly higher than among the general population. Benzodiazepines are often used in conjunction with other drugs by those who seek to use drugs for recreational purposes. Approximately 80% of those who abuse benzodiazepines are polydrug abusers. In a study conducted among Australian heroin users, 91% of the two hundred and twenty-two participants had used benzodiazepines. Of those who had used benzodiazepines, 67% were currently using the drug on a regular basis. In a study by the National Institute of Drug Abuse, 73% of heroin users used benzodiazepines weekly for more than one year. Those who abuse alcohol are also at risk of becoming dependent on other drugs such as benzodiazepines.

In response to an article published in *The American Journal of Addictions* regarding the safety of prescribing benzodiazepines for the treatment of insomnia and anxiety in substance abuse patients, Edgar P. Nace of Texas Southwestern Medical School published his view in *The Brown Digest of Addiction Theory and Application*. Dr. Nace argues that substance abuse patients are at a greater risk of abusing benzodiazepines than the general population and, therefore, doctors should use caution when prescribing the drug. He cites that in samples of known substance abusers, 10% of the sample population were dependant on benzodiazepines at the time and over 50% were abusers of the drug.

Benzodiazepines have varied uses for those who are addicted to other drugs. While few use benzodiazepines alone for recreational purposes, drug abusers may take benzodiazepines to boost the effects of opioids or to alleviate withdrawal symptoms. For example, some may take benzodiazepines between heroin “fixes” to dull the negative feelings such as anxiety which they may feel. In cases where other drugs an abuser takes become unavailable, he may take benzodiazepines alone in high dosages to placate his cravings. Many abusers also state that they use benzodiazepines to prolong the “high” they receive from taking recreational drugs such as heroin and cocaine. Alcoholics use benzodiazepines to alleviate anxiety which results from chronic alcohol intake as well as to produce the pleasurable effect induced by mixing the drug with alcohol.

Short-acting benzodiazepines are more commonly used by substance abusers who benefit from the drugs’ rapid effects. However, clonazepam, which has a long-half life, is also a known benzodiazepine “street drug,” so it would seem that the delayed effects characteristic of the drug do not deter abusers. In addition, lipophilic benzodiazepines, which have the ability to cross the blood-brain barrier, and other benzodiazepines which have shorter half-lives and are highly potent are usually preferred by substance abusers. The Center for Substance Abuse Research notes that benzodiazepines are likely to be abused due to the sedative state which they induce. As all benzodiazepines are sedatives, every variety of the drug has some degree of potential for abuse.

Toxicity and Substance Abuse

The different varieties of benzodiazepines available vary in potency. Alprazolam is approximately twenty times more potent than diazepam. Therefore, those who are prescribed 6mg of alprazolam daily, a common dosage in the United States, are taking the equivalent of 120mg of diazepam, which is considered a very high dose. Doctors are made aware of these differences as administering a drug with too high a potency can prove very harmful. However, those who take the benzodiazepines for recreational purposes are unaware of the different posed by different benzodiazepines. Generic drugs sold on the street are often unmarked or inappropriately labeled and an overdose of flurazepam or temazepam can result in fatality (Ashton, 2002a).

Benzodiazepines have additive effects with other drugs with sedative actions including other hypnotics, some antidepressants (e.g. amitriptyline [Elavil], doxepin [Adapin, Sinequan]), major tranquillisers or neuroleptics (e.g. prochlorperazine [Compazine], trifluoperazine [Stelazine]), anticonvulsants (e.g. phenobarbital, phenytoin [Dilantin], carbamazepine [Atretol, Tegretol]), sedative antihistamines (e.g. diphenhydramine [Benadryl], promethazine [Phenergan]), opiates (heroin, morphine, meperidine), and, importantly, alcohol. Patients taking benzodiazepines should be warned of these interactions. If sedative drugs are taken in overdose, benzodiazepines may add to the risk of fatality (Ashton, 2002b).

Adverse Effects in the Elderly

The risks normally posed by benzodiazepines are amplified in elderly populations. The negative effects which result from combining benzodiazepines with other drugs are more likely to surface in elderly patients who commonly take other medications regularly. In addition, elderly patients are more sensitive to dosage and, therefore, can more easily fall prey to the dangers associated with taking benzodiazepines which are too potent. Psychomotor skills are affected by benzodiazepines, thus slowing the body’s responses. This can be very detrimental in elderly patient who may have slower responses even without taking the drug. An increased number of hip fractures and falls in elderly patients have been attributed to benzodiazepine use.

The effectiveness of benzodiazepines is found to be lower in elderly patients, while the negative effects are increased. Therefore, when it comes to the elderly, the drug is recommended for short term use only. In practice, however, benzodiazepines are usually prescribed to the elderly long-term. Despite the guidelines which have been instated as a result of much research, 80% of elderly benzodiazepine patients receive treatments for over two years. (Note: Long-term use is defined as treatment lasting more than two weeks.) Benzodiazepines can offer much needed relief for sleep disorders, so it is not surprising that those receiving the treatment and benefitting from the drug would not want to stop taking it. In addition, many elderly patients would prefer to continue taking the medication rather than suffer from the withdrawal symptoms which they would experience if the drug's administration were discontinued.

Falls and Fractures

While many associate benzodiazepine use with hip fractures and injurious falls, the studies conducted have not provided consistent conclusions. A study conducted in France hoped to resolve this conflict by following a very large population of those over sixty-five years of age for up to ten years.

In this study, the individuals who qualified had experienced an injurious fall. An injurious fall was defined as one which resulted in hospitalization, fractures, head trauma, or fatality. Controls were selected at random from the numerous eligible subjects available. The mean age of the sample was seventy-eight. For the purposes of analyzing results, the group was divided between those above eighty years of age and those below the age of eighty. A very significant correlation was found between benzodiazepine use and injurious falls in those above the age of eighty. "The population attributed risk of benzodiazepine use on injurious falls in subjects aged >80 years was estimated using an aged-stratified model as 28.1%." Those conducting the study estimated that should the rate of injurious falls in the general population of France mirror the statistics found in their study, 71,000 injurious falls could be expected every year in those >80 years. Of those falls 20,000 would be related to benzodiazepine use. Of those 20,000 falls, 1,800 would be fatal. In those below the age of eighty a strong correlation could not be defined (Pariente, et al., 2008).

In a study conducted by Dr. Bula, of Centre Hospitalier Universitaire, Lausanne, Switzerland, no correlation was found between injury and those using benzodiazepines chronically as opposed to those who were non-chronic users. Dr. Bula's team followed 304 patients above the age of seventy-five for a six month period. However, chronic users of benzodiazepines were noted more likely to become delirious during their stay in the hospital. As mental impairment is one of the negative side effects associated with benzodiazepine use, it is possible that the chronic users also experienced other negative side effects which went unobserved by Dr. Bula's team.

"Driving Under the Influence"

As benzodiazepines are known to affect cognition, especially in elderly populations, driving under the influence of benzodiazepines has become an issue. The rate of car accidents per mile involving elderly people is double than of those who are middle aged. Slowed reaction time, impaired joints, and vision problems are often to blame. A study conducted by McGill University in Montreal brought attention to a new culprit. The study examined the driving records and related documents of 225,000 people between the ages of 67 and 84. A rate increase of 45% was found in the number of car accidents resulting in injury involving those who had started taking benzodiazepines within the week prior to the accident. It is thought that during this time the patients were

still adjusting to the side effects of the drug such as daytime drowsiness and overall slower motor coordination. However, even among those who had assumedly already adjusted to the medication, the rate of accident was 26% higher among those taking benzodiazepines for as long as one year than those not receiving the medication. In addition, long-lasting benzodiazepines which linger in the blood stream for longer periods of time were related to higher rates of accidents (“Driving Under the Influence,” 1997).

Of Doctors and Dependence

Doctors’ disregard for the guidelines of benzodiazepine administration can lead to many negative side effects including toxicity, difficulty sleeping, falls, and impaired motor skills. Unfortunately, doctors commonly continue to prescribe benzodiazepines to their elderly patients although they are only recommended for short-term use.

In a unique study conducted by a collaboration of doctors and professors from various parts of the United States, doctors were questioned about their seemingly irresponsible practice. Their reasoning was usually centered on the fact that their patients were old and in need of peace or sleep, and the doctors were sought to provide whatever relief they could. They were not very concerned with the patients becoming dependent or addicted, as many doctors felt that little harm would come if their patients could continue to take safe dosages of benzodiazepines for the rest of their lives. Others feared that stopping a patient’s benzodiazepine supply would cause them to lose the patient. They believed that a patient who is accustomed to taking a certain benzodiazepine would simply switch to another doctor who would provide the desired prescription. Below are some of the more memorable responses provided by the doctors as to why they continually prescribe benzodiazepines despite the risks:

“You’d like to say, well, I can just put a great big brick wall in front of me and the patient with benzodiazepines but it doesn’t work that way,.. You feel like you’ve gotta give the patient something to help.”

“It’s literally like taking candy from a baby and people that have enjoyed the effects of that class of drugs don’t wanna give it up. I can’t lose patients over this.”

“It’s just so much easier to just prescribe something and just walk away.”

“I’m not worried about fifteen or twenty years down the road I’m gonna still be giving her Ativan. She’s not gonna be alive in twenty years down the road and I’m sort of surprised she’s alive now... She really needs it. If it helps her get through her days better, great.”

All the doctors interviewed were aware that there were additional risks involved in prescribing benzodiazepines to elderly patients. Many of the doctors interviewed seemed to be making their decisions on moral grounds rather than on scientific ones. While some find fault in the practices of these doctors, many actually agree with their practices believing that if monitored, benzodiazepine dependence can benefit the patient while doing minimal harm (Cook, et al., 2007).

CONCLUSION

In order to prevent the negative side effects associated with long-term exposure, benzodiazepines should not be administered or taken for extended periods of time. Patients should adhere to the dosages prescribed by their doctors and not seek to increase their doses or obtain additional dosages from other sources. In the event that a patient does become dependent on benzodiazepines, dosages should be reduced gradually. Long-acting drugs may be replaced by short-acting

ones to aid the gradual withdrawal process. Anti-convulsants are also used to curb anxiety which may arise as a result of withdrawal. These methods of weaning a patient off of benzodiazepines can minimize the backlash of symptoms which usually accompany withdrawal.

While most authorities claim that benzodiazepines are rarely abused by the general population, those who abuse other substances are highly susceptible to abusing benzodiazepines. Doctors are warned to take care when prescribing benzodiazepines to substance abusers; some even suggest that doctors avoid prescribing it to that demographic altogether. If a patient who is a substance abuser must be prescribed benzodiazepines, his intake should be carefully monitored.

Elderly patients are believed to be more susceptible to the side-effects associated with taking benzodiazepines. Therefore, additional care should be taken to ensure they receive proper dosages. The effects the drug may have on the patient should be observed in order to evaluate if the patient is able to drive safely and perform other daily tasks unimpeded.

As benzodiazepines are highly beneficial and an effective treatment for the treatment of insomnia and anxiety, they should be prescribed for the general public. However, extra care should be taken when prescribing the drug to those demographics which are additionally susceptible to the negative side-effects and risks posed by the use of benzodiazepines.

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