Attitudes Toward Benzodiazepines Over the Years

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Benzodiazepines have been used extensively for the treatment of anxiety and related disorders since the 1960s. Although they have been proven to be effective as first-line treatment for anxiety disorders, during the 1980s public perception and concern for abuse liability and physical dependence with long-term use gave rise to a great deal of controversy. Negative perceptions toward the use of benzodiazepines for treating anxiety not only caused severely ill patients to go untreated or undertreated but also called into question whether the illness itself was worthy of treatment. Although new pharmacologic and psychological treatments for anxiety are available, psychopharmacologists continue to endorse benzodiazepines as primary or adjunct treatment for anxiety disorders. The intent of this article is to provide a historic overview of these issues and to offer some general clinical principles to help minimize the risk of abuse and dependence with benzodiazepine use.

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A recent case study, described by Samantha A. Stewart, M.D., elsewhere in this supplement,[1] brought to light the need for an update on the current state of benzodiazepine use in patients with anxiety. Dr. Stewart raises many pertinent issues reminiscent of issues that have been raised over the decades, and her case provides an opportunity to examine controversies about the use of benzodiazepines in clinical practice.

During the mid-1980s and early 1990s, I reviewed the patterns of benzodiazepine use at a meeting of the American College of Psychiatrists. In this article, I will provide a retrospective of my notes from 15 to 20 years ago in terms of our understanding and use of benzodiazepines then, as well as offer some insight into their use today.

OVERVIEW

Benzodiazepines became widely available in the 1960s and have been prescribed to hundreds of millions of people over the past 4 decades. Benzodiazepines are effective antianxiety and hypnotic medications and have favorable side effect profiles compared with other psychotropic medications. The rapid onset with low toxicity and the desirable therapeutic actions of benzodiazepines as anxiolytics, sedatives, anticonvulsants, and muscle relaxants[2] have led to their continued use in treating anxiety disorders today. Side effects include sedation and ataxia, but these are usually not sustained, and there are no known irreversible effects from long-term administration. Tolerance to antianxiety effects appears rare, and the biological mechanisms of action of benzodiazepines are among the best understood of any intervention. Benzodiazepines offer symptomatic relief for some of humankind's most prevalent and distressing conditions.

Despite the favorable aspects of benzodiazepine use, 3 issues have caused confusion and concern over the years: (1) a trivialization of anxiety disorders, which was implicit in the anti–benzodiazepine sentiment during the 1980s, (2) a concern that these agents were being overprescribed and abused, and (3) a concern for potential physical dependence and withdrawal reactions when discontinued.

TREATMENT ATTITUDES

During the 1980s, depression and psychosis were viewed as biological illnesses, while persistent anxiety was not. Not treating someone who would benefit from medication is underprescribing, and not using adequate doses (as with antidepressants) is undertreatment. A review of data from a 1979 survey[3] of patients meeting DSM-III criteria for generalized anxiety disorder (GAD) revealed that only 27% had received a benzodiazepine in the prior year. Patients either received a benzodiazepine for anxiety or no treatment at all; of patients who met clinical criteria for treatment of anxiety and were candidates for therapy, 73% went without medication. A decade later, the situation had not improved. A 1990 review[4] of Epidemiologic Catchment Area data indicated that the

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majority of anxious patients with high levels of psychic distress had not received drug treatment.

The treatment concerns of the 1980s carried into the 1990s, although fewer patients went untreated because of newer antidepressants being used for anxiety. Nearly one third of patients in a 1989–1991 sample of adults with anxiety disorders did not receive any medication for treatment of their anxiety disorder; in a 1996 follow-up, almost one third still were not receiving medication.[5] There was a decrease in benzodiazepine treatment and an increase in antidepressant treatment in 1996 for GAD patients who did not have comorbid depression or another anxiety disorder. These findings represented a shift in the type of medications prescribed for GAD, from exclusive benzodiazepine treatment to the combination of benzodiazepine and antidepressant treatment.

The underprescription of benzodiazepines in the 1980s was fueled by the perception that patients who sought treatment for their anxiety (particularly with benzodiazepines) were seeking a "high" or a "buzz," which distorted the truth about the anxiolytic effects of these agents as well as the need for treatment. Implicit in the anti–benzodiazepine sentiment was a trivialization of anxiety disorders and anxious distress. The idea was that anxiety is always transient, a reflection of the human condition, and stands for or is a symptom of something else. Systematic scrutiny[6] of anxious patients in the 1990s helped reverse some of this prejudice by confirming that patients who receive treatment are ill, have high levels of psychic distress, and generally meet criteria for anxiety or panic disorders. Since severe anxiety has been associated with a high risk of suicide,[7–10] the price paid for undertreatment is quite high. The change in attitude toward anxiety disorders and the introduction of antidepressants that are effective against anxiety led to less undertreatment of these disorders, although concern about abuse liability and physical dependence remained associated with benzodiazepines.

ABUSE LIABILITY

Concern over the chronic use and potential abuse of benzodiazepines motivated a comprehensive probability-based national household survey of the medical use of psychotherapeutic medication conducted in 1979 and published in 1984.[3] Findings from this study showed that long-term use (i.e., daily for ≥ 1 year) of anxiolytics was relatively rare, occurring among only 15% of all anxiolytic users, which is a rate of 1.6% of all adults between the ages of 18 and 79 years in the general population. In regard to benzodiazepines specifically, 11% of the U.S. population had used a benzodiazepine in the past year. Occasional use, defined as using the medication for 1 to 2 days at a time, was reported by 45% of the population, and two thirds reported using these agents regularly for periods less than 2 weeks. Eighty percent of those who had used benzodiazepines in the past year reported that the longest period of daily use was less than 4 months.

The authors concluded that many chronic benzodiazepine users are older, meet diagnostic criteria for anxiety disorders, and have multiple health problems.[3,11] These patients are usually monitored by their physicians at regular intervals. The study did not support the stereotype of benzodiazepine users. Studies in the 1990s found that, except in patients with preexisting chemical dependency, abuse of benzodiazepines is rare.[12] While experts agree that benzodiazepines pose a higher risk of dependence and abuse than most potential substitutes, they pose a lower risk than older sedatives and recognized drugs of abuse.[13] However, in the 1980s, in response to the perceived addictiveness of benzodiazepines, some states (New York, for example) and some countries enacted legislation[14] (a triplicate prescription program) intended to regulate indiscriminate prescribing of benzodiazepines and quell concerns of the potential for addiction and abuse with long-term use. The New York State triplicate prescription program took effect on January 1, 1989. The initial response was large decreases in benzodiazepine prescriptions but large increases in prescriptions for older, less safe therapeutic agents such as meprobamate and methyprylon (Table 1).[15] A retrospective analysis[16] of sedative-hypnotic overdose in New York City for the years 1988 and 1989 showed that while there were fewer total benzodiazepine overdoses in 1989 compared with 1988, there was a statistically significant increase in nonbenzodiazepine sedative-hypnotic overdoses. In 1990, the American Psychiatric Association Task Force on Benzodiazepines concluded that benzodiazepines are not drugs of abuse, although benzodiazepine abuse is common among people who are actively abusing alcohol, opiates, cocaine, or sedative hypnotics.[17]

In fact, anxiety may be a causal risk factor for alcoholism. Anxiety disorders that can be comorbid with alcoholism include panic disorder, social phobia, obsessive-compulsive disorder, GAD, and posttraumatic stress disorder.[18] Although treatment of an anxiety disorder can rarely, if ever, be expected to cure alcoholism, the identification of and treatment for the anxiety would be expected to improve the prognosis for the alcoholism or help to prevent its progression if caught early. Ciraulo et al.[19] reviewed the literature on benzodiazepine use among alcoholics exposed to these drugs during detoxification who were continued on them for the treatment of anxiety and insomnia and found that prevalence of use was greater than in the general population but comparable to other groups of psychiatric patients. Because alcoholics appear susceptible to benzodiazepine abuse, physicians must endeavor to rule out chemical dependency in their patients prior to initiating treatment with benzodiazepines.

By 1999, an international group of experts recommended the use of benzodiazepines for anxiety disorders, even for long periods.[13] Most experts today would de-

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Table 1. Effect of New York State Benzodiazepine Restrictions on Alternative Psychotherapeutic Medications Prescribed in 1988 and 1989 (in thousands of prescriptions)[a]

	New York State			US Total Minus New York State		
Medication	1988 (95% CI)	1989 (95% CI)	% Change	1988 (95% CI)	1989 (95% CI)	% Change
Meprobamate	122 (118–126)	275 (268–282)	+125	2005 (1983–2027)	1826 (1803–1848)	–9
Methyprylon	22 (21–24)	41 (39–43)	+84	123 (119–127)	104 (100–108)	–15
Ethchlorvynol	17 (15–18)	22 (21–23)	+29	218 (212–224)	178 (172–184)	–18
Butabarbital	46 (44–48)	60 (57–63)	+31	715 (703–727)	608 (596–620)	–15
Hydroxyzine	530 (520–540)	608 (597–619)	+15	6829 (6783–6875)	6756 (6710–6802)	–1.1
Chloral hydrate	43 (41–45)	102 (98–106)	+136	529 (519–539)	527 (517–536)	–0.4
Buspirone[b]	154 (149–159)	333 (325–341)	+116	1782 (1761–1803)	2194 (2173–2215)	+23.1
Fluoxetine[b]	147 (142–152)	356 (341–371)	+142	2754 (2727–2780)	5778 (5751–5805)	+109.8

[a]Data from Weintraub et al.[15]
[b]Prescriptions for new anxiolytics (buspirone) and antidepressants (fluoxetine) as alternatives to benzodiazepines increased both nationally and in New York State.

scribe anxiety disorders as recurrent or chronic disorders requiring treatment beyond the short term. These disorders are not usually cured, but rather controlled. Regular monitoring is important in patients who are prescribed benzodiazepines over the long term, especially because physical dependence can develop over time.

PHYSICAL DEPENDENCE

Physical dependence has traditionally been considered to be present when discontinuation of a medication results in a withdrawal syndrome that has a predictable onset, duration, and course and that can be suppressed by readministering the medication.[20] Benzodiazepine discontinuation syndrome is characterized by rebound anxiety, agitation, insomnia, and sensory disturbances and is worsened by longer administration, higher dose, and abrupt discontinuation.[21–24]

Studies[21,25,26] in the early 1980s indicated that regular, long-term administration of benzodiazepines at therapeutic dosage levels can produce physical dependence, leading to symptoms of withdrawal upon abrupt termination (rather than gradual taper). In addition, a 1990 comparison[27] of the effects of abrupt discontinuation of therapeutic doses of short half-life versus long half-life benzodiazepines revealed that discontinuation syndrome occurred earlier and was more severe with short half-life than with long half-life benzodiazepines. Hence, it is always recommended to gradually taper benzodiazepines when attempting to discontinue them, especially with short half-life agents.[21–24,27,28]

Although discontinuation syndrome is an almost inevitable consequence of abruptly stopping even modest therapeutic doses of a benzodiazepine, and ongoing benzodiazepine use even without dose escalation can lead to discontinuation syndrome,[27] withdrawal distress is associated with almost all psychotropic therapies, including β-blockers and tricyclic antidepressants, yet these patients are not labeled as physically dependent. Even the selective serotonin reuptake inhibitors (SSRIs), which were heralded as safe and effective treatments for depression and anxiety in the late 1980s and the 1990s, came to demonstrate a discontinuation syndrome.[29] People misunderstand the difference between physical dependence and abuse. Dependence only means care must be taken when stopping the drug; dependence does not imply abuse, drug-seeking, or lack of benefit.

Patients who have tolerated and responded to benzodiazepine treatment without excessive side effects are frequently reluctant to discontinue and often relapse upon discontinuation. Clinicians must distinguish rebound symptoms from relapse. Some studies[28,30] have shown that subgroups of patients who are unable to discontinue with slow taper alone successfully discontinued by using combined drug taper and behavioral techniques.

While long-term treatment could be necessary, some general clinical principles may help to minimize the necessity of chronic benzodiazepine treatment for acute problems, and thereby minimize physical dependence. First, distinguish acute symptomatic distress driven by recent psychosocial events from an Axis I disorder. Second, at the outset of treatment, provide patient information about the goals and limitations of benzodiazepine pharmacotherapy, including the meaning of physiologic adaptation and its implications. Third, adopt a dynamic stance to treatment designed to determine the lowest effective dose, reevaluate in the short term and over the long term, and make intermittent, structured attempts to taper.

CONCLUSION

Twenty years ago, my predictions for the foreseeable future were that benzodiazepines would remain a pharmacologic mainstay of the clinical management of anxiety and that new developments in understanding of the pharmacologic modification of benzodiazepine receptor efficacy would yield therapeutic strategies to diminish the chief clinical concern of physical dependence and the attendant possibility for some patients of discontinuation syndrome. To some extent, the initial success of buspi-

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rone, which became available in the late 1980s, reflected the promise of a nonbenzodiazepine agent with efficacy for anxiety. With a slow onset of action (as long as 4 weeks to full therapeutic effect), buspirone lacked the reliable early efficacy of the benzodiazepines but may have been more suitable than benzodiazepines for the treatment of some chronically anxious patients.[31]

In the 1990s, many clinicians favored benzodiazepines with relatively short half-lives over longer-acting agents because of their lower risk of cumulative sedation, psychomotor impairment, and amnestic effects.[32,33] At the same time, many other clinicians favored drugs with long half-lives because they are less likely to produce an intense discontinuation syndrome.[32,34] Today, newer antidepressant medications, particularly SSRIs, have become increasingly recognized as the pharmacologic treatment of choice for several anxiety disorders,[35,36] despite their lack of a broad-spectrum acute anxiolytic effect. Recent analyses[37] of service utilization data between 1987 and 1999 from 2 nationally representative surveys indicated a trend toward declining use of benzodiazepines, although they continued to be used by nearly one third of outpatients treated for anxiety disorders in 1999. Some expert psychopharmacologists continue to endorse benzodiazepines as a primary or adjunct treatment for several anxiety disorders.[13]

Given the heterogeneity of patients and disorders for which benzodiazepines are prescribed alone or adjunctively, no set of guidelines serves all, but increased circumspection with respect to prescribing is in order for those with previous chemical dependency[18] and for the elderly.[11,38–41] Prescribing is not carefree but requires monitoring to obtain an optimal benefit-risk ratio. The lowest effective dose and duration should be used. Intermittent reviews for possible taper and discontinuation are clearly necessary. The use of supplemental medication or behavioral therapy to enhance taper is a promising strategy. With increased understanding of the mechanisms of physical dependence may come efficient and effective strategies for minimizing discontinuation symptoms.

Regular, long-term use of benzodiazepines was controversial in the 1980s despite the fact that benzodiazepines are less toxic in overdose than alternatives, are safe, and have little liability for abuse among patients without a history of abuse. The essential clinical questions of the 1980s were: Do people who get benzodiazepine treatment merit it? and Do people who merit treatment for anxiety get it?

Today's answer to the first question is a positive one. Over the last several years, substantial progress has been made both in the recognition of anxiety as a disorder and in the pharmacologic and psychological treatment of anxiety disorders. Benzodiazepine-treated patients are not automatically viewed as drug-seekers like the old stereotype. But the answer to the second question reveals little progress. Many people with anxiety disorders do not receive any treatment for their symptoms. Benzodiazepines or other treatments can be used safely to provide these patients with relief.

Drug names: buspirone (BuSpar and others), butabarbital (Butisol Sodium and others), fluoxetine (Prozac and others), hydroxyzine (Vistaril, Atarax, and others), meprobamate (Miltown, Tranmep, and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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