Having practised during the era when barbiturates were used as anxiolytics and hypnotics, I have a great appreciation for benzodiazepines. Unlike barbiturates, sudden withdrawal was never fatal, and suicide was virtually impossible if benzodiazepines were used alone. The first drug of this class, chlordiazepoxide (Librium) was approved in the USA in 1961, followed by diazepam (Valium) in 1969, which stayed at the top of the best-selling prescription drug list for a decade. Originally touted as having neither addiction potential nor causing a withdrawal syndrome, anecdotal reports in the late 1970s followed by more reliable reports in the 1980s established some evidence of abuse potential and discontinuation symptoms. Although these problems were relatively mild, sensationalistic lay press reports fuelled a perception that benzodiazepines were overused, dangerous drugs, and some states, such as New York, made them controlled substances, subject to similar prescribing restrictions as narcotics and barbiturates.


Concerns about the dangers of benzodiazepines prompted the American Psychiatric Association to convene a task force to review the drugs’ potential hazards. The Task Force Report, published in 1990, attempted a rational, evidence-based review of patterns of prescribing, clinical use, dependence, toxicity and abuse. This chapter examines prescribing, short and long-term use, and dependence, and concludes that “general concerns about the over-prescribing and misuse of medications often do not hold up when they are translated into specific research questions and confronted by relevant data”.

Moreover, the Task Force noted that 60% of people who were legitimate candidates for anxiolytics had never sought or received any treatment.

Roy-Byrne’s report is a primary care evaluation of adequacy of treatment for panic disorder. Patients were recruited from primary care clinics in the Seattle area, and diagnosed by questionnaire plus telephone interview. Fifty-eight patients were followed for 1 year, receiving ‘augmented usual care’: the diagnosis had already been made, their physicians received at least an hour of didactics on panic disorder, and medications were provided free. Only half the patients reported taking effective medication (antidepressants or tranquillizers); the majority of patients received selective serotonin uptake inhibitors (SSRIs). Benzodiazepines were used in 25 instances (often in combination with an SSRI), but in all cases they were used in inadequate dosages and duration. The authors conclude that panic disorder is undertreated in primary care, even in this ‘best case’ scenario.

Comment

The Task Force Report, although over 10 years old, is still a standard reference for benzodiazepine use. Its points—that there is undue reluctance to use minor tranquilizers, and that many people are undertreated—still hold, and are borne out by the Roy-Byrne study. Other relevant literature includes a review of 2719 adult out-patient charts (medical and psychiatric) for evidence of benzodiazepine abuse that found no patients meeting the criteria. Another study, of long-term alprazolam users, found no dose escalation with long-term use.3 Tyrer’s 19884 paper on minor tranquilizers notes an absence of evidence that benzodiazepine dependence leads to dangerous long-term sequelae, and blames “excessive media attention” for distortion of scientific attitudes.

Shader RI, Greenblatt DJ. Use of benzodiazepines in anxiety disorders. N Engl J Med 1993; 328: 1398–1405. The section ‘Choice of specific medication’ suggests that with benzodiazepines as a class, the similarities are more striking than the differences, with trials comparing different drugs failing to demonstrate consistent differences in efficacy. All are more effective than placebo. Physician
preferences and marketplace forces made diazepam the leader until the early 1980s, when alprazolam was introduced; it supplanted diazepam by 1988. In recent years, clonazepam prescribing has markedly increased. Even for panic disorder, for which alprazolam is FDA-approved, other benzodiazepines (clonazepam, diazepam and lorazepam) are similarly efficacious.

Comment
All benzodiazepines work by potentiating γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter of the brain. They vary in rapidity of onset and duration of action. In theory, a drug that is effective quickly promotes reinforcing behaviour and, consequently, abuse—more so than one with a slow onset. Thus, diazepam (rapid onset) was preferred by drug abusers to the slower-acting oxazepam. In Sweden, where oxazepam was prescribed more frequently than diazepam, most prescription forgeries were for diazepam. Intermediate-acting alprazolam and lorazepam appear to have similar abuse potential to diazepam. Triazolam (also rapid-onset) produced similar drug-liking scores to diazepam in sedative abusers. Withdrawal symptoms occur sooner and are more severe with short half-life drugs (e.g. alprazolam and lorazepam) than in those with long half-lives (valium and clonazepam). The recent increase in clonazepam use is partially due to a perception that this drug has less abuse potential. A patient of mine, however, informs me that clonazepam is available for illicit sale at her Alcoholics Anonymous meetings. Shader and Greenblatt’s point on the overall similarities of the benzodiazepines is well taken.


Shader’s review in the section ‘Initiation and maintenance of treatment’ comments on need for long-term use. Duration of treatment should be tailored to underlying illness. Patients with persisting, unremitting symptoms may require continuous treatment. Symptoms frequently return when benzodiazepines are discontinued (or when placebos are substituted). While most people do not need prolonged therapy, some with anxiety or panic disorder may need to be treated indefinitely to lead productive and comfortable lives.

Salzman’s Clinical Crossroads describes a painful tug-of-war between an elderly woman who has been maintained for many years on alprazolam, 1 mg. q.i.d., and her doctor’s attempts to taper it off. The patient cannot comprehend what the problem is, and the doctor, despite obsessively pushing the patient to reduce the drug, is not so sure either. Ultimately, some equilibrium was achieved with paroxetine 10 mg. q.d. and alprazolam 5 mg. b.i.d. The discussant comments that addiction, which implies deliberate misuse, is not the same as dependence, and that drug discontinuation syndromes are not unique to psychotropics. He also feels benzodiazepine dependence may not be significant, provided the medication is effective and safe, and restates the point that long-term administration commonly is helpful for chronic medical illnesses and anxiety disorder, citing the Task Force report as a reference.

Comment
The US Federal Drug Administration (FDA) labelling includes the caution that benzodiazepines have not been studied systematically beyond 4 months’ usage; an occasional letter from a managed care organization reminds me of this. However, as stated above, there are situations where chronic use becomes appropriate. The need for continuing therapy should be reassessed periodically. Discontinuation should be attempted, gradually, after several months’ therapy, and return of symptoms helps to identify the subgroup that requires long-term therapy.

There are factors that suggest benzodiazepine usage may become chronic. A prior history of substance abuse confers an increased risk of dependence and difficult withdrawal. To some extent, a family history does the same. Even social drinking is associated with more difficult withdrawal. Patients with borderline personality disorder are at great risk for dependence, and benzodiazepines are contraindicated. Withdrawal symptoms can occur after only 8 weeks of therapy. Dosage level generally does not affect withdrawal, provided that the drug is tapered. Some observers feel that those in need of chronic therapy should take regular daily dosing, not merely ‘as needed’.

It should also be noted that studies on abuse potential were done on patients with pre-existing substance abuse. These patients clearly prefer barbiturates and methaqualone to benzodiazepines (and prefer benzodiazepines to buspirone). Blinded studies of healthy volunteers or of subjects with anxiety disorder (without substance abuse history) show no preferences for benzodiazepines over placebo.


The ‘epidemiology of vascular aging’ (EVA) study was conducted on non-institutionalized volunteers in Nantes, France. A total of 1389 subjects (mean age 65 years) were interviewed at baseline, 2 and 4 years, and assessed for benzodiazepine usage and cognitive functioning. The latter included the Mini-Mental State Examination.
(MMSE). It was determined that 22.4% of the sample took benzodiazepines on at least one occasion. Users were classified as episodic, recurrent or chronic, depending on whether medications were being taken at one, two or all three intervals. Only chronic users differed from non-users, with a three-point or greater drop in MMSE score being the parameter of decline. Fifteen per cent of non-users and 26% of chronic users evidenced decline, the absolute risk (over 4 years’ regular use) being 11%.

Wang’s retrospective study of 1222 hip fracture patients in New Jersey (mean age 82 years) finds a relative risk increase of ~50% for moderate-dose benzodiazepine takers. No absolute risk figure is available. Unlike previous work, shorter half-life agents were no safer than those with longer half-lives.

Comment
In a 1984 study, 33% of all long-term benzodiazepine users were elderly. Long-term users tend to be older, and sicker. The first report of hip fracture increase (1987) found that hypnotics–anxiolytics with short half-lives did not increase the risk, while long-acting preparations did, although slightly less than antidepressants and antipsychotics. Drug absorption and metabolism are slower in the elderly, while target receptor sensitivity is increased, resulting in greater sedation, ataxia and paradoxical excitement. Dosing should be lower in the elderly, and some consider lorazepam or oxazepam to be the best benzodiazepines for this population, due to short half-lives and favourable metabolism and clearance. Tapered benzodiazepine withdrawal was tolerated better in a group of habituated elderly than in comparable younger patients.

Final considerations
Benzodiazepines are relatively safe drugs that are probably under- rather than overprescribed. Periodic reassessment of chronic users is appropriate, although generalized anxiety disorder and panic disorder are chronic conditions for which long-term treatment may be necessary. In the more recent era of safer antidepressants, these agents may be able to supplant minor tranquilizers for the control of chronic anxiety in many patients. Long-term benzodiazepine use is appropriate for some patients.

References