History of Benzodiazepine Dependence

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Abstract — The benzodiazepines were developed in the 1950s, some introduced in the 1960s, and many more since then. Pharmacologically, they are sedative/hypnotics akin to alcohol, chloral, the barbiturates, and meprobamate. All have been widely used both within and outside the licit medical context. Usage of benzodiazepines increased dramatically during the 1960s and early 1970s; tranquilizer but not hypnotic usage has since declined. Both abuse and misuse were documented early, but the incidence was deemed low in view of the widespread prescription. Normal-dose physical dependence was first suspected in the early 1970s but it was not until the early 1980s that scientific evidence was adduced to establish its reality and frequency. Further studies have revealed the complex nature of the withdrawal syndrome. A reaction has set in against these drugs, with attempts to limit them to short-term use.

Keywords – alprazolam; dependence; benzodiazepines; dose; abuse.

INTRODUCTION

THE BENZODIAZEPINES WERE DEVELOPED in the 1950s and many were introduced in the 1960s. Many of the people involved in the story of the benzodiazepines are still active in psychopharmacology and psychiatry. Any attempt at a history of one particular aspect of the benzodiazepines must inevitably be impressionistic because many issues are still unresolved and the contributions of various individuals to the topic too recent and even current to be assessed dispassionately. This historical approach is even more difficult for a medical scientist like myself who has worked continuously on the benzodiazepines for 30 years. During the latter half of that time, my views on the benzodiazepines became increasingly maverick, although in the U.K. at least the consensus has moved close to my viewpoint.

This essay, therefore, must be seen within the context of looking back at events well within a single professional lifetime, within the geographical limitations of concentrating on one country, the U.K., and within the biases inescapable in one so long involved in con-

troversy. I have attempted to give a balanced account; the reader must judge if I have succeeded.

BEFORE THE BENZODIAZEPINES

"And Noah . . . planted a vineyard: and he drank of the wine, and was drunken. . . ." Despite this, the Bible tells us that Noah survived for many years. The use of alcohol goes back about 8000 years and it is probable that it originally had a mostly religious and highly controlled role in primitive societies. Later it became used medicinally, often as an anxiolytic and was abused by some. When the Arabs introduced the science of distilling into Europe in the Middle Ages, the alchemist and his customers hailed alcohol as the long-sought elixir of life. The Gaelic "usquebaugh," meaning water of life, the term for whiskey, was regarded as a panacea. But by the 18th century with the introduction of cheap gin, the curses of alcohol had become apparent.

Opium also has a history extending over thousands of years and was regarded by Sydenham in 1680 as the most universal and efficacious of "the remedies which it has pleased Almighty God to give to man to relieve his sufferings." Like alcohol, opium and its derivatives were also taken to relieve anxiety. Like alcohol, its addictive properties became increasingly ap-

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parent. During the 19th century, De Quincey, a habitué, dubbed it "dread agent of unimaginable pleasure and pain."

The 19th century also witnessed the effects of the Industrial Revolution, transforming alchemy into chemistry and old wives' nostrums into pharmaceutical remedies. Nitrous oxide was introduced as a dental and surgical anesthetic, as were ether and chloroform. The first psychotropic drug to institute the noble tradition of introduction by mistake was bromide. Because potassium bromide was believed to lessen sexual urges and because epilepsy was thought to be a consequence of masturbation, bromides were introduced by Locock for the treatment of epilepsy, apparently with gratifying results! By the 1870s, bromides were used very widely as sedatives and, again, the dependence potential eventually became apparent.

Two organic chemicals were synthesized and introduced as sedatives. Chloral hydrate has retained some usage in its solid derivative forms in the elderly; paraldehyde, however, is obsolete: both are associated with abuse and dependence.

The most widely used synthetics were the barbiturates. Barbituric acid was prepared by Adolf von Baeyer working in Kekule's laboratory. The first hypnotic barbiturate, Barbital ("Veronal"), was introduced by Fischer and von Mering in 1903, followed by phenobarbital ("Luminal") in 1912. Amobarbital came on the market in 1923. About 2500 barbiturate compounds were synthesized over the succeeding years and about 50 were marketed, of which a dozen or so survive. The dependence-producing potential of these compounds became increasingly apparent and together with alarm over the dangers in overdose led to campaigns in the 1970s to replace the barbiturates with the benzodiazepines. Other compounds with similar pharmacological properties were introduced but met a similar fate as their dependence potential and toxicity became apparent. They include ethchlorvynol, ethinamate, carbromal, glutethimide, methyprylon, and methaqualone.

The story of meprobamate, in retrospect, seems like a dress rehearsal for that of the benzodiazepines. This story begins with the discovery of mephenesin in 1946 by Berger and Bradley (Berger, 1970). Mephenesin is a muscle relaxant with too short a duration of action for clinical use in anxiety disorders. Meprobamate ("Miltown", "Equanil") was developed in 1950 as a longer-acting compound. It was widely promoted and widely prescribed as an anxiolytic, but was found to have an alarming dependence potential. By 1964, there existed "ample evidence that it could induce physical dependence in man" (Essig, 1964). Although still available, and indeed quite widely used in some countries because of its cheapness (as are the barbiturates), it has been largely supplanted by the benzodiazepines.

THE INTRODUCTION OF THE BENZODIAZEPINES

The story of the benzodiazepines begins in Cracow in Poland in the mid-1930s. Dr. Leo Sternbach was working on a chemical grouping called the heptoxdiazines (Sternbach, 1980). He went to the USA and resumed work on these compounds in the Chemical Research Department of Hoffmann-La Roche, U.S.A. in Nutley, New Jersey. They seemed biologically inactive. However, one Ro#5-0690, was investigated further and in 1957 was found to have hypnotic, sedative, and antistrychnine effects similar to those of meprobamate (Cohen, 1970). To the surprise of the chemists, this compound was found to have undergone a molecular rearrangement to become a 1:4 benzodiazepine.

The first clinical tests nearly led to the drug (then called methaminodiazepoxide, and later called chlor-diazepoxide) being discarded because it was given in too large a dose to geriatric patients, resulting in dysarthria and ataxia. Eventually, its clinical effectiveness was established, and it was introduced in 1960. Its even more successful congener, diazepam, followed in 1963.

Many other compounds were introduced either as daytime anxiolytics ("tranquilizers") or nighttime hypnotics or both. The most successful have been nitrazepam, flurazepam, temazepam, and triazolam as hypnotics, and diazepam, lorazepam, and alprazolam as tranquilizers. The last is the current market leader in terms of value. The dates of introduction in the U.K. of various benzodiazepines in terms of dosage forms are shown in Table 1. The market for anxiolytics is currently worth \$2 billion worldwide, that for hypnotics \$650 million.

THE GROWTH OF BENZODIAZEPINE USAGE

There is no doubt that the usage of benzodiazepines increased dramatically during the 1960s and early 1970s. This gave rise to the perception that the widespread use of anxiolytics and hypnotics is a new phenomenon, reflecting the latter half of the 20th century as an "Age of Anxiety." Nothing could be further from the truth. The growth in benzodiazepine usage has been almost entirely at the expense of older products, notably the barbiturates. This change was encouraged by the pharmaceutical industry as newer, more profitable benzodiazepines replaced the older barbiturates.

In 1975, the year in which benzodiazepine sales peaked in the U.S.A., total anxiolytic and hypnotic sales accounted for about 10% of all prescriptions, only a percent or so higher for those in the 1950s and 1960s. Since 1975, sales of anxiolytics declined until about 1981 and have since risen slightly. In the U.K.,

TABLE 1
Year of Introduction of Benzodiazepines to U.K.

Generic Name	Brand (Manufacturer)	Sold Since
1. Chlordiazepoxide	Librium et al. (Roche)	1960
2. Diazepam	Valium et al. (Roche)	1963
3. Nitrazepam	Mogadon et al. (Roche)	1965
4. Oxazepam	Serenid (Wyeth)	1966
5. Medazepam	Nobrium	1971
6. Lorazepam	(Roche) Ativan et al. (Wyeth)	1972
7. Clorazepate	Tranxene (Boehringer)	1973
8. Flurazepam	Dalmane (Roche)	1974
9. Temazepam	Euhypnos (FCE)	1977
	Normison (Wyeth)	1977
10. Triazolam	Halcion (Upjohn)	1979
11. Clobazam	Frisium (Hoechst)	1979
12. Ketazolam	Anxon (Beecham)	1980
13. Lormetazepam	Noctamid (Schering)	1981
14. Flunitrazepam	Rohypnol (Sauter)	1982
15. Bromazepam	Lexotan	1982
16. Prazepam	(Roche) Centrax	1982
17. Alprazolam	(Warner) Xanax (Upjohn)	1983

prescriptions are mostly dispensed through the National Health Service. About 15% of all prescriptions are for hypnotics and anxiolytics. Again this figure has hardly changed in the past decades. Prescriptions for anxiolytic benzodiazepines in the U.K. have fallen considerably since 1975, but those for hypnotics have remained steady. Indeed, now, more prescriptions are written for hypnotics than for anxiolytics.

Nevertheless, such replacement of one group of sedative/hypnotics for another is no reason for complacency. Firstly, the use of medicines generally has been increasing, partly but not entirely as a result of changing demography, with an increasing proportion of elderly in the population. Therefore, the absolute amount of anxiolytic and hypnotic use has been increasing in many Western countries. Secondly, much of the usage of sedatives and hypnotics may always have been excessive and inappropriate, perhaps based on habituation and dependence.

ABUSE AND DEPENDENCE

The confusions and controversies that have attended the history of benzodiazepine dependence reflect those more generally in the addiction field (Lader, 1988). The lack of consensus among experts concerning the dependence potential of the benzodiazepines hinges on whether the reality of normal therapeutic dose physical dependence can be established to each expert's satisfaction. Until recently, dosage escalation was regarded as a cardinal and essential feature of dependence, that is, tolerance was inextricably linked to dependence and abuse.

Consequently, it is helpful to distinguish, however arbitrarily, between three main conditions:

- 1. *Drug abuse* with regular or intermittent selfadministration of large doses of benzodiazepines, outside the medical context. Drug-seeking behavior is the rule.
- 2. Drug misuse with regular oral ingestion of large amounts of benzodiazepines, sometimes but not always obtained on prescription. Such usage typically starts within the medical context, but the dosage is increased beyond normal therapeutic levels. If supplies are restricted, drug-seeking behavior ensues.
- Physical dependence at normal therapeutic doses as manifested by a withdrawal syndrome of the sedative/alcohol type on discontinuation, abrupt or tapered. Drug-seeking behavior will occur if injudicious attempts are made to restrict the supply.

Too often, data obtained concerning one type of problem has been used injudiciously to support a viewpoint concerning another type of dependence.

ABUSE OF BENZODIAZEPINES

The scientific literature contains many instances of benzodiazepine abuse. Marks collected 151 cases worldwide of benzodiazepine dependence within the framework of multiple drug abuse or alcoholism, plus 250 less definite cases (Marks, 1978). As he points out, assigning individual cases to the "abuse" or "therapeutic" groups is difficult. It is unclear how many people become dependent within the clinical situation, and then resort to the "black market" for excess illicit supplies. Furthermore, the nature and degree of possible benzodiazepine dependence in people who are currently dependent on other drugs and/or alcohol is difficult to estimate.

According to Cooperstock and Hill (1982), polydrug use was a common pattern among some benzodiazepine users. One common pattern that emerged in the 1970s was for opioid abusers to use oral benzodiazepines to "come down" from the "high." However, in the 1980s in the U.K. a more serious abuse emerged. Temazepam was available in liquid-filled capsules and

abusers were extracting the fluid and injecting it intravenously. The burgeoning problem was contained by reformulating the capsules to contain a solid but rapidly absorbed form of temazepam.

In many countries, abuse of benzodiazepines gave rise to alarm and was instrumental in the World Health Organization's recommending the scheduling of benzodiazepines in the early 1980s. Signatories to the 1971 Convention on Psychotropic Substances have brought in Scheduling Regulations, usually of a fairly mild nature.

HIGH-DOSE DEPENDENCE

Two studies carried out in the early 1960s established the potential of the benzodiazepines to induce a physical dependence state when the drug was given in high dose for several weeks. The first involved 36 chronically ill psychiatric patients who were administered 300 to 600 mg/day of chlordiazepoxide for 2 to 6 months (Hollister, Motzenbecker, & Degan, 1961). These doses are several times the usually recommended clinical dose, but the patients tolerated them. The drug was abruptly discontinued in 11 patients with singleblind placebo substitution but because of the long elimination half-lives of some of the active metabolites of chlordiazepoxide, bodily concentrations presumably took some time to dissipate. Depression supervened in 6, and aggravation of the psychoses in 5. Insomnia, agitation, and loss of appetite developed in other patients, and major convulsions supervened in three. Symptoms started about 2 days after cessation of the benzodiazepine, became severe between the 4th and 8th days, and had largely waned by day 10. Parallel data were obtained in the second study involving high doses of diazepam (Hollister, Bennett, Kimbell, Savage, & Overall, 1963).

Thus, the existence of physical dependence in patients taking high doses of benzodiazepines was established right from the initiation of benzodiazepine use. However, as Hollister was to emphasize later, these studies involved very artificial conditions of forced high-dose use for several months. What such studies cannot tell us is how many patients who are started on therapeutic courses of benzodiazepines escalate their doses to such high levels that physical dependence is inevitable.

Throughout the 1960s and 1970s, the scientific literature is peppered with case reports of patients who had escalated their dose of tranquilizer to above the upper limit of the recommended therapeutic range. For example, Peters and Boeters (1970) described eight cases of physical dependence on diazepam, average dose 60–80 mg/day. In another study of two patients, withdrawal from 60 and 120 mg, respectively, was accompanied by convulsions and confusional states (Venzlaff, 1972). Woody and his colleagues (Woody,

O'Brien, & Greenstein, 1975) described two patients taking 100-150 mg of diazepam daily who developed insomnia, tremor, and grand mal seizures on stopping the medication. Bliding (1978) encountered four cases of withdrawal reactions from oxazepam, the most prominent symptoms being anxiety, tension, tremor, and palpitations. Patients within the high-dose category have typically taken 2-5 times the recommended therapeutic doses of the various benzodiazepines.

However, little notice was taken of these reports. Part of the problem was the widespread perception of the safety of the benzodiazepines. During the 1960s, the medical profession realized that the benzodiazepines were surprisingly safe in overdosage, compared with their predecessors, the barbiturates. This awareness coincided with a pandemic of suicidal attempts, particularly in young women. So impressed were the British doctors that they mounted a campaign under the auspices of the British Medical Association to phase out the barbiturates. Implicit in that initiative in the mid-1970s was acquiescence in the growth in use of the benzodiazepines.

Coupled with many reports of the safety of benzodiazepines was the paucity of reports on abuse and misuse, with escalation of dosage. Despite the several hundred reports in the literature, Marks (1978) claimed that only 118 of those published up to mid-1977 contained fully verified cases of physical dependence with a definite withdrawal syndrome or carefully documented cases of psychological dependence. He concluded reassuringly:

Dependence on benzodiazepines occurs rarely under conditions of clinical use and then usually only after prolonged administration at above average dosage. Clinically it resembles that described as "barbiturate" or "alcohol-barbiturate" type. . . . (p. 1)

The dependence risk with benzodiazepines is very low and is estimated to be approximately one case per 5 million patient months "at risk" for all recorded cases and probably less than one case per 50 million months in therapeutic use. . . . (p. 2)

This anodyne conclusion was almost entirely based on patients who had escalated their dose beyond therapeutic levels, that being the way they had come to medical notice. Although there was criticism of Marks's conclusion at the time, pointing out that case reports are a useless epidemiological reference frame (Benzodiazepine withdrawal, 1979), most prescribers accepted it as consistent with their clinical experience: patients did stay on the same dose indefinitely, tolerance was uncommon, and therefore dependence was unlikely.

About this time, the U.K. Regulatory Authorities became concerned about the extensive long-term use of benzodiazepines. Following the lead of the Institute of Medicine (USA) and the conclusions of the White House Office of Drug Policy and the National Insti-

tute of Drug Abuse (USA), the Committee on Review of Medicines (1980) concluded that there was little evidence that hypnotics retained their sleep-promoting properties within 3 to 14 days of continuous use or that anxiolytics were effective beyond 4 months. However, in the absence of proper epidemiological surveys, they concurred with Marks's low estimate of dependence risk. They were particularly concerned, however, with the question of withdrawal symptoms and urged gradual withdrawal even after short courses of benzodiazepines at therapeutic doses.

By the middle of 1981, the number of publications on benzodiazepines had risen substantially, the tally of cases had doubled, and Marks (1983) partly recanted.

NORMAL-DOSE DEPENDENCE

The extensive usage of the benzodiazepines was beginning to raise doubts in a few clinicians' minds by the early 1970s. Astute observers noted an increasing cohort of long-term users. The oft-repeated assertion that this just reflected the chronic nature of anxiety disorders failed to reassure some. But the alternative explanation—that patients could become physically dependent on therapeutic doses—was so dissonant with accepted teachings on dependence that it was dismissed by almost all authorities.

However, one study, that of Covi and his colleagues (Covi, Lipman, Pattison, Derogatis, & Uhlenhuth, 1973) was consistent with this view. In this study and a preceding one (Covi, Park, Lipman, Uhlenhuth, & Rickels, 1969), a minor withdrawal syndrome was found in anxious patients discontinuing chlordiazepoxide after 20 weeks' use. None of the patients took more than the prescribed dose. The authors also raised the possibility that patients who persist with benzodiazepine treatment may represent an "addictive personality type," although they had no data to support this speculation. These studies, both prospective, should have received more attention. However, Covi and his colleagues stressed the minor nature of the symptoms, did not design their studies specifically to evaluate withdrawal, and wrote up their results in a complex and confusing way. Furthermore, the patients had been treated with other psychotropic drugs, such as phenobarbital. The study failed to make an impact.

Another publication comprised a review of the literature on diazepam dependence and then a survey of 50 diazepam users (Maletzky & Klotter, 1976). The review of literature is admirably critical and points out that none of the studies reviewed used controls sufficient to disprove the possibility that diazepam induced dependence. Their own study comprised an interview of 50 patients taking diazepam. The data show clearly that patients tended to increase their dosage and had difficulty discontinuing, experiencing anxiety, tremor,

and insomnia. The authors argue cogently that this constitutes a withdrawal syndrome because sometimes the patient had been free of anxiety when the drug was initially prescribed or the initial anxiety had resolved. Also, many of the patients (17 of 24 who had attempted discontinuation) complained of new symptoms. There were no predictors of drug use or dependence. This study should have had a major influence, setting the alarm bells ringing among the medical profession. It did not. The authors themselves state:

The retrospective, uncontrolled nature of most of the data reported herein makes this study merely suggestive (p. 111).

The authors point out the need for a prospective, systematic study, affirmed their intention to do so, but never did. Finally, the report was published in a specialist journal in the addiction field and did not come to general attention.

Two clinicians in the U.K. continued their jeremiad. I wrote a paper entitled "Benzodiazepines – The opium of the masses?" (Lader, 1978), and an ex-associate of mine, Peter Tyrer, drew attention to the "Benzodiazepine Bonanza." Almost simultaneously, we instituted studies to explore the possibility that long-term benzodiazepine users might be physically dependent and undergo definite withdrawal reactions of the sedative/ hypnotic type, similar to those associated with barbiturate and alcohol use. Tyrer conducted his studies within a clinical context substituting placebo (or propranolol) for diazepam or lorazepam (Tyrer, Rutherford, & Huggett, 1981). My own studies were laboratorybased (Petursson & Lader, 1984). These studies established unequivocally that normal-dose dependence as manifested by a physical withdrawal syndrome was a real entity and supervened even if the dosage was tapered off. Tolerance with escalation of dosage was not a prerequisite for physical dependence. Indeed, one of our studies compared the withdrawal syndromes in small groups of patients withdrawing from high- or low-dose usage: the syndromes were identical (Hallstrom & Lader, 1981).

It became accepted that normal-dose benzodiazepine could occur, but controversy raged as to whether this was a common feature. Certainly, the patients I studied were in a way self-selected—that is, they had tried to stop their medication, had withdrawal symptoms, reinstituted their drug, and sought my help. It was impossible to know whether this was the tip of a very large iceberg or whether these patients were uncommon. More recent studies such as that by Busto, Sellers, Naranjo, Cappell, Sanchez, & Simpkins (1986) have established that about 15%-25% of long-term (over 12 months) users undergo a definite withdrawal syndrome. Only a few percent experience major distress. However, no large-scale prospective studies have 58 M. Lader

been carried out to establish with any precision the precise parameters of the epidemiology of benzodiazepine withdrawal.

A further development has been the realization that withdrawal may be prolonged (Ashton, 1984) or associated with major depressive disorder (Olajide & Lader, 1984).

Recently, appreciation of the hazards of long-term benzodiazepine usage has led to parallel guidelines being issued by the U.K. Committee on Safety of Medicines and the Royal College of Psychiatrists. These guidelines restrict benzodiazepines to short-term use, stress the need to establish a definite indication, and warn against abrupt withdrawal. In similar vein, in the U.S.A., Schweizer, Case, & Rickels (1989) have averred "we have unpublished data which demonstrate that many patients, once they have been withdrawn from their maintenance benzodiazepines, show more improvement on clinical measures of anxiety and depression than they did during their chronically medicated state."

The widespread usage of the benzodiazepines has inevitably led to thousands of people becoming dependent, perhaps 500,000 in the U.K. and twice that number in the U.S.A. where long-term use is less common. Patients who have become dependent and have either been unable to withdraw or have only done so with great symptomatic distress justifiably feel aggrieved against their doctors and the benzodiazepine manufacturers for not warning them about the risk. In the U.K. about 2000 people have started legal proceedings, coordinated by about 300 firms of lawyers. It is the largest civil action ever.

It is interesting to examine the different attitudes towards benzodiazepine use between the U.K. and U.S.A. The U.S.A. has also seemed more concerned about abuse and high-dose use of benzodiazepines reflecting the much greater drug addiction problem in general there (American Psychiatric Association, 1990). The U.K. has concentrated its attention on normal-dose benzodiazepine dependence partly because most of the early and original research was carried out in the U.K. and was effectively publicized, and partly because chronic usage is high. Yet, other countries where usage is even higher, such as Belgium and France, seem blissfully unaware of the problem.

The situation in the U.S.A. will change. The leading benzodiazepine there is now alprazolam, which like lorazepam is highly potent and appears to be associated with more dependence problems than, say, diazepam. Usage of alprazolam in high dosage for long periods in the management of panic disorders must inevitably lead to a dependence problem of major proportions. Severe reactions such as seizures and delirium may follow abrupt discontinuation (Breier, Charney, & Nelson, 1984; Levy, 1984; Noyes, Perry,

Crowe, Coryell, Clancy, Yamada, & Gabel, 1986). In one interesting account, withdrawal delirium from alprazolam was unresponsive to diazepam, and the alprazolam itself had to be reinstituted (Zipursky, Baker, & Zimmer, 1985).

In clinical studies, withdrawal from alprazolam needs careful management. In one study 15 of 17 patients had recurrent or increased panic attacks and 9 had significant new withdrawal symptoms (Fyer et al., 1987). Rebound anxiety was noted in 22% of patients undergoing a 4-week taper from alprazolam; in 28% rebound panics occurred. Out of 33 patients, 4 had three or more significant withdrawal symptoms (Pecknold & Swinson, 1986). In a large-scale multicentre alprazolam/placebo comparison, a subset of 126 patients was carefully studied during and after a 4-week taper period (Pecknold, Swinson, Kuch, & Lewis, 1988). Of the 60 alprazolam-treated patients, 16 (27%) experienced rebound panic attacks, and 21 (35%) had some form of withdrawal syndrome although it was marked in only 6.

Along with withdrawal and rebound at the end of alprazolam treatment, attention has been drawn to daytime interdose symptom recurrence with an increasingly short period of drug effectiveness, so-called "clock watching." Presumably tolerance with rebound occurs after each dose: this is characteristic of shorteracting benzodiazepines. Related to this is early morning "rebound"—patients wake feeling anxious and shaky until they take their first dose of the day.

Will history repeat itself with alprazolam and the last decade of the 20th century see a major dependence problem in the U.S.A. and elsewhere? Let us hope that this time we are sufficiently forewarned to limit the duration and the dosage of alprazolam to the minima.

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