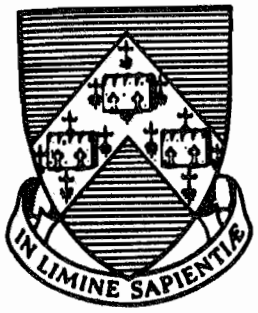

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Adverse Effects of Benzodiazepines

by
Claire Gudex

DISCUSSION PAPER 65

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ADVERSE EFFECTS OF BENZODIAZEPINES

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ABSTRACT

The growing realisation that the benzodiazepines have potential for causing serious harm has caused concern due to their wide and common use. This has stimulated interest in the costs and benefits of their use.

This paper is a review of the adverse effects of benzodiazepines, and concentrates on four areas of particular concern: drug dependence with the consequent withdrawal symptoms; psychological effects while on the drugs; use by the elderly; and tolerance to the drug effects.

Although the phenomenon of a benzodiazepine withdrawal syndrome is generally accepted, there is still controversy over the frequency amongst users. A number of major studies are reviewed here, and the main methodological issues are discussed. These include definition of the withdrawal symptoms, selection of subjects, and use of double-blind, placebo-controlled conditions.

The studies investigating psychological impairment with benzodiazepine use deal mainly with motor performance and co-ordination, although there is a large group of studies looking at the effect of the drugs on memory.

Although the studies reviewed make a considerable contribution to the understanding of the effects of benzodiazepines, they focus on physiological and specific psychological variables, rather than more global measures of functioning and behaviour. It is suggested here that this emphasis needs to change in order to obtain a clearer picture of how benzodiazepines affect quality of life. Future studies should also be prospective in design, and

include clear criteria for the selection of subjects and for the definition of withdrawal symptoms.

ADVERSE EFFECTS OF BENZODIAZEPINES

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INTRODUCTION

Until about 20 years ago, symptoms of anxiety and insomnia were mainly treated with barbiturate drugs. These drugs were known however to be associated with some degree of dependence and subsequent problems with withdrawal, and when the benzodiazepines (BZs) were introduced they quickly supplanted the barbiturates and became the most widely used of all psychotropic drugs. During the past 25 years, it is estimated that over 500 million people worldwide have taken a BZ. They are widely supposed to be at least if not more effective than barbiturates in treating a variety of symptoms, including anxiety, insomnia, muscle spasm, stress-related disorders, epilepsy, or as a pre-operative medication (Lader, 1989). They are also believed to have fewer side effects, to be much safer in overdose, and to be much less liable to produce dependence and abuse problems. This last supposition is the subject of much contention (Uhlenhuth, 1988) however, and the recent decrease in prescriptions for BZ in treating anxiety (Lader, 1989) reflects the growing concern of both medical and lay people regarding long-term side-effects and physical/psychological dependence.

Despite the apparent decline in short-term use, long-term BZ use is still common: in the UK about 1.5% of the adult population have taken these drugs continuously for at least one year; while half of these have taken a tranquillizer/hypnotic for at least 7 years: this represents a quarter of a million people in the UK (Lader and Petursson, 1983).

The wide and common use of the benzodiazepines, together with the growing realisation that there is potential for serious harm, has stimulated

considerable interest in the benefits and costs of their use.

This paper is a review of the adverse effects of BZs, and concentrates on four areas of particular concern:

1. Drug dependence with consequent withdrawal symptoms
2. Psychological effects while on the drugs ("residual effects")
3. BZ use by the elderly
4. Tolerance.

MECHANISM OF DRUG ACTION

The BZs available on the NHS 'selected list' are given in Table 1, together with an indication of the duration of action. The drugs are similar in their psychodynamic properties, and although they can be divided into those used for anxiety and those used for insomnia, nearly all are effective for treating either symptom.

BZs increase the actions on an inhibitory substance in the nervous system, and act on the spinal cord as well as in many areas within the brain, including the cerebellum (important for balance and co-ordination), limbic areas and cerebral cortex (thought and decision-making, movement and sensation). This makes the BZ drugs useful for a variety of syptoms but also raises the possibility of a range of side effects. It has also been suggested that they may affect endocrine activity, including release of the hormone prolactin, causing changes in breast tissue (Beary, 1983).

The length of a BZ drug's half-life appears to have no clear-cut relationship to onset of action, and is of relatively little importance for a patient's response. Of more relevance is the speed of absorption of the drug, and the rate and extent of distribution within the body. For example, the long half-life drug diazepam is very quickly absorbed, while the short half-life drug oxazepam and intermediate half-life drug temazepam are absorbed slowly (Rickels, 1982).

Table 1 Benzodiazepines for Anxiety and Insomnia

Name	Half-Life (hrs)	Accumulation	Residual Effects
Used for anxiety			
Chlordiazepoxide (Librium)	20-90	+++	
Diazepam (Valium)	20-90	+++	
Oxazepam (Serax)	6-28	+	
Lorazepam (Ativan)	8-24	±	
Used for insomnia			
Nitrazepam	16-40	+++	+++
Temazepam (Restoril)	6-10	+	+
Lormetazepam	8-12	+	+
Loprazolam	6-12	+	+
Triazolam (Halcion)	4-10	-	±

With use of a BZ, maximal improvement in the symptoms being treated is usually obtained within the first six weeks of treatment, and no measurable additional improvement occurs after that, even if the daily dosage is increased (Rickels, 1982).

BENZODIAZEPINE WITHDRAWAL SYNDROME

One of the main concerns about BZ use is the potential for dependence. This can take two forms: psychological dependence and physical dependence. The former refers to craving for a drug and includes drug-seeking behaviour, while physical dependence can only be identified when the drug is stopped, by the occurrence of withdrawal symptoms. Although psychological and physical dependence are defined as separate phenomena, they may occur together and be related e.g. if withdrawal symptoms are promptly and repeatedly relieved by taking the drug again, this may stimulate or reinforce craving for the drug. (These resulting psychological and physical phenomena are sometimes together called an abstinence reaction). Reports of psychological dependence alone are however uncommon for the BZs and the primary concern is physical dependence.

As early as 1961 a report of a withdrawal syndrome associated with high doses of chlordiazepoxide was published (Hollister, 1961). Since then studies have extended the findings to other diazepines, and the characteristic set of symptoms has become known as the benzodiazepine withdrawal syndrome.

This was thought initially to occur only after prologned BZ use but it has been noted after only 3-week usage (Pecknold et al, 1982). It can occur at both high and low drug doses, even within the therapeutic range, and usually starts to emerge in the first week after stopping the drug. A wide range of symptoms may be seen, including anxiety, insomnia, anorexia, muscle twitching, unsteadiness, delirium, and a variety of perceptual changes such as tingling, pins and needles, and hypersensitivity to light and noise. Many of these symptoms are unpleasant, but they may also constitute a severe

illness, in which the patient is frightened, in intense pain, and genuinely bedridden (Ashton, 1984).

No specific treatments exist for the withdrawal syndrome, which commonly lasts for up to six weeks, although tapering the BZ dose more slowly may help. Some relief may be offered by other drugs such as sedative antidepressants, or the substitution of a longer-acting BZ, but results from the literature are conflicting (Patterson, 1988; Lader and Olajide 1987; Sullivan and Seller 1986).

Although the range and potential severity of the BZ withdrawal symptoms are now familiar and unquestioned, there is still controversy over the frequency of dependency amongst users of these drugs. A large number of reports have been published since the original 1961 paper concerning withdrawal symptoms, but the drawing of reliable conclusions has been hampered by important differences between studies, not the least of which is the type and dosage of BZ used, as well as by a number of major methodological issues. These issues have been highlighted in several review papers (Noyes et al 1988; Roy-Byrne and Hommer, 1988; Lader 1987; MacKinnon and Parker 1982), and can be discussed under five main themes.

1. The most basic recurring problem is that the symptoms of the BZ withdrawal syndrome imitate to a considerable degree, the symptoms for which the drug was taken in the first place (usually anxiety and/or insomnia). This has forced investigators to make clearer definitions and criteria for withdrawal symptoms such as perceptual or motor problems (e.g. tremor, muscle twitching, unsteadiness). Petursson and Lader (1981) reported a number of

perceptual changes as being unique to BZ withdrawal, but even these may be experienced by people suffering from anxiety. Rodrigo and Williams (1986) found that phenomena such as hypersensitivity to taste and smell, and unusual tastes and smells, were not uncommon in physically healthy, tranquilizer-free subjects experiencing anxiety. Apart from seizures and delirium, there may in fact be few withdrawal symptoms that may not also occur in anxiety disorders, or indeed even in healthy subjects (Merz and Ballmer, 1983).

Waiting for a sufficient time period is often suggested as a way to make a distinction, as withdrawal symptoms should decrease over time, while anxiety would continue indefinitely. However there is disagreement about whether the more subtle withdrawal symptoms can last much longer, and whether even marked and early occurring "withdrawal symptoms" in patients with pre-existing anxiety disorders might really constitute an exacerbation of their original anxiety symptoms, so-called "rebound" anxiety i.e. anxiety of greater magnitude than that observed prior to treatment.

2. One of the most common design problems among the studies of BZ withdrawal, is the lack of double-blind, placebo-controlled conditions. Even so, Winokur and Rickels (1981) observed "pseudowithdrawal" reactions in two patients who continued to receive diazepam in a double-blind placebo-controlled study. The patients and physicians appeared to have been influenced by their expectations, and perceived changed reactions even when medication

stayed the same. Tyrer et al (1983) not only observed rebound anxiety in 50% of patients who were switched from diazepam to placebo, but also observed rebound in 22% of those who were blindly continued on active drug.

3. The selection of subjects raises another issue. Many of the studies published, and particularly those dealing with long-term BZ usage, are based on subjects who are concerned about drug dependence, or have already found some difficulty in discontinuing the drug. These subjects may not be representative of long-term BZ users. There is a related issue of whether subjects are also taking additional drugs or have a history of alcohol or drug abuse. Mellor and Jain (1982) reported that it took them three years to find ten 'pure' diazepam abusers. While, Wolf et al (1989) found that only one quarter of their 792 subjects with BZ abuse/dependence were 'pure' BZ users. Fontaine et al (1984) specifically excluded patients with insomnia as the chief complaint, as well as patients who had physical illness, history of psychotic episode, BZ sensitivity, drug or alcohol addiction, epilepsy, mental retardation.

4. Another problem is compliance, particularly where the persistence of unpleasant withdrawal symptoms pushes subjects back into restarting the drug. The proportion of subjects who drop out in the studies varies, but has reached nearly 50% in some cases (Rickels et al 1986; Tyrer et al 1981).

5. A question related to the definition of withdrawal symptoms, is how long observation should continue after discontinuing the drug. A period of at least 2 to 3 weeks is necessary to separate withdrawal symptoms from original symptoms, and as Ashton (1984) found withdrawal symptoms may continue for at least up to 6 months.

In order to draw some conclusions on the incidence and effect of withdrawal symptoms, a number of studies have been identified which provide useful comparative data, bearing in mind the methodological problems discussed above. Twenty-seven studies are reviewed here, with the focus being on larger, controlled studies, with pre-determined criteria for withdrawal symptoms. Because duration of drug use appears to be an important determinant in frequency of BZ withdrawal symptoms, the studies have been divided into short-term BZ use, i.e. less than one year (Table 2) and long-term use (Table 3).

Many more articles and letters have been published which report on withdrawal problems but these offer information on only a few patients, or are observations rather than specifically designed studies, and are not discussed nor referenced here.

Tables 2 and 3 show the range of conditions and subjects which have been used in studies investigating withdrawal symptoms after BZ use. Even amongst the studies dealing with either short-term or long-term BZ use, there is considerable variation in design, whether in terms of drug and dosage used, length of observation, or method of measurement of symptoms. The incidence

TABLE 2: STUDIES OF WITHDRAWAL REACTIONS AFTER SHORT-TERM USE OF BENZODIAZEPINE

STUDY	DRUGS	DAILY DOSAGE	DURATION OF DRUG USE	DESIGN OF STUDY	OBSERVATION PERIOD	ORIGINAL PATIENT DIAGNOSIS	MEASUREMENT METHOD	WITHDRAWAL SYMPTOMS
Covi et al 1973 n=39	CDX	45 mg	10 or 2 weeks	Abrupt WD Blind	2 weeks	Drugs given for study	POMS	Rebound symptoms and new symptoms
de Figueirdo et al 1981 n=60	LZ CB	3 mg 3 mg	4 weeks	Abrupt WD	1 week	-	-	No rebound symptoms No new symptoms
Lapierre et al 1982 n=40	CB DZ	30 mg 15 mg	4 weeks	Abrupt WD	3 days	-	-	No rebound symptoms No new symptoms
Pecknold et al 1982 n=29	HZ OZ	120 mg 45 mg	3 weeks	Abrupt WD Blind	8 weeks	-	HAS	47% ataxia Rebound and new symptoms
Rickels et al 1983 n=108	DZ placebo	25 mg -	6-34 wks	Abrupt WD Blind	2-10 wks	GAD	HAS, CAS, HSC	5/108 withdrawal symptoms
Fontaine et al 1984 n=43	BMZ DZ placebo (n=13)	18 mg 15 mg -	4 weeks	Abrupt WD, n=16. Gradual WD, n=14 Blind	3 weeks	GAD	HAS, SRSS	Abrupt WD: 7/16 RA Gradual WD: 0/14 RA
Murphy et al 1984 n=40	DZ Buspirone	11.4 mg 7.7 mg	6 or 12 weeks	Abrupt WD Blind	2 & 8 wks	-	CPRS	More symptoms in DZ group
Power et al 1985 n=21	DZ placebo	15 mg -	6 weeks	Abrupt WD Blind	2 weeks	GAD	HAS, Kellner	New symptoms and rebound anxiety
Mellman & Uhde 1986 n=10	ALPZ	1-12 mg	4-22 mths	Gradual WD	-	Panic disorder	Anxiety, Blood pressure, pulse, cortisol	4/9 anxiety 4/9 ↑ BP and P 8/9 ↑ cortisol
Fyer et al 1987 n=17	ALPZ	2.5 mg -8.5 mg	3-13 wks	Gradual WD	-	Panic disorder	-	14/17 new symptoms
Pecknold et al 1988 n=109	ALPZ placebo	4.8 mg -	8 weeks	Gradual WD	6 weeks	-	-	Rebound symptoms and new symptoms
Feet et al 1988 n=27	DZ placebo	10 mg -	14 weeks	Abrupt WD Blind	2 weeks	Primary non-agitated depression	CPRS Working activity	Higher depression scores and less working activity in DZ group

TABLE 3 STUDIES OF WITHDRAWAL REACTIONS AFTER LONG-TERM USE OF BENZODIAZEPINE

STUDY	DRUG	DAILY DOSAGE	DURATION OF DRUG USE	DESIGN OF STUDY	MEASUREMENT METHOD	WITHDRAWAL SYMPTOMS	COURSE	SUBJECTS
Bowden & Fisher 1980 n=23	DZ	28 mg	3.3 years	Abrupt WD Blind	HAS	1/10: WD symptoms	-	-
Tyrer et al 1981 n=40	DZ LZ	10 mg 4 mg	3.6 years	Abrupt WD	-	45% new symptoms	Peak at 10 days	Ready to discontinue drug
Petursson & Lader 1981 n = 16	DZ LZ CB	17 mg 5 mg 30 mg	1-16 yrs	Gradual WD Blind	HAS DSST	100% WD symptoms 10 severe reactions	4 weeks	Anxiety or depression or personality disorder and difficulty in discontinuing drug
Hallstrom & Lader 1981 n=10	DZ	20 mg or 135 mg	2-20 yrs (7.8 yrs)	Gradual WD	HAS	9/10 anxiety; 2/10: psychosis; 1/10: seizure; 6/10: perceptual changes	Peak at 10 days; ↓ by 30 days	Difficulty in discontinuing drug
Mellor & Jain 1982 n=10	DZ	60-120 mg	3-14 yrs (5.5 yrs)	Gradual WD	Alcohol WD rating scales	10/10: anxiety, insomnia 8/10: perceptual changes	5-6 weeks	Primary diagnosis of DZ dependence
Laughren et al 1982 n=24	DZ control (n=8)	17 mg	1-12 yrs (5 yrs)	Abrupt WD n=8 Gradual WD n=8 Blind	HAS	No differences between WD groups or control group	-	High baseline HAS
Hopkins et al 1982 n=78	DZ	2-15 mg	90% more than 1 yr	Gradual WD	-	41% unable to stop drug	-	-
Rickels et al 1983 n=21	DZ	25 mg	2.9 yrs	Abrupt WD Blind	HAS, HSC, CAS	9/21: WD symptoms (43%)	Restarted on DZ	Interested in discontinuing drug
Tyrer et al 1983 n=36	DZ	5-20 mg (11 mg)	3.2 yrs	Gradual Blind	CPRS	44% WD symptoms	8 weeks	Ready to discontinue drug
Lader & Petursson 1983 n=22	DZ	17 mg	7 years	Gradual WD Blind	HAS Symbol copying time	100% anxiety; 20/22 sleep disturbance; 7/22 impaired memory & concentration	4 weeks	Difficulty in discontinuing drug
Ashton 1984 n=12	DZ	30 mg	3-22 yrs (10 yrs)	Gradual WD	-	12/12 Difficulty walking 11/12 Agoraphobia	Up to 6 months	Requested help to discontinue drug
Busto et al 1986 n=40	DZ	14-16 mg	6 years	Abrupt WD n=19 Gradual WD n=21	HSC, SAS, CVS, MADRS	Abrupt WD: 60% contacted clinic due to WD symptoms cf 14% gradual WD group	4 weeks	Difficulty in discontinuing drug
Rickels et al 1986 n=65	DZ LZ ALPZ CZPT	15 mg 4 mg 3 mg 18 mg	Most more than 3 yrs	Abrupt WD Blind	-	82% WD symptoms	Restarted on drug	Interested in discontinuing
Cappell et al 1987 n=42	?	?	?	Gradual WD	-	60% WD symptoms	-	-
Rickels et al 1988 n=61	CZPT Buspirone	15-60 mg 10-40 mg	6 mths (but 40% had previous BZ use)	Abrupt WD Blind	HAS,HSC POMS	CZPT: 72% WD symptoms cf. 9% buspirone group	4 weeks	GAD or panic disorder

Figure 1 Abbreviations used in Tables 2 and 3

CDX	=	chlordiazepoxide
LZ	=	lorazepam
CB	=	clobazam
DZ	=	diazepam
HZ	=	halazepam
OZ	=	oxazepam
BMZ	=	bromazepam
ALPZ	=	alprazolam
CZPT	=	clorazepate

POMS	=	Profile of Mood States
HAS	=	Hamilton Rating Scale for Anxiety
CAS	=	Covi Anxiety Scale
HSC	=	Hopkins Symptom Checklist
SRSS	=	Self-Rating Symptom Scale (32 item)
CPRS	=	Comprehensive Psychopathological Rating Scale (65 item)
Kellner	=	Kellner and Sheffield Self-Rating Scale of Distress
DSST	=	Digit Symbol Substitution Test (subtest of Wechsler Adult Intelligence Scale)
SAS	=	Weissman and Bothwell Social Adjustment Score
CVS	=	Clark Vocabulary Score
MADRS	=	Montgomery and Asberg Depression Score

WD	=	withdrawal
RA	=	rebound anxiety
GAD	=	generalised anxiety disorder

of withdrawal symptoms also shows considerable variation, and in fact shows a range from 0% to 100%.

The definition used for withdrawal symptoms is important: in two separate studies Tyrer et al (1981, 1983) used two definitions. One was the development of two or more new symptoms, and the other was an increase in self-ratings of symptoms of 50% or more above baseline followed by a return to lower values. In the 1983 study 44% and 50% of patients were identified as experiencing withdrawal symptoms, depending on which definition was used, compared to 45% and 27% in the 1981 study.

Bearing in mind such issues however, the larger and better designed studies (e.g. Rickels et al 1983, Tyrer et al 1983, Rickels et al 1986) suggest that the incidence is probably between 40 and 80%, and if a definition is used which requires new symptoms, the incidence approximates 50%, at least for the type of subjects participating in such studies.

Roy-Byrne and Hommer (1988) note that despite the high use of BZs by older people, withdrawal in the elderly has not been well studied. Preliminary reports have suggested that in the elderly it can commonly present as confusion and delirium (Foy et al 1986). This is in contrast to the infrequent occurrence of delirium in studies of younger people and may indicate that results of studies to date are not necessarily universally applicable.

Factors contributing to the development of withdrawal symptoms are primarily dose, duration, concurrent medication, and pharmacokinetics of individual BZ drugs.

Generally the higher the dose and the longer the BZ is taken, the greater the risk of developing moderate to severe withdrawal reactions. As already noted, while it is generally believed that withdrawal symptoms occur in patients taking doses larger than those therapeutically recommended, they can also occur with doses within the therapeutic range.

Although withdrawal symptoms are by no means absent after short-term BZ use (see Table 2), they are more frequent with longer duration of use. Abrupt discontinuation also appears to lead to more frequent and severe withdrawal reactions than with gradual withdrawal, and more rapidly eliminated drugs are probably associated with more severe reactions.

One other factor suggested as a contributor to withdrawal symptoms, is personality. Tyrer et al (1983) found that passive and dependent personality traits were good predictors of withdrawal symptoms. As Ashton (1984) notes, individuals with certain personality characteristics are more likely to be prescribed BZ, for example high neuroticism scores on the Eysenck Personality Questionnaire.

Effect on quality of life: although these studies are becoming better-designed, with more attention to important factors mentioned above, their focus on specific clinical symptoms gives only indirect information on how patients are actually affected by these symptoms. It may be inferred that problems with sleep, giddiness, pain are distressing to patients, but few of the studies attempt to investigate this aspect further. Two of the studies stand out in their attempt to measure broader effects on patient functioning. Feet et al (1988) assessed the ability of their patients to continue

employment, while Ashton (1984) noted that several patients experienced agoraphobia, to the extent that six patients were completely unable to go out of the house alone. In order to get a wider view of the effect of BZ withdrawal on people's quality of life, these broader aspects will need to be investigated.

Finally, studies of long-term BZ withdrawal have not been prospective in design. In other words, patients were not studied before receiving treatment and baseline measures were not obtained. Baseline measures are important in order to be able to compare symptoms upon withdrawal, with the original symptoms which required the BZ to be started.

Rebound Insomnia

A small number of studies have looked specifically at the phenomenon of rebound insomnia, which is one of the problems in withdrawal. It is generally defined as a worsening of sleep compared with pre-treatment levels. Bixler et al (1985) use a more specific definition, i.e. a statistically significant increase or an increase of at least 40% in the mean group value of total wake time for a single withdrawal night or the entire withdrawal condition as compared to baseline.

The consensus is that rebound insomnia occurs immediately and intensely following abrupt withdrawal of rapidly eliminated benzodiazepines (e.g. triazolam), and less frequently and also delayed and in a milder form, following withdrawal of slowly eliminated drugs. Dose appears also to be an important factor in determining the occurrence of rebound insomnia. Bixler et al (1985) found that the magnitude of rebound insomnia increased

progressively with each increment in dosage for two rapidly eliminated drugs. Other factors which may be involved in sleep disturbances are the length of drug administration, tolerance to its effects, and the functional state of the benzodiazepine receptors in the brain.

Gillin et al (1989) found that the exact type of insomnia varied from study to study, but for most, the sleep disturbance was characterised by reduced total sleep time, as well as reduced sleep efficiency. The risk of rebound insomnia may be greater in middle-aged or older patients who have been treated for at least two weeks, compared with young patients or normal controls treated for a week. This may have clinical relevance, as hypnotics are often recommended in the management of transient insomnia occurring in otherwise healthy, normal sleepers.

Kales et al (1983) identify a new phenomenon of early morning insomnia that is similarly associated with benzodiazepines having relatively short elimination half-lives. This condition also consists of a worsening of sleep, but it occurs during the final hours of sleep during actual drug administration, whereas rebound insomnia occurs after drug withdrawal. Early morning insomnia may not be unique to benzodiazepines, as rebound insomnia is, as alcohol for example, also increases wakefulness during the second half of the night.

As Gillin et al suggests, future studies of sleep disturbance should include measurement of several sleep variables e.g. total wake time, wake time after sleep onset, sleep efficiency, time in bed. A sufficient number of withdrawal nights should also be included to determine whether delayed rebound insomnia is occurring.

PSYCHOLOGICAL IMPAIRMENT WITH BENZODIAZEPINE USE

Administration of BZ does appear to impair psychomotor function, with resulting effects on motor speed, visual/motor co-ordination, as well as cognitive function. People taking BZs are therefore cautioned about driving or operating dangerous machinery when on medication.

There has been growing concern also over reports that long-term BZ use may cause generalised intellectual impairment (Hendler, et al 1980, Bergman et al 1980). There have been few studies which investigate this aspect of BZ use, however, and the seven studies reviewed below, deal mainly with motor performance and co-ordination.

The first four studies are based on results of laboratory tasks which subjects undertook under test conditions. The first two deal with short-term BZ use, while the second two investigate long-term use. (See Table 4).

Morgan et al (1984) measured day time impairment of patients who were taking a BZ to help them sleep. Impairment of both manual dexterity and card-sorting was seen, although only in the morning, and despite subjects having little awareness of impaired alertness.

Only one BZ drug (flurazepam) impaired performance on psychomotor tasks in the study by Wesnes and Warburton (1984). Subjects were healthy university volunteers, and had not been prescribed any psychoactive medication during the previous 6 months.

Table 4 Studies of Psychological Impairment with Acute or Chronic BZ Use

STUDY	DRUG DOSAGE	DURATION OF DRUG USE	TEST
Morgan et al 1984 n=12	LZ 0.5-1 mg TZ 0.5 mg placebo	3 weeks	Manual dexterity Card sorting
Wesnes & Warburton 1984 n=24	FZ 30 mg TMZ 40 mg	10 hours	DSST, Rapid Information Processing Task CFF
Luckie et al 1986 n=43	DZ 5-20 mg LZ 1-10 mg CZPT 3.75 - 15 mg ALPZ 0.75 - 6 mg	1-15 years	DSST, symbol copying test, CFF, word recall, subjective mood scales
Golombok et al 1988 n=145	BZ up to 30 mg	At least 1 year n=50 Never or less than 1 year n=61 Successfully withdrawn n=34	National reading test, DSST, symbol copying test, verbal recall, recognition memory, category sorting test, state anxiety inventory.

Figure 2 Abbreviations used in Table 4

LZ	=	lorazepam
TZ	=	triazolam
FZ	=	flurazepam
TMZ	=	temazepam
DZ	=	diazepam
CZPT	=	clorazepate
ALPZ	=	alprazolam
BZ	=	benzodiazepine
DSST	=	Digit Symbol Substitution Test
CFF	=	Critical Flicker Frequency

In a larger study, Lucki et al (1986) gave subjects a battery of six tests, and found that the performance of the chronic BZ users did not differ from age- and sex-matched anxious subjects. However acute administration of BZ to 22 of the chronic users, did cause significant impairment on several of the tests. The authors concluded that regular long-term use of BZ does not necessarily produce serious psychomotor or cognitive impairment. However many patients take BZ medications several times a day, and the short-term memory impairment which was noted, may then have a greater impact in groups such as cardiac patients or the elderly.

The most recent study is that of Golombok et al (1988), who investigated a wide range of cognitive functions, including reading ability, reaction time, memory and learning. They found that long-term BZ use was associated with cognitive impairment, particularly in the areas of visual-spatial tasks, and the ability to sustain attention on a repetitive task under time pressure.

Important methodological issues arise here also. Because of the nature of investigation using a battery of tests in a short time period, care has to be taken that learning effects are not influencing the results of the tests. As Lucki et al (1986) point out, this is more of a problem when testing acute effects, as retesting is carried out within hours usually, as opposed to weeks in chronic users.

In addition, the impaired performance of long-term BZ users on psychological tests may not be due to the medication, but to the original anxiety for which the drug was prescribed. Golombok et al (1988) however found that the results were unchanged after the effects of anxiety had been

accounted for, and furthermore the tests showing impaired performance were not the ones which might be expected to be affected by anxiety, i.e. those depending on efficient short-term storage of information.

These same authors also excluded subjects who had medical or psychiatric conditions which might have influenced the results, but noted that to exclude subjects who had also been prescribed tricyclic antidepressants would have changed the nature of the sample so much as to no longer be representative of long-term BZ users. On testing for the effect of these drugs, no significant differences were found, but it again raises the issue of subject selection.

As with Morgan et al (1984), Golbombok et al found that subjects were not aware of their impaired abilities. The cognitive effects of long-term administration of BZs may not simply be debilitating but may also be dangerous. Two studies have investigated the effects on car driving. Hindmarch (1986) estimated that up to 10% of drivers involved in car accidents had been taking psychoactive drugs, and that these drugs (of which BZs are the most commonly prescribed) are responsible for the loss of 200,000 lives world-wide on the roads each year.

Smiley and Moskowitz (1986) found that diazepam adversely affected steering control in a computer-based driving simulation test, in comparison with placebo. Subjects became less responsive, suggesting either that the motor response was impaired or that less effort was being made to keep the car in the lane.

A seventh article, by Curran (1986), reviews the effects of BZs on human memory. A large number of studies, from 1973 to 1985 are summarised, and results are presented in a comprehensive table. Anterograde amnesia (where information acquired before taking the drug is retained intact) appears to be a common effect of all BZs, although its onset and duration vary with the particular drug, its dose and route of administration. Memory impairments also increase with task difficulty. The authors note several important methodological issues. Firstly drug-related memory impairments may be more pronounced in the elderly, and the majority of studies have been conducted using healthy, young subjects, usually male. Gender and anxiety also affect performance on memory tasks.

Secondly, most memory tasks which have been used in drug studies are unrepresentative of everyday memory requirements and so performance on laboratory tests may be of little relevance to everyday remembering. Clearly the ability to remember is also a function of the meaningfulness of the stored data.

Curran makes a series of extremely useful suggestions for future work in this area. A call is made for more stringency in the criteria used to select memory tasks, and it is recommended to use at least one standard task to allow comparability between studies. The tasks also need to be designed to avoid confounding factors such as poor attention span or sedation having an undue influence.

In the one study that investigates psychological and social effects of BZs on a broader scale, Caplan et al (1985) elicited subjective reports of

life quality, affect, performance, stress, social support, control and coping. Standardised interviews were conducted with 675 subjects, with each subject undergoing four interviews approximately 6 weeks apart. Just over half of the subjects reported using diazepam at some time during the course of the study. Overall however, there was little evidence that diazepam had any social effects, either harmful or beneficial. Although there was a modest positive relationship between diazepam use and distress, multivariate analyses controlling for levels of stress and health indicated no notable effects of drug use on any of the social or psychological indicators, including anxiety. Several possible explanations are suggested including the possibility that the effects of diazepam use were short-lived rather than long-term, and that the drug may have been taken in anticipation of anxiety rather than after its occurrence.

BENZODIAZEPINE USE IN THE ELDERLY

It has already been noted on two counts that the elderly may constitute a group at special risk from adverse effects of BZ drugs.

They may be more likely to take BZ drugs several times a day, which increases the chance of memory impairment (Lucki et al, 1986), but they may also present with different symptoms of BZ effects, particularly on withdrawal (Foy et al, 1986). In a much earlier paper, Castleden et al (1977) found that subjects over the age of 69 years made significantly more mistakes in a psychomotor test than did subjects under 40 years of age. The difference was suggested to be due to an increased sensitivity of the ageing brain to the BZ (in this case, nitrazepam).

Swift et al (1984) noted that many elderly people in the community take BZs for long periods, and these may be expected to cause major problems of unwanted sedation, in view of less efficient metabolic elimination in the elderly. 253 subjects were visited in their homes and asked a series of questions concerning drug use, effectiveness and side effects, as well as tested on standing and walking ability and cognitive function. However, even where plasma concentrations of the drug were high, there were few persistent problems with any of unwanted sedation, unsteadiness or mental confusion. It was emphasised however that long-term BZ use may produce a different picture to acute or short-term use in respect of side effects.

[At the other end of the age span, adverse effects of BZs on the foetus have been noted. Rementeria and Bhatt (1977) identified withdrawal signs in

neonates that were attributed to intrauterine exposure to diazepam. The babies were irritable, had abnormal nervous reflexes, and were more prone to vomiting].

TOLERANCE

Tolerance is said to occur when, following repeated administration, a given dose of a drug produces a decreased effect, or conversely, increasingly larger doses must be administered to obtain the effects observed with the original dose. One of the causes is probably increased action of liver enzymes which break down the drug.

Studies show differences between variables with respect to tolerance. Lader and Petursson (1983) compared physiological responses to diazepam, of 8 chronic BZ users and 8 controls. Upon acute administration of diazepam, the BZ users showed an increase in EEG activity as did the controls, but heart rate, and growth hormone release did not increase as expected i.e. these responses were showing tolerance to the diazepam. Subjective tolerance was also found. Both patients and controls experienced a mild and brief episode of euphoria within 5 minutes of the injection of diazepam. Thereafter the controls felt drowsy and sedated whereas the chronic BZ users, although prior to the injection were somewhat less alert, showed no such change.

Swift et al (1984) noted that approximately 90% of their 253 chronic BZ users gave no history of dosage increase over the duration of therapy, with the majority claiming continued satisfaction with drug efficacy. However the UK Committee on the Review of Medicines (CRM) concluded that sedative hypnotic drugs have not been demonstrated to be effective over long periods of time, and further noted that "there was little convincing evidence that benzodiazepines were efficacious in the treatment of anxiety after 4 months' continuous treatment".

SUMMARY

This paper has reviewed the major short and long-term adverse effects of the benzodiazepines.

Although the phenomenon of a BZ withdrawal syndrome is generally accepted, controversy remains regarding the incidence of dependency, and results vary as to number and type of symptoms experienced. The incidence is probably between 40 and 80%, but attention needs to be given to five main methodological issues: (1) definition and criteria of the withdrawal syndrome; (2) study design ie. use of double-blind, placebo-controlled conditions; (3) selection of subjects; (4) compliance; and (5) length of observation period.

Adverse effects also arise during BZ use, even before withdrawal is attempted. Both psychomotor and cognitive functioning may be impaired, and amnesia is a common effect of all benzodiazepines.

Even short-term BZ use can lead to the development of tolerance, causing larger doses of drug to be administered, and it was noted that the elderly are a group at special risk from adverse effects of BZ drugs.

Due to the variations in study design and focus, it was a difficult task to summarise the adverse effects of the benzodiazepines. Reporting systems such as that operated by the US Food and Drug Administration (Bixler et al, 1987) will make a valuable contribution to the understanding and knowledge of BZ effects. However in order to see these effects in terms of how patients'

everyday lives are impaired, there needs to be a change in focus from physiological and specific psychological variables, to more global measures of functioning and behaviour. None of the studies reviewed here include a health status measuring tool or a quality of life index. It is therefore difficult to assess the degree to which benzodiazepines affect patients' social life, employment opportunities, or family relationships, and therefore to measure the full costs to the individual or to society.

Studies also need to be prospective in design, thus providing a baseline measurement with subsequent follow-up, and allowing a clearer picture to emerge of BZ effects, and their development as time on the drug lengthens. Comparison with controls is also essential, with close attention paid to selection of subjects and to criteria for adverse reactions.

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