BENZODIAZEPINE DEPENDENCE
A REVIEW

David Cassar

ABSTRACT

Benzodiazephines are a very widely used class of drug with worldwide sales exceeding $1000 million. Although a considerable number of prescriptions are for long term users there is no convincing evidence that benzodiazepines remain effective over long periods. Dependence occurs even with regular therapeutic dosage for more than a few weeks. Also discontinuation may lead to rebound anxiety and a withdrawal syndrome. The latter will usually need management in its own right and this often can be carried out by general practitioners. Prevention of dependence, after all a iatrogenic disorder, must be our future aim.

Initial prescribing has to be appropriate and other forms of intervention should be considered. Non specialised GP counselling is as effective as benzodiazepines in the treatment of minor affective disorder.

Benzodiazepines are the most frequently prescribed drug in the Western World. At present one in five people in developed countries are given minor tranquillisers at a point during their life; 11 - 17% are prescribed benzodiazepines at some time during a year, 1.5 - 3% take them continuously for more than a year and 0.7% take benzodiazepines for more than seven years (1,2). A further look at figures indicates that at a conservative estimate there are thus seven thousand long term users in Malta, and at least 40 on the list of each established GP. Prevalence is higher in women and increases with age. There is however a positive sign. Benzodiazepine prescribing is decreasing and this is attributed to a greater professional and public awareness of the risks and side effects.

Benzodiazepines act at specific pharmacological receptors found in most areas of the brain but in greater concentrations in the cerebral cortex, limbic system and cerebellar cortex. The receptor is thought to consist of a benzodiazepine recognition site, a GABA receptor and chloride channel, and benzodiazepines act by increasing affinity for GABA thus potentiating the inhibitory effect of the neurotransmitters. There are at least two subtypes of receptors with different affinities for different benzodiazepines. This may account for the differences in the sedative and anti-anxiety actions and possibly also the potential for dependence of the various products.

THE BENEFITS AND RISKS

Benzodiazepines have an important place in the treatment of epilepsy and disorders of muscle tone. But they are mostly used in the management of anxiety and insomnia. In the latter conditions the SHORT TERM therapeutic potential is well recognised (3). But are they as effective over prolonged periods? Long term users include older people, those with chronic physical and associated emotional problems, those with chronic or recurrent psychiatric problems, those with inadequate social support and also repeated attenders to medical practices. Are these people deriving benefit?

In 1980 the "Committee on Review of Medicines" in the U.K. stated that there is "Little convincing evidence that benzodiazepines were efficacious in the treatment of anxiety after 4 months continuous treatment" (4); and before it in 1979 the Institute of Medicine and the National Institute of Drug Abuse in the USA in a joint statement declared that there is "Little convincing evidence that sedative hypnotics including benzodiazepines continue to be effective when used nightly over long periods" (4).However Rickels et al together with a small number of authors do maintain that some chronically anxious patients receive continuing benefit from benzodiazepine therapy and that for them long term use may be justified (5). The risks and side effects must also be considered. These are numerous and may be serious in nature. They include day-time sedation and drowsiness; cognitive impairment with effect on memory and attention, and deficient visuospatial ability (6); decreased psychomotor performance with impaired judgement and coordination; larger Ventricle/Brain ratios than controls indicating loss of neuronal substance (7); dependence; a withdrawal syndrome which may include seizures and psychosis; potentiation of the central depressant effect of alcohol and barbiturate drugs - such combinations can be dangerous; confusion in the elderly and overdosage. It is thus obvious that long term treatment is not without considerable risk.

DEPENDENCE

There is incontrovertible evidence that a clinical syndrome of dependence exists (5,8,9,10,11,12) and this is demonstrated at different levels. At the physiological and physical level there is symptom specific tolerance to side effects (13) and a withdrawal syndrome on stopping the drug. At a psychological or cognitive level craving for the drug occurs and there is a need to go on taking the drug because of its production of pleasurable effects or removal of unpleasant ones. Lastly at a behavioural level one finds drug seeking both by legitimate and illicit means.

Factors leading to dependence are multiple. Peturrson and Lader have shown clearly that therapeutic levels are not protective (14). Even subclinical doses induce pharmacological and receptor changes and there is no safe low dose. However the risk does rise with increased dosage (15). On the other hand the risk decreases when the drug is administered on a flexible, intermittent and PRN basis rather than continuously (3). Duration of treatment is a major factor. Although dependence may occur following administration for as little as 4 to 8 weeks (8,10), the risk and severity increase with the length of treatment (8). A propensity

DAVID CASSAR MD, BCPSYCH (LOND.)
ST. LUKE'S HOSPITAL AND
MOUNT CARMEL HOSPITAL, MALTA.

for dependence may also be related to properties of the molecule. Some benzodiazepines appear to be more dependence producing than others and this relates especially to short acting formulations such as Lorazepam and Alprazolam (9,15). However, differences are hard to document, let alone prove and suspicion rests mainly on there being more severe withdrawal reactions with short acting than with long acting compounds. Personality also plays a role and individuals who are labile, sensitive, impulsive and with poor coping strategies are more prone to becoming dependent.

BENZODIAZEPINE DISCONTINUATION

Discontinuation of treatment may lead to various phenomena including anticipatory anxiety, rebound anxiety, a withdrawal syndrome and relapse. These may overlap and it is important to distinguish and manage each in its own right.

Anticipatory Anxiety may be very pronounced especially in long term users. Sometimes referred to as "pseudowithdrawal" because it may be confused with the withdrawal syndrome, it however occurs very early on in the tailing off of benzodiazepines (Fig.1). It is due to a fear of withdrawal symptoms, fear of lack of coping skills, and a fear of relapse, and is especially prominent in subjects who have failed to withdraw previously.

Rebound Anxiety is by definition anxiety where the symptoms are quantitiatively more severe than baseline, and transient in nature. It occurs towards the end of benzodiazepine discontinuation (Fig.1) and is much more severe and common when the drug is stopped abruptly. Although it may occur even after treatment for 3 weeks it is generally found in less than 50% of patients (15). The only way of distinguishing it from relapse is by observing the symtoms for a few weeks where rebound anxiety will abate.

The Withdrawal Syndrome typically begins in the first week after stopping the drug but may develop following reduction in dosage. It usually lasts for one to six weeks but rarely may persist for months. The syndrome is clearly distinguishable from a simple re- emergence of pre-existing disorder due to the development of new symptoms together with a marked accentuation of previous ones. Although all symptoms can be attributed to an anxiety state, key symptoms are very typical of the withdrawl syndrome. These include increased sensory perception such as photophobia, hyperacusis, paraesthesiae, hypersensitivity to touch and pain, and hyperosmia, gastrointestinal disturbances, headaches, muscle spasms, vertigo and sleep disturbances. Together with these a very large number of symptoms have been described, which can basically be divided into three groups; psychological, somatic and perceptual. The more important of these are summarised in Table 1.

The withdrawal syndrome has been shown to occur in circa 45% of people on benzodiazepines (15). Factors predisposing to its development and severity are very much related to the factors influencing dependence mentioned earlier. Withdrawal reactions may occur in patients on low therapeutic doses (14) but will be more severe the higher the dose (15). Again incidence and severity are much decreased if benzodiazepines are only taken intermittently but withdrawal symptoms may occur even with a duration of treatment of a few weeks (10, 16). Discontinuation of drugs with a short half life will lead to a more rapid onset of symptoms and a much sharper peak in severity (9,15,17,18). For example onset of symptoms for Lorazepam is 18 hours and Diazepam 5 days; peak severity for Lorazepam is 2 1/2 days and Diazepam 15 days. This is usually considerably more distressing for subjects and leads to a greater drop out rate. The speed of discontinuation will also influence the development of the syndrome and abrupt or rapid termination will lead to a greater incidence and severity of symptoms.

TABLE 1. BENZODIAZEPINE WITHDRAWAL SYMPTOMS

Psychological

- Anxiety, tension, panic
- Agitation and restlessness
- Irritability
- Anergia
- Impaired memory and concentration
- Depression
- Depersonalisation
- Agoraphobia
- Insommia
- Aggression

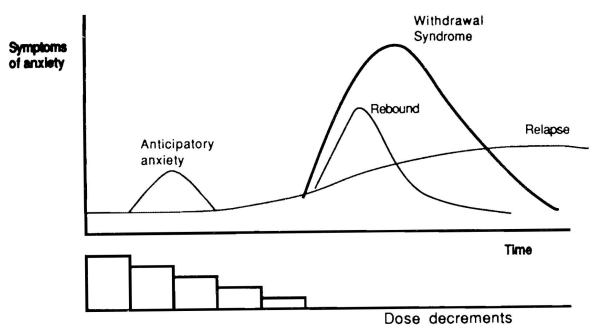
Somatic

- Anorexia and weight loss
- Nausea and retching
- Sweating
- Tremor and muscle twitching
- Palpitations
- Headache
- Chest pains
- Muscle pains
- Seizures
- Confusion and Delirium

Perceptual

- Altered sensation: Hyperacusis, tinnitus
  - Photophobia
  - Hyperosmia
  - Metallic taste
  - Paraesthesiae
- Incoordinations
- Sense of movement, vertigo
- Visual hallucination
- Paranoid reactions

Figure 1.



MANAGEMENT

The question of whom to withdraw must first be raised. Success depends a great deal on the motivation of the patient. This is often lacking and forcing withdrawal on an uncooperative patient is an exercise in futility. However every patient should be counselled as to the nature of

dependence and its problems. Their drug use should be monitored and they should be encouraged to withdraw whenever it appears appropriate. The majority of patients can be withdrawn in a community setting by GP's, or on an outpatient basis. However hospital admission may be considered in the case of multiple failed attempts. In subjects on very high doses, and in those with a history of seizures, psychosis or confusional state, admission is desirable.

A great deal of emphasis must be put on simple psychological support. Prior to starting discontinuation the patient must be informed about the possibility of having rebound anxiety and a withdrawal syndrome and these should be described thoroughly. A person needs to know that any distress experienced may be intense but of limited duration, and that there is a good possibility that there will be no need for further tranquilliser treatment. Fears andmisconceptions have to be looked for and explored and reassurance given. Anticipatory anxiety may be extreme especially towards the end of withdrawal. Continual support must be ensured, the subjects preferably seen weekly and a means of telephone contact provided (15). During withdrawal the original sources of anxiety may become clear and these will need separate exploration and management. Also one needs to warn and guard against drug substitution such as increased alcohol consumption, increased smoking or abuse of non prescribed drugs. It is very helpful to involve the spouse or other family members and explanations and reassurance should be provided to them as they will be a valuable source of support. Recently there has been a flourishing of self-help groups in the United Kingdom and as with Alcoholics Anonymous they may be of considerable help.

From the pharmacological aspect some clinicians recommend substitution of short acting preparations with long acting ones and stabilisation, as a first step in order to avoid severe and precipitate withdrawal reactions. Here care must be taken to substitute the dose adequately as inadequate substitution will itself lead to withdrawal. Equivalent doses of various benzodiazepines are included in Table 2. Initially dosage is tapered in steps ranging from 0.5 to 2.5 mg Diazepam or equivalent (8) every week or more rapidly if withdrawal symptoms are not marked. If considerable withdrawal symptoms do appear one may need to proceed more slowly, the next decrement being introduced when symptoms have ameliorated sufficiently for the patient to accept consequent accentuation. An occasional PRN dose may be allowed. Towards the end there may be an increase in symptoms and one may have to discontinue even more slowly giving small doses on alternate days. Discontinuation is usually over 6 - 8 weeks but programmes of up to sixteen weeks have been recommended in difficult cases. Programmes that are too long should generally be avoided to prevent the withdrawal syndrome from becoming a neurotic focus. Further psychological adjuncts include the use of relaxation skills, stress management, assertiveness training, problem solving and social skills training but these mostly lie in the realm of the trained psychiatric or psychological professional.

Other pharmacological agents are sometimes used. Beta Blockers may attenuate but do not prevent some of the somatic symptoms (19,20). Antidepressants may be used as a psychological crutch and also have anxiolytic effect. They have a definite role in the management of depression complicating withdrawal and also, in patients with a past history of severe depressive illness, antidepressant cover should be used during benzodiazepine discontinuation. However neurotics tend to be particularly sensitive to the anticholinergic side effects and drugs with low anticholinergic activity should be used. Major tranquillisers in low dose have been used by some workers but side effects can be marked and as with antidepressants there is a risk of seizures. Buspirone, a 5HT1A inhibitor is a relatively new anxiolytic with a different mechanism of action to benzodiazepines. Until now it has not exhibited rebound or withdrawal phenomena and not shown a propensity for dependence. However it has only been partially effective or failed in the management of benzodiazepine withdrawal (21,22). Clonidine an alpha 2 adrenergic antagonist has been used effectively in the management of opiate withdrawal, however with benzodiazepines its effects have been mixed but mainly negative. Measures of outcome have varied from centre to centre. However on follow up in general, results are encouraging: 70% of subjects are well, with absent or minimal psychiatric abnormalities; 15% are moderately improved and coping relatively well without regular anxiolytics, some responding to antidepressants; 15% do not improve and resume benzodiazepines (23,24).

TABLE 2. DIAZEPAM EQUIVALENTS FOR ANXIOLYTIC AND HYPNOTIC TREATMENT

Benzodiazepine Name Generic (Trade)	Dose (mg) equivalent to Diazepam	Conversion factor to Diazepam equivalent
Anxiolytics		
Diazepam (Valium)	5.0	X 1
Alprazolam (Xanax)	0.5	X 10
Bromazepam (Lexotan)	2.5	X 2
Clorazepate (Tranxene)	7.5	X 2/3
Chlordiazepoxide (Librium)	10.0	X 1/2
Lorazepam (Ativan)	0.5	X 10
Oxazepam (Serenid)	15.0	X 1/3
Hypnotics		
Diazepam (Valium)	15.0	X 1
Lormetazepam (Noctamid)	1.0	X 15
Nitrazepam (Mogadon)	10.0	X 3/2
Temazepam (Normison)	20.0	X 3/4
Triazolam (Halcion)	0.25	X 60

Courtesy of Department of Psychopharmacology, Institute of Psychiatry, University of London.

PREVENTION

A discussion of benzodiazepine dependence would be incomplete without considering prevention. Thoughtful prescribing must be the hallmark. The type of disorder has to be considered and prescription needs to be appropriate. In cases of major stress or adjustment reactions with severe DISABLING anxiety, benzodiazepine use is justified. However in situations of acute stress such as bereavement, prescription should be avoided because it decreases coping skills and impedes the natural grieving process. In cases of generalised and unfocused anxiety neurosis, where the neurosis is handicapping other drugs can be used and there is now good evidence that antidepressants are more effective than benzodiazepines in this group (25,26). The case for hypnotics is similar. Their use in situations of recent onset insomnia in a setting of severe stress and unfamiliar surroundings is justified. However regular prescription can lead to dependence and rebound insommia on termination. In chronic cases psychological intervention is usually more appropriate.

When benzodiazepines are to be used the duration of treatment should be set in advance, should be for a short period and in lowest possible dose, preferably using intermittent and flexible dosage. If long term treatment is essential in patients with poor coping strategies, then intermittent prescribing is advocated. Patients need to be informed of benzodiazepines' potential for dependence and their drug use monitored. Prescription should be avoided in patients who abuse alcohol or drugs and in those with unstable personality disorder. Finally non-pharmacological intervention should be considered. General practitioner counselling need not be intensive or specially skilled. It has been shown that 10-15 minutes of listening, explanation, advice, reassurance and encouragement are as effective as benzodiazepines in the treatment of minor affective disorder (27,28,29). They also ensure greater patient satisfaction. The medical professional cannot but continue to practice his Hippocratic oath and follow the adage: PRIMUM NON NOCERE.

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