SECOND
EDITION

THE BENZODIAZEPINES

USE, OVERUSE, MISUSE, ABUSE?

by John Marks

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John Marks

MA MD FRCP FRCPsych

Fellow, Tutor and Director of Medical Studies
Girton College, Cambridge

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Preface

In 1978 I wrote a monograph on the overuse, misuse and abuse of the benzodiazepines based on my experience within the Roche organization during the development and marketing of the benzodiazepines, and subsequently within academic medical practice. This monograph, *inter alia*, reviewed the published cases of reputed benzodiazepine dependence from 1960 to mid 1976 and attempted to assess the risk of dependence and abuse.

Since 1978 medical and lay interest in the question of the benzodiazepines has continued. Some of the lay media comment has been emotional and inaccurate and has led to medical problems, though it is clear that the overall interest and discussion of the issues has been beneficial for good medical practice.

The 1978 monograph stressed that high dosage and simultaneous ingestion of other substances of dependence were the main factors in the genesis of dependence. Since then it has become clear that while these are important factors, dependence can occur at normal therapeutic dosage.

Other changes that have occurred since 1978 have been the large number of new benzodiazepines that are available; the overall fall in the use of these substances in most countries and developments in our knowledge of cellular mechanism of actions of the benzodiazepines.

In consequence of these various factors a substantial revision of the monograph appeared necessary and this I have done. As on the previous occasion I have benefited greatly from discussions that I have had with psychiatrists, pharmacologists and legislators in many parts of the world. I should like to acknowledge especially the help given me by John Ward and Jean Kilshaw. However, the interpretation and any errors of commission and omisson are mine alone.

Cambridge, March 1985 JOHN MARKS

Glossary

Abstinence syndrome The syndrome which occurs in drug-dependent people when the drug is withheld. It usually involves both physical and psychological manifestations, the nature of which varies with the drug on which dependence exists. It is also termed withdrawal reaction (q.v.) or withdrawal syndrome.

Addiction A term which is still widely used but which is variously understood and defined by physicians, sociologists and lawyers. It should be discarded for scientific literature and replaced by the term dependence (q.v.) as defined by the World Health Organization.

Crutch phenomenon The reaction to some drugs (e.g. glyceryl trinitrate, psychotropics) which is akin to psychological dependence (q.v.) but in which the patient feels the need to *carry* the drugs in case problems arise.

Drug Any substance which when taken into the living organism may modify one or more of its functions.

Drug abuse Persistent or sporadic excessive drug use inconsistent with or unrelated to acceptable medical practice; cf. 'Misuse' (q.v.). The term abuse covers a wide range of different types of inappropriate use.

Drug dependence A state, psychic and sometimes also physical, which results from the interaction between a living organism and a drug, which is characterized by behavioural and other responses that always include a compulsion to take the drug on a continuous or periodic basis in order to experience its psychic effects and sometimes to avoid the discomfort of its absence. Tolerance may be present.

Misuse Medical or lay use of a drug for a disease state not considered to be appropriate by the majority. This has a close relationship with the

term 'abuse' but the latter can probably best be considered in the more general context of 'affect modification' for personal gratification, whereas the former implies an attempted therapeutic effect, however misguided.

Overuse Excessive medical or lay use of a drug, in terms of length of therapy or severity of disorder treated, for diseases in which there is accepted evidence of therapeutic effect.

Physical dependence The drug, or one or more of its metabolites, has become necessary for the continued functioning of certain body processes. This creates in the dependent person on withdrawal of the drug true physically determined and clinically recognizable signs (the abstinence syndrome – q.v.). These are usually heavily overlaid with psychologically determined symptoms and often manifestations of the disease for which the drug was originally taken.

Pseudo withdrawal reaction A reaction which mimics the abstinence syndrome (q.v.) except that the drug has not actually been withdrawn. It stems from an expectation of problems generated by media anecdotal reports.

Psychoactive substance Any substance which influences mental processes.

Psychological dependence This involves purely emotional components with no physical signs on withdrawal. It runs at one end of the spectrum from the degrees of subjective pleasure or relief of symptoms that are experienced from the drug, through the emotional drives that lead the person to persist in its use, to the change in lifestyle, behaviour and personal involvement where the life pattern revolves around drug taking and the company of others similarly involved. At this extreme the drug use provides a total deviant career often lived as a member of a subculture of drug users alienated by behaviour or law from normal society. It can be regarded as a pharmacological, an anxiety avoidance or a positive operant conditioning response to the drug itself.

Psychotropic substance Any substance which, according to WHO definition, influences mental processes and on which dependence occurs. In general parlance it has been used extensively for any medicine for mental disorders but in view of the WHO definition this use should probably be dropped.

Rebound phenomenon An overreaction of the body processes immediately after suppression by drug activity is removed. It is a common reaction to many drugs.

Tolerance (sometimes referred to as '**acquired tolerance**') The need to employ increasing doses of a drug in order to produce the same effect. This may depend on altered sensitivity of the cell receptor, on increased rates of metabolism of the drug or changes in cell transmitter substances.

Withdrawal reaction (also called '**withdrawal syndrome**') The reaction which occurs when a drug, given for some time, is suddenly withdrawn. It includes the abstinence syndrome (q.v.) with drug dependence; return of the disorder previously controlled by the treatment; pseudo withdrawal reaction (q.v.); crutch phenomenon (q.v.); rebound phenomenon (q.v.).

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1
The General Problem of Dependence and Abuse

> That humanity at large will ever be able to dispense with Artificial Paradises seems very unlikely. Most men and women lead lives at the worst so painful, at the best so monotonous, poor and limited that the urge to escape, the longing to transcend themselves if only for a few moments, is and has always been one of the principal appetites of the soul. Art and religion, carnivals and saturnalia, dancing and listening to oratory – all these have served, in H. G. Wells' phrase, as 'doors in the wall'. And for private, everyday use, there have always been chemical intoxicants. All the vegetable sedatives and narcotics, all the euphorics that grow on trees, the hallucinogens that ripen in berries or can be squeezed from roots – all, without exception, have been known and systematically used by human beings from time immemorial. And to these natural modifiers of consciousness modern science has added its quota of synthetics – chloral, for example, and benzedrine, the bromides, and the barbiturates.
>
> Most of these modifiers of consciousness cannot now be taken except under doctor's orders, or else illegally and at considerable risk. For unrestricted use the West has permitted only alcohol and tobacco. All the other chemical 'doors in the wall' are labelled 'dope', and their unauthorized takers are 'fiends' (Huxley, 1959).

> There is scarcely any agent which can be taken into the body to which some individuals will not get a reaction satisfactory or pleasurable to them, persuading them to continue its use even to the point of abuse (Eddy *et al.*, 1965).

At the present time, indeed for many centuries past, there can be few people throughout the world who do not 'overuse', 'misuse' or 'abuse' some drug. For many the drugs that are 'overused' are caffeine (from tea

or coffee), nicotine (from tobacco) or alcohol (from beer, wine or spirits), all socially accepted normal ingredients of everyday life in most communities. For a smaller group the 'misuse' concerns commonly prescribed medical substances, e.g. barbiturates, amphetamines. For an even smaller group there is the less socially acceptable or frankly unacceptable 'abuse' of specific substances such as solvents, morphine and related analgesics, cannabis, or hallucinogens.

Each of these substances is usually taken to provide some form of positive pleasure or to relieve stress, anxiety, depression or pain.

Much of this field of study is still covered with confusion, not only because the socially acceptable practices of one generation or community are the legally enforceable abuses of another, but because much of the terminology that has been employed has become subject to lack of general agreement.

The term that is still in the widest general use is 'addiction', but because of the differences that exist in its understanding there is a growing tendency to use the word 'dependence' and to adopt the World Health Organization's definitions (WHO, 1950). The basic terms are 'drug', 'drug abuse' and 'drug dependence' and the World Health Organization's definitions for these terms have already been given in the glossary.

The WHO recommendation (WHO, 1964) is that when drug dependence is being discussed the type should be specified because there is considerable variation in the possible features, in their intensity and in their importance to the individual and to society. The question of types is discussed later (p. 7) and as more studies are undertaken the recognized number of types is extended. To these basic WHO definitions it is convenient to add certain others, namely 'misuse', 'overuse' and 'tolerance' and these terms are also defined in the glossary. These definitions will be used in this monograph to minimize confusion.

The World Health Organization definition of dependence can with advantage be elaborated to include the concept of physical and psychological dependence (see glossary), though in many instances this distinction appears to be somewhat arbitrary.

One further term which can cause confusion in its usage is 'psychotropic'. By basic definition any substance that can lead to dependence must be psychoactive, i.e. alter the mental processes. Such substances, and particularly those used for therapy of mental disorders, have been termed 'psychotropics' or 'psychotropic substances'. However, the UNO definition reserves the term 'psychotropic' for a substance which leads to dependence (UNO, 1971a) and the term psychoactive is therefore probably more appropriate as the general term for the group.

A BROADER CONCEPT OF 'PSYCHOTROPICS'

It has already been stressed (p. 3) that there are few of us who do not resort to some form of 'drug' (taking that term in its wide WHO definition), in a manner that must come broadly within the format of psychological dependence. That is to say there is an unnatural drive towards the 'drug' for a pleasure-seeking goal. For most of us the 'drug' concerned is one of the socially accepted beverages; tea, coffee or alcohol, although even within these socially accepted drinks a spectrum of dependence becomes immediately apparent with alcohol at the high-risk end but with caffeinism also recognized as a problem (Greden, 1974; Gilbert, 1976; Greden *et al.*, 1981).

Each of these substances can be classed as a psychotropic 'drug' by the UN/WHO definition, for there is a mood change as a result of its ingestion, and some measure of dependence.

It is then important to realize that the concept of psychotropic can be extended beyond the realm of drugs, for a broad range of human activities can be used to produce a mood change. What is then apparent is that on each of these some measure of psychological dependence occurs assayed in terms of an unnatural drive towards that pleasure-seeking goal. This may just consist of the need for the cup of tea on waking up; the obsessional completion of *The Times* crossword; the cultivation of prize blooms or vegetables; the irrational drive to watch some form of sport on a regular basis. It extends in well over 50% of the populations of developed countries into the socially acceptable but true 'addictions' of smoking, drinking and gambling.

Peer and priest, senator and serf, doctor and dustman alike experience one or more excessive pleasure-seeking drives. We should consider each of these activities within a wider concept of 'psychotropics' and perhaps speak of those that are socially acceptable as the 'social psychotropics'.

However, the concept of social acceptability immediately raises a value-judgement. Within the group of the psychotropics such a judgement is difficult for there are no scientifically definable borders or limits between the various grades of dependence that exist – rather we should view the whole range of psychotropics as a spectrum (Figure 1). At one end of the scale are the commonplace socially unacceptable patterns of those dependent, for example, on heroin. But how do we assign a rating order for the intermediate dependences? It is difficult to do so scientifically, for we are biased by the social fashions of our culture, nation and age and by our own predilections and aversions. But even if we establish a rating order, it is very difficult to define the border between acceptability and non-acceptability without value-judgements subject to bias. The United Nations' Convention (UNO, 1971a) adopts the concept of 'public health and social problems' when the need for action is considered.

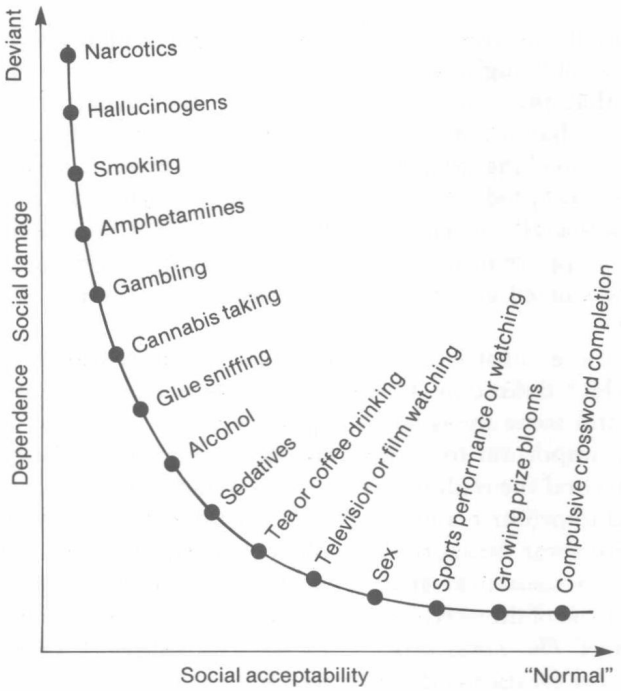

Figure 1 The broad concept of psychotropics as the range of pleasure-giving activities of the community for which some measure of unnatural drive (or dependence) exists. Examination shows that the rating order of the individual activities must represent the bias of the author. While the extremes can be labelled 'Deviant' and 'Normal' with accuracy and ease, the limit of social acceptability depends upon a value judgement influenced by political, social and individual factors

This view of drug misuse as an example of a broad range of pleasure-seeking drives has been denied by others (Keup, 1982), but it is still regarded as a useful working hypothesis which explains the wide-ranging activity of pleasure-seeking within the community. It stresses that drug misuse involves not only factors related to the substance itself, but also to the host and the environment (Stepney, 1980).

Just as normal levels of anxiety can be an important drive for the examinee or athlete, and morbid anxiety can destroy the ability, so can nearly all these pleasure-seeking drives stimulate work for good or evil. The social object should be to encourage that for good and attempt to remove the component that brings evil. Education (p. 5) will help this, but legislation rarely does so and should be reserved for those activities where the dangers to society as a whole are greatest. This is considered in more detail on pp. 7 *et seq.*

Thus the problem of dependence on drugs, the topic that is of prime interest to us, must be viewed not in isolation but as part of the wide realm of a full spectrum of 'psychotropics', many of which can be 'overused' or indeed 'abused', and which give rise to dependence.

Specifically we are concerned with the benzodiazepines, a group of therapeutic substances on which dependence and abuse can occur. This monograph considers benzodiazepine dependence and abuse and the factors that influence it. It attempts to put the dependence and abuse in clinical perspective and to define how the benzodiazepines should be used in clinical practice to reduce the risks while maintaining the therapeutic benefits.

TYPES OF DRUG DEPENDENCE

The WHO expert committee has recognized that different groups of drugs produce different types of dependence and that the type should be specified. The currently accepted types, the main classes of drugs involved and the clinical characteristics of the dependence are shown in Table 1. Apart from noting the great variety of types that are now recognized, the majority of classes can be ignored for the purpose of the present monograph and attention can be concentrated on the groups of ethanol and barbiturate/sedative. There are still divergent opinions on whether they should be grouped together – for both show psychological and physical dependence with virtually identical withdrawal reactions – or whether they should be separated. In favour of their being put into a single group is the extensive cross-tolerance that can occur among drugs with similar actions, regardless of chemical structure, and the partial effectiveness of one group in ameliorating the withdrawal efffects of the other.

Thus, for example, severe ethanol withdrawal reactions can be prevented by barbiturates (Essig *et al.*, 1969), phenothiazines (Sereny and Kalant, 1965), benzodiazepines (Sereny and Kalant, 1965; Kaim, 1973), chloral hydrate and paraldehyde (Kaim *et al.*, 1969). Conversely ethanol is partially effective in the prevention of barbiturate withdrawal phenomena (Frazer *et al.*, 1957). Such sedatives, however, have no specific effect on the morphine-type withdrawal syndromes, although other members of that group can cross-substitute (e.g. methadone for morphine) – and sedatives can reduce the severity of some of the manifestations.

Despite this evidence of cross-substitution between ethanol and the barbiturate/sedatives it is probably wiser to regard them as separate groups at the present time. Benzodiazepine dependence is clearly recognized as falling within the sedative type, though the incidence and severity differs substantially from that of some other sedatives (e.g. methaqualone).