PROGRAMME ON

SUBSTANCE ABUSE

RATIONAL USE OF

BENZODIAZEPINES

WORLD HEALTH ORGANIZATION

ABSTRACT

Benzodiazepines are among the most widely prescribed drugs in the world, used mainly as anxiolytics or hypnotics. With their wide array of therapeutic uses and their popularity among physicians and patients, benzodiazepines have raised some concern about problems of dependence and abuse.

Because of the clinical and public health importance of these questions, the World Psychiatric Association (WPA) set up a Task Force to review this matter in 1992. The Task Force report provided the basis for the development of this document, which presents an objective review of the issues regarding benzodiazepines, and a guide for their clinical usage.

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1. GENERAL INTRODUCTION

Since the introduction of chlordiazepoxide and diazepam into medical practice during the 1960s, benzodiazepines have become one of the most widely used groups of medications. Because of the clinical and public health importance of the efficacy, safety and regulation of benzodiazepines, the variety of claims and counterclaims about these issues, the World Psychiatric Association (WPA) set up a Presidential Task Force to review this area in 1992. The WPA Task Force report provided the basis for the development of this document by WHO, with the help of those experts listed in **Annex 1**.

The initial draft focused on the psychiatric use of benzodiazepines, with psychiatrists as the target audience. In view of the fact that most benzodiazepines are prescribed by primary care practitioners, it was subsequently decided to include non-psychiatric indications, thus adding primary care practitioners to the target audience. It was also agreed to make this document useful for Ministries of Health to develop, as required, informational or educational materials on the rational use of benzodiazepines.

Terminology has been an issue in developing this document **(Annex 2)**. ICD-10 terminology (WHO, 1992) has been used as far as possible, particularly in discussions requiring clinical accuracy, such as the chapter on Indications. In other chapters, some of the terms in common usage have been employed in the sense described in **Annex 3**, even though they may not entirely correspond to ICD-10 terminology.

The intention of this document is to provide an overview on the pharmacology and clinical use of benzodiazepines. As such, it contains reviews and benzodiazepine papers as references, but does not include an exhaustive bibliography.

2. EPIDEMIOLOGY: MEDICAL USE OF BENZODIAZEPINES

2.1 Introduction

General practitioners prescribe about 80 per cent of benzodiazepines, which are the most frequently prescribed drugs after drugs for heart and circulatory problems (Woods, Katz & Winger, 1992). An average of 10 per cent of the population uses benzodiazepines as tranquillizers and/or hypnotics, one-third on a regular basis and the rest for longer periods of time (more than 180 days), who are called long-term users (Balter et al., 1984). Although medical use of benzodiazepines is indicated for anxiety and insomnia, benzodiazepines are more effective in the treatment of severe anxiety than in long-term insomnia. Since most concerns surrounding benzodiazepines originate in their potential for long-term use and dependence, it is relevant to document which patient populations are using benzodiazepines, why, and for how long.

2.2 Indications

Benzodiazepines were originally marketed to alleviate anxiety, stress and insomnia, and are additionally used as muscle-relaxants, anti-convulsants, and premedication for anaesthesia (Hollister, 1985). Recent reviews advise to restrict the use of benzodiazepines in general practice for anxiety disorders and sleep disorders. In some countries benzodiazepines are used during alcohol withdrawal; in other countries this indication is questioned, due to possible shifts of dependence from alcohol to benzodiazepines. Also the prescription of benzodiazepines for muscle spasms and back pain is not common practice any longer (see also chapter on Indications).

In all studies concerning prescription patterns of benzodiazepines, it is noted that scarce information is given on diagnosis and/or indications for benzodiazepine prescriptions on patient charts, in contrast to prescriptions of various other (non-psychotropic) drugs (Buchsbaum et al. 1986). A marked discrepancy exists between the recognized indications for benzodiazepines and conditions for which users perceived they received the drugs. In nearly half of benzodiazepine purchases, the users mentioned indications not

supported by the recent literature. Misconceptions among patients, poorly- informed patients, as well as substandard prescribing practices, are all possible explanations (Olfson & Pincus 1994). But also in recent prescription and hospital studies, it was found that initial benzodiazepine prescriptions were given in 35 and 38.5 per cent of cases respectively for other reasons than the recognized indications (van der Waals et al., 1993) (Zisselman et al., 1994).

Although some benzodiazepines are advised to be used for indications of anxiety, some for panic attacks and again others for insomnia due to overlapping properties, no epidemiological studies can be solely based on types of benzodiazepines or Defined Daily Doses (DDDs). Only scattered epidemiological information on indication and prescription of certain types of benzodiazepines, in combination with consumption, is available.

All recent publications have similar recommendations for the duration of treatment, especially for the elderly: "Clinicians should endeavour to use the lowest benzodiazepine doses, that are therapeutic, for the briefest period of time, usually for no more than 2 to 4 weeks of continuous use" (American Psychiatric Association, 1990). Epidemiological studies give little insight into the duration of the prescriptions and the duration of the use. Some longitudinal studies concerning a small population using benzodiazepines over several years do show, however, that a proportion of benzodiazepine users continue to use benzodiazepines over several years (Isacson et al., 1992).

2.3 Sales data

Sales data on benzodiazepines in different countries are mostly collected by the Institute of Medical Statistics (IMS) (Instituut voor Medische Statistiek, 1991). The IMS is an international research company that obtains sales data from a number of countries concerning pharmaceutical products. The sales data in the European Community are given in counting units (cu's) which means the smallest unit of a product, i.e. one tablet, one ml, one capsule etc. The sales of benzodiazepines includes sales to hospitals in some countries, but not in others (Belgium, France, Greece and Ireland). Still, the sales in Belgium and France are higher than in other EU countries (in France 60 cu benzodiazepines are sold per inhabitant compared to Germany, 18). Overall the cu's per inhabitant have slightly increased from 28 in 1978 to 30 in 1990, despite the fact that Germany and the UK showed a decrease in sales. While in 1978 the sales data did not differ much between the countries (17-38 cu's), this difference increased in later years (18 to 60 cu's per inhabitant). The most striking increase in sales is seen in short-acting benzodiazepines. Belgium sells the most, and Ireland the least, but the rise in sales is similar in all countries. The impact of negative publicity in the 1980s is not reflected in sales data. For instance in France, where the public and physicians must have received an abundance of information on triazolam, sales remained higher than in any other EU country. Also in Brazil, Canada, Japan and the United States, an increase in benzodiazepine sales is noted. This trend was more explicit for hypnotics (47 per cent) especially in the short-acting benzodiazepines, than in tranquillizers (13 per cent) (Woods, Katz & Winger, 1992). Retail data supports the findings of wholesale data. The countries with the highest volumes of pharmacy sales of benzodiazepines in 1989 were, in descending order, the US, France, Japan, Italy , UK, the former GDR, Spain, Brazil and Canada. But pharmacy sales indicate a wide variation in rates per capita exposure, the highest being France, while the US rates are in the middle of the above countries.

Unfortunately, however, unlike DDDs, the sales data in cu's cannot show the doses nor number of patients using benzodiazepines.

2.4 Prescription data

Over the years, a gradual decline in benzodiazepine prescription has been noticed in Western Europe and the US. Surveys in Western European regions have found patterns of benzodiazepine-prescribing similar to those found in the US through a 1991 study conducted by the National Disease and Therapeutics Index. Based on a national sample of privately practising physicians, this study indicated that more than 80 per cent

of the office visits at which a benzodiazepine was prescribed, were visits made by patients seen previously by the prescriber. Two out of every three such prescriptions represented long-term therapy. During the 1980s, anxiolytic prescriptions written by primary care physicians decreased from 53 to 46 per cent of all benzodiazepines prescribed. However, the percentages issued by psychiatrists increased in the same period from 19 per cent in 1981, to 23 per cent in 1991. Prescriptions issued to patients in the offices of physicians increased from 59 to 69 per cent, and prescriptions in hospitals decreased. Also, the proportion of these prescriptions written for patients whose principal diagnoses were mental disorders, increased from 45 to 59 per cent. Almost half of the hypnotics were prescribed to patients whose primary diagnoses were mental disorders or sleep disturbances; an additional quarter were prescribed for surgical aftercare (Woods, Katz & Winger, 1992). A study based on the same data, but focusing solely on hypnotics, showed that benzodiazepine prescriptions for insomnia declined by 30 per cent from 1987 to 1991, while the prescription of anti-depressants to treat insomnia increased by about 100 per cent. The decreased prescription of benzodiazepines for insomnia was more striking for inpatients than for outpatients (Walsh & Engelhardt 1992). A US survey of office-based physicians found primary care physicians responsible for more than 70 per cent of prescriptions for benzodiazepine anxiolytics and hypnotics. Mental disorders were the diagnoses for only 40 per cent of patients given benzodiazepines, about 20 per cent of those given benzodiazepine hypnotics (Woods, Katz & Winger, 1992). A Belgian study among general practitioners showed similar figures: 43 per cent of patients received benzodiazepines for mental complaints (De Maeseneer, 1989).

Most studies show that women, or at least women over 45 years of age, are nearly twice as likely as men to receive benzodiazepine prescriptions. The rate of prescription increases consistently with age, at least to about the age of 65. After that age, the rate of anxiolytic prescriptions declines slightly, but in most regions, the rate of prescriptions for hypnotics continues to increase with age (Isacson & Smedby, 1988; Simpson et al., 1990). Studies of prescription records of non-psychiatric outpatients in several countries show that a relatively small proportion of the patient population receives the majority of benzodiazepine prescriptions. These patients are those who continue to receive prescriptions for long periods of time, often with a relatively high frequency of dose. The repeat prescriptions are often obtained without direct contact between patient and physician. A Canadian study revealed that the prescription rate increases with age for both sexes but that women over 65 received 44 per cent of all benzodiazepine prescriptions (Rossner, 1987). In the UK, a study comparing urban and rural practices found that general practitioners treated patients with anxiety disorders mostly with psychoactive drugs. Tricyclic antidepressants were prescribed in 59 per cent of these cases, second generation antidepressants in 32 per cent, benzodiazepine anxiolytics in 35 per cent, and benzodiazepine hypnotics in 18 per cent. (Some patients were simultaneously prescribed more than one of these four types of medication). The general practitioners expressed sensitivity as to issues of over-prescription, both of benzodiazepines and drugs in general, but still used drug treatment more than any other form of therapy. The prescriptions of longest duration were for benzodiazepine anxiolytics - 38 weeks in urban practice and 24 weeks in rural practice (Tyrer, Casey & Sievewright, 1988). At an Australian university hospital, the probability of filling at least ten prescriptions for different drugs during a 3-month period increased with patients' age and with the number of visits and admissions, but not with patients' sex. Benzodiazepines were the drugs most commonly prescribed to the polypharmacy group, i.e., patients receiving more than ten prescription drugs. For this group, 64 per cent of medications were benzodiazepines, as compared to 37 per cent for a control group receiving fewer prescriptions (McMillan et al. 1986).

Inpatient studies in most countries found that about 30 per cent of non-psychiatric patients are prescribed benzodiazepines. In English hospitals, the percentage across age groups is lower (about 19 per cent), consistent with other data showing a decline in anxiolytic use in the UK since 1985 when new restrictions were established (Busto et al., 1990). An association between hospital admission and the start of benzodiazepine use is acknowledged in some studies (Surendrakumar et al., 1992; Hecker et al., 1992), and rejected in others (Braylay et al., 1989) but patient population characteristics might be responsible for different outcomes. For example, a hospital start-up of benzodiazepines would be more likely among non-psychiatric patients than among psychiatric patients who have often taken these drugs before admission. After discharge, hospital patients who had already used benzodiazepines tend to resume their pre-admission

level of use; however, of patients who start benzodiazepines in hospital, about 5 per cent continue their use after discharge (Edwards et al., 1991).

2.5 Consumption of benzodiazepines

Pharmacy records give an indication of which patients actually repeat the prescriptions written by their physicians. Since 1989, pharmaceutical information has been studied in the Netherlands: which medication was repeated, when, and in what dose; age and sex of patient and prescriber, and patient's insurance (Herings, 1991). The resulting data show that after oral contraceptives, benzodiazepines are the most prescribed chronic medication in the Netherlands. More than 10 per cent of the total adult population is using benzodiazepines, and one third of this group has used them long-term, i.e., longer than 180 days. Twice as many women as men are using benzodiazepines. Of people over 60, 25-30 per cent are using benzodiazepines; of these, 40-50 per cent have used them long-term. Since people over 60 use many other medications, their high percentage of benzodiazepine use is believed to be associated with high general morbidity.

Population surveys can yield data to complement pharmacy and physician data on prescriptions, since actual consumption can differ from patterns suggested by prescription records. Population studies assist in the definition and analysis of actual benzodiazepine users, the time and rationale of the initial prescription, and the number of months or years of use. Interesting data have come from national and regional surveys and from surveys of particular population groups within a nation or region.

Balter and co-workers were the first to initiate cross-national surveys in the US and several European countries (Balter et al., 1974, 1984). Findings in the US confirmed sales and prescription studies, i.e., from 1979 to 1990, the annual use of anxiolytic benziodiazepines declined from 11.3 to 8.3 per cent of the adult population. Use of hypnotics remained stable at 2.6 per cent of the population. In 1979 and in 1990, the majority had used benzodiazepines regularly for a short period (less than one month) but from 1979 to 1990, short-term users declined and long-term users increased. This difference was most pronounced among users of anxiolytics. In 1979, 15 per cent of these people (1.5 per cent of the population) used the medication for longer than one year; in 1990, the number of long-term users had risen to 25 per cent (2 per cent of the population) (Balter, 1991). In the UK, a similar study showed that in 1985, 55 per cent of benzodiazepine users used the drugs on a regular basis (daily or almost daily). Of these, 20 per cent had used the drugs less than one month, and 52 per cent had used them for more than one year. Twice as many women as men were using benzodiazepines. Of all users, 15 per cent said they had tried to stop taking the drugs. Difficulty in discontinuing the medication was linked to age (over 45 years) and duration of use, but not to the kind of benzodiazepine nor to the sex of the users (Dunbar et al., 1989). Comparing data with Balter, these researchers concluded that overall prevalence of use might have declined, but long-term regular use of benzodiazepines had increased substantially. These researchers also studied concurrent use of alcohol, nicotine, and caffeine among benzodiazepine users. They found that current users of benzodiazepines were less likely to use alcohol than past users, who in turn were less likely to use alcohol than non-users of benzodiazepines. This difference could in part be explained by age differences between groups (i.e., alcohol use tends to decline with age) (Dunbar et al., 1989). Predictors for long-term use are age, gender, previous use, a combined use of tranquillizers and hypnotics, and prescriptions from more than one prescriber, low level of education, and in women social problems have been described.

In most surveys worldwide, the same trend was seen: women were approximately twice as likely to report use, and their rate of use increased with age. Several studies report various sociodemographic factors. For example, prevalence of use was higher among never-married, widowed, or divorced persons than among those currently married. Use was higher in lower income groups than in higher income groups. Use was higher in whites than in blacks. All studies found that retired people used most, followed by unemployed people, with employed people using the least (Rawson & d'Arcy, 1991; Blennow et al., 1994).

Regional surveys give the most specific information on benzodiazepine use within communities, and report demographic variables among users. Various prevalence studies have found great similarity among European countries (i.e., Denmark, Germany, Spain, Sweden and the UK) and in the US. Current use, i.e., use at least once in the month prior to investigation, ranged from 5 to 8 per cent of the population. Daily use was reported by 2.5 to 3 per cent. In all studies, more women than men were using hypnotics and anxiolytics (of which 80 per cent were benzodiazepines), and older people were using more than younger people. Benzodiazepine use was found to be much higher among outpatients (i.e., people routinely visiting a clinic to see a specialist) than in the community at large. A case control study of outpatients in Barcelona showed that users had significantly more chronic physical disorders (particularly cardiovascular and musculoskeletal) than controls. They were also significantly more likely to have psychiatric disorders, according to a self-rated psychiatric scale (SCL-90R). The mean duration of benzodiazepine treatment in these patients was 50 months.

2.6 Conclusion

Sales data of benzodiazepines, especially the short-acting benzodiazepines, are showing an increase in sales. This contradicts the fact that benzodiazepine use is declining gradually. All major surveys in the US and the UK suggest, however, that the long-term use of benzodiazepines has increased in the last ten years. Less than half of the patients that use benzodiazepines receive these for recognized indications. Even less patients receive benzodiazepines for the advised duration of time. All studies and surveys find that prevalence of use is higher in women than in men and highest in the older population, and that older patients fill a higher percentage of benzodiazepine prescriptions than younger patients. Older populations with more physical complaints are more likely to receive benzodiazepines from their primary care physicians or in hospital when they are treated for somatic complaints.

3. PHARMACOLOGY

3.1 Introduction

The present chapter summarizes the clinical pharmacodynamic and pharmacokinetic properties of benzodiazepines. The goal is to better prescribe these compounds in the field of anxiety, sleep disorders and as anticonvulsant drugs, but the full list of clinical uses is much longer and is still growing (Hollister & Shader, 1993).

All pharmacokinetic parameters are overviewed: absorption, blood protein binding, distribution, metabolization and half-lives. A new approach is taken to find the relationship between brain concentrations and receptor bindings in order to give an explanation of their duration of effect.

A careful evaluation of pharmacological properties of anxiolytic agents is necessary to enable clinicians to address appropriate anxiolytic treatments. When considering "classic benzodiazepines," several thousand have been synthesized and more than thirty are, at present, available worldwide for medical use.

Although there are many similarities among the various benzodiazepine compounds, there are also significant differences. It had been widely considered that these agents were virtually identical pharmacodynamically, with pharmacokinetic factors accounting for the clinically important differences between them.

Large quantitative variations in the intrinsic affinity for the receptor sites require an appropriate adjustment of dosage in order to compare the clinical activity of various benzodiazepines.

After this adjustment it is even more difficult to distinguish substantial qualitative differences in their clinical efficacy. Therefore pharmacokinetic factors, particularly those concerning onset and duration of action, became the main reasons why certain benzodiazepines were recommended for particular clinical applications.

3.2 Benzodiazepine receptors

In the 1970s, several groups of researchers found specific benzodiazepine binding sites in the brain (Bossman et al., 1977; Braestrup & Squires, 1977; Möhler & Okada, 1977). Evidence that these benzodiazepine receptors localized on neurons in the CNS mediate the pharmacological actions of benzodiazepines is provided by the strong correlation between potencies of various benzodiazepines in displacing tritiated benzodiazepines from benzodiazepine receptors in vitro. This mediation is also demonstrated by the benzodiazepine potencies as anticonvulsants, anxiolytics and muscle relaxants and in various animal models of inhibited behaviours (Young & Kuhar, 1980).

The benzodiazepine receptor belongs to the GABA-A receptor complex. The GABA-A receptor is the most abundant inhibitory receptor in the mammalian brain. It has a heteropolymeric structure that forms a chloride-channel (Barnard et al., 1988). The binding of two molecules of neurotransmitter to the specific recognition site on the GABA-A receptor opens the ion channel and triggers an inflow into the cell, that hyperpolarize the neuron, preventing activation by the incoming depolarizing stimuli. This Cl inward flow may be modulated both by endogenous substances and by drugs which operate as positive or negative allosteric regulators. GABA action may be affected by isosteric receptor antagonists, that have been suggested to bind to the extra-cellular domain of the receptor. Allosteric regulation is operated by two different classes of compounds:

a)   those that act on the extra-cellular domain; and
b)   those that act on the channel domain of the receptor with both classes including positive and negative allosteric modulators.

The positive modulators acting on the extra-cellular domain include benzodiazepines, imidazolopyridine (zolpidem), cyclopyrrolones (zopiclone, suriclone), imidazopyrimidine (divaplon), triazolopyridazine (CL 218872), pyrazolopyridine (ICI 190622) (Blanchard et al. 1979) (Stephens & Kehr, 1985). The list of the negative modulators mainly consists of β-carboline derivatives. Positive and negative allosteric modulators that interact with the extra-cellular domain of GABA-A receptor are antagonized by the imidabenzodiazepinone, flumazenil. On the other hand, drugs which bind within the channel domain can act as both positive (barbiturates and steroid hormone derivatives) or negative (pregnenolone sulphate and picrotoxin) allosteric modulators.

3.3 Pharmacokinetic parameters

The correct use of benzodiazepine anxiolytics requires a knowledge of pharmacokinetic and pharmacodynamic parameters. The impact of pharmacokinetic factors on clinical action has to be investigated in theoretical models in which pharmacodynamic variables must be considered as consistent with drugs in the body. In the context of pharmacokinetic concepts, two assumptions have been made: plasma benzodiazepine levels positively correlate with benzodiazepine concentrations at brain receptor sites; and clinical efficacy correlates with plasma concentrations above the minimal effective concentration, below which no clinical effects are expected. Whereas the first notion is well accepted since benzodiazepine are highly lipophilic and rapidly achieve equilibrium across the blood brain barrier, an opinion of minimal effective concentration may change with the different clinical effects being examined and the methods used to quantify them.

3.3.1 Absorption

The time required for the onset of action, that is the time period between drug ingestion and the point at which clinical action occurs, is not equivalent to the interval at which peak plasma levels are reached. For instance, for clonazepam, the onset of clinical action occurs within 20-30 minutes of ingestion, whereas the peak of plasma concentration is achieved between one and two hours after oral ingestion.

Those benzodiazepines which are rapidly absorbed from the gastrointestinal tract have a prompt clinical action, whereas those which are slowly absorbed have a much slower onset of action. After oral administration, the absorption of diazepam, alprazolam, desmethyldiazepam (e.g. formed from its precursor clorazepate), flurazepam (leading to its aldehyde and hydroxyethyl metabolites) midazolam and triazolam is very rapid. The peak plasma concentration occurs about one hour after ingestion. Such rapid absorption accounts for the acute subjective high drowsiness, "spaced-out" feeling and/or motor impairment after the drug is ingested. Diazepam has a very high systemic bio-availability, lorazepam, oxazepam and prazepam (which reach the systemic circulation only in the form of active metabolites) are absorbed more slowly and achieve peak plasma concentration within two hours of oral administration.

Rapid onset of action after oral dosage may represent a desirable objective for the treatment of sleep onset disorders. Conversely, for the treatment of anxiety, the benefits of a rapid onset of clinical effects are much less clearly defined. Whereas many subjects consider the prompt onset of action provided by rapidly absorbed benzodiazepines to be helpful, others experience the same effects as disturbing and undesirable. Therefore both slowly and rapidly absorbed benzodiazepines have to be available, the choice depending upon the specific clinical situation as well as the sensitivity of the individual subject. All else being equal, benzodiazepine absorption can be affected by several factors including food, concurrent therapy and position of the body. Thus a slowed and decreased absorption occurs in the reclining position, in the presence of food in the stomach or when a benzodiazepine is administered together with an aluminium-containing antacid.

The contents of some tablets and hard gelatin capsules are less rapidly absorbed than the soft gelatin capsules containing benzodiazepines dissolved in polyethylene glycol.

Irrespective of routes of administration, plasma concentrations reached with benzodiazepines show high inter-individual variations. The inter-subject variability is also observed for all other pharmacokinetic factors. After intramuscular injection of diazepam or chlordiazepoxide, absorption is slow (the plasma levels peaking at 10-12 hours) and variable in duration (though eventually complete). As a consequence clinical effects may be delayed and unpredictable. Therefore, for these drugs the intramuscular route should be avoided. Lorazepam, clonazepam and midazolam on the other hand are well absorbed following i.m. injection. As the rates of intramuscular absorption of these drugs are superior than that obtained with an oral dose, the peak levels in the blood are higher and the clinical effect greater.

Rectal administration of benzodiazepines is rarely used because of the relatively low concentrations obtained with this route. An exception is found with diazepam which can achieve acceptable plasma levels when administered rectally in children.

In a few countries, benzodiazepines are available in a form for sublingual administration. Lorazepam has been developed in this form with the idea that, by passing the gastrointestinal tract, the minimal effective concentration is achieved more rapidly and the time of onset of clinical effect is similar to that obtained with the intramuscular route. However, no significant differences have been found between the absorption rates of the sublingual and the standard oral tablets.

When benzodiazepines are given by oral or intramuscular administration, the absorption rate from the gut or from the site of injection appears to be the rate-limiting step in onset of clinical activity. Indeed, intravenous administration, bypassing absorption, results in a more rapid onset of activity, mainly determined by the time it takes for the drug to diffuse across the blood brain barrier. This explains the small variability in time of onset of action exhibited by various benzodiazepines whose metabolites are extensively bound to serum proteins.

3.3.2 Blood protein binding

The extent of binding varies considerably between drugs and ranges from about 70 per cent for alprazolam to nearly 99 per cent for diazepam. The primary binding protein for benzodiazepine appears to be albumin although triazolobenzodiazepines may bind to some degree to all acid glycoprotein. This binding decreases the concentration of free active drug in equilibrium with the sites of action and elimination, thereby decreasing the intensity of action but prolonging the effect and slowing the elimination.

Glomerular filtration of many benzodiazepines is low because of their extensive serum protein binding. Conditions of hypoalbuminaemia occurring with age or with disease states including cirrhosis, renal insufficiency or severe burns, results in higher levels of free active drug. In this case, side effects such as drowsiness might be more frequent, since only unbound drug molecules have access to the central nervous system. Therefore, the displacement of a benzodiazepine from plasma binding sites by another drug could modify its effect and possibly lead to drug interactions between this class and other pharmacological agents. However, very few clinically significant interactions involving benzodiazepines appear to be based on competition for common plasma protein binding sites.

3.3.3 Distribution

After peak plasma levels are achieved during the distribution phase, benzodiazepines exhibit an initial rapid decline in plasma concentration which then levels off into a more gradual decrease during the elimination phase. Therefore the curve representing plasma clearance shows a biphasic profile consistent with a two compartment model. In the initial phase (the alpha phase) the rate of decrement of plasma drug concentration is the result of drug distribution from the central (serum and brain) to peripheral compartments (including adipose tissue, skeletal muscle and liver).

The extent of peripheral distribution (as determined by volume of distribution) increases with benzodiazepines that are more lipophilic. After distribution equilibrium is attained, the rate of drug disappearance from plasma enters a slower phase, the beta phase, which is indicative of drug elimination from the body, mainly by liver biotransformation and kidney clearance.

3.3.4 Metabolism and drug interactions

Hepatic metabolism accounts for the biotransformation of all benzodiazepines. The two major pathways involved are microsomal oxidation, including N-dealkylation or aliphatic hydroxylation, and subsequent conjugation by glucuronic transferases to form glucuronides that are excreted in the urine. The pattern and rates of metabolism depend on the individual drugs. For benzodiazepines with a substituent group at position 1 or 2 of the diazepine ring, the first step of metabolism involves removal of the substituent with the formation of N-desalkylated biologically active compounds. Nordiazepam is the major metabolite common to the biotransformation of clorazepate, diazepam, halazepam and prazepam (Shader et al., 1981).

The subsequent step results in hydroxylation at position 3 which yields an active compound (e.g. oxazepam from nordiazepam). The conjugation of the 3-OH compounds with glycuronic acid represent the last stage.

The 3-OH benzodiazepines - oxazepam, lorazepam and temazepam - by virtue of the 3-OH group, can be directly conjugated (Bourin, 1986). The glucuronide metabolites are pharmacologically inactive and are excreted in the urine as such. The 7-nitro benzodiazepines, clonazepam and nitrazepam, are metabolized by reduction of 7-nitro groups to form inactive amines which are then acetylated before excretion. Alprazolam and triazolam are metabolized principally by initial hydroxylation of the methyl group on the fused triazolo ring. Midazolam is rapidly metabolized, primarily by hydroxylation of the methyl group on the fused imidazolo ring. Since benzodiazepines do not seem to induce synthesis of hepatic microsomal enzymes, prolonged administration usually does not induce accelerated metabolism of other drugs or of benzodiazepines. Oxidation (which results in active metabolites) is influenced by factors such as age, liver impairment and inhibition of liver enzymes by other drugs (cimetidine, oral contraceptives, isoniazid, phenytoin, propranolol, disulfiram) (Patwardhan et al., 1980; Sellers et al., 1980; Shull et al., 1976). Conjugation is much less influenced by these factors, and therefore, theoretically at least, benzodiazepines metabolized by conjugation are safer to use in the elderly or in patients with liver diseases. Renal insufficiency may impair excretion of glucuronide metabolites causing their accumulation, but this has not been demonstrated to have pharmacological consequences since the metabolites are inactive. There is one situation in which interactions become important and that is with suicidal overdose. Although benzodiazepines are benign in overdose when taken alone, they potentiate the effects of other CNS depressants (e.g. alcohol) with sometimes lethal effects.

3.3.5 Half-life and duration of effect

In general, benzodiazepines may be classified into three major groups, according to their elimination half-life;

a) Long-acting, such as diazepam, clobazam and clorazepate. In fact, these display half-life values which exceed 24 hours and, in the process of liver biotransformation, they generate long half-life active metabolites. Therefore, they accumulate extensively during repeated administration.

b) Intermediate and short-acting, such as alprazolam, clonazepam, chlordiazepoxide, lorazepam, lormetazepam, oxazepam, nitrazepam and temazepam. Their half-life values range from 5 to 24 hours, and compounds metabolically generated are non-active.

c) Ultra short-acting, such as triazolam and midazolam. These have half-life values of less than 5 hours and are essentially non-accumulating agents.

Indeed, the duration of pharmacological activity of benzodiazepines does not correlate directly with the plasma concentration profiles of these drugs. For instance, the pharmacokinetic profile would suggest that lorazepam, with a rapid elimination half-life, would be a shorter acting benzodiazepine than diazepam, if there were a direct correlation of effect with pharmacokinetics. However, lorazepam has been shown to have a longer duration of pharmacological activity, suggesting that factors other than plasma half-life also have to be considered when assessing the duration of the pharmacological effects of benzodiazepines.

3.3.6 Brain concentration and receptor binding

Benzodiazepines have to cross the blood-brain barrier (BBB) to elicit their pharmacological effects. The physicochemical properties which influence the rate and extent of drug entry into the cerebrospinal fluid (CSF) and brain are protein binding, lipid solubility and ionization constant. Drug molecules which are lipophilic, non-ionized and not bound to proteins may readily cross the BBB and a rapid distribution may be achieved between blood, CSF and brain. More precisely, their entry into CSF/brain (and hence the onset of pharmacological activity of benzodiazepines) is dependent on their lipophilicity. The more lipophilic the compound, the more rapid the onset of clinical activity. The amount of a benzodiazepine available to enter the CSF/brain compartment is limited by protein binding, since only the free fraction of the total benzodiazepine in the blood can cross the BBB. After entry into the CSF/brain compartment, affinity for binding to the benzodiazepine receptor influences both the pharmacological potency and the duration of activity of these compounds. Lorazepam and nitrazepam have a greater affinity for the receptor than diazepam and chlordiazepoxide (Olsen & Towbin 1990). The elimination half-life of nitrazepam, for example, is 27 and 68 hours in the blood and in CSF respectively, whereas compounds such as diazepam and chlordiazepoxide exhibit the same elimination half-life in both blood and CSF. These particular benzodiazepines exhibit longer elimination half-lives in CSF than in plasma and prolonged clinical effects. The release of nitrazepam and lorazepam from receptor sites would thus become the rate-limiting step in drug clearance from the body rather than metabolism *per se*.

Therefore, the free drug concentration-time profile, along with association and dissociation rate constants for the receptor, can be used to establish the time course of receptor occupancy and the clinical effect profile. In addition, the relative contribution of active metabolites to the actual duration of the pharmacological action of benzodiazepines has to be evaluated. As reported above, many benzodiazepines are biotransformed into pharmacologically active metabolites, which in turn appear in the systemic circulation in an unconjugated and therefore potentially clinically important form. The assessment of the clinical importance of metabolites involves the simultaneous consideration of several aspects, including:

a)   the quantitative extent to which a specific metabolite is formed;

b)   the extent to which it reaches brain receptor sites; and

c)   the affinity of the individual metabolite to the receptor site.

The following examples may be helpful in understanding this issue. During prolonged treatment with diazepam, plasma levels of its metabolite desmethyldiazepam equal or exceed those of the parent compound. Desmethyldiazepam's lipophilicity is similar to that of diazepam (Greenblatt 1978), but the active metabolite has a higher affinity for the binding site. Taken together, the data suggest that desmethyldiazepam contributes to the clinical activity of diazepam to an important extent during chronic therapy. On the other hand, during chronic treatment with clobazam, its metabolite desmethylchlobazam yields plasma concentrations exceeding those of the parent drug by two-fold at least. The brain/free plasma level ratios between the two compounds are similar. However, since the binding affinity of desmethyl-clobazam is more than ten fold inferior to that of clobazam, it is unlikely that the metabolite can participate in the clinical action of clobazam. For both flurazepam and quazepam their active metabolite desalkylflurazepam has about a six-fold higher affinity for benzodiazepine binding sites than do either parent compounds whereas for alprazolam, midazolam and triazolam, their metabolites show lower affinity for binding sites than do the

parent compounds. Thus, knowledge of both receptor binding affinities and pharmacokinetic properties of benzodiazepines may be helpful in the rational clinical use of these drugs. This will be especially important during chronic medication with drugs that have active metabolites with higher affinity for benzodiazepine binding sites than the parent compound (Bourin & Bradwejn, 1992). The limited data available on factors influencing the plasma concentration-effect relationships for benzodiazepines demonstrate clear changes in the pharmacodynamics after multiple doses, suggesting the development of tolerance and a subsensitivity in patients with panic disorder. The influence of factors such as age, disease and drug interactions on the pharmacokinetic-pharmacodynamic relationship remains less clear.

3.4 Clinical importance of pharmacokinetics

3.4.1 Anxiolytic use of benzodiazepines

Anxiety is the main indication for use of benzodiazepines (Perry et al., 1990). For this indication, a constant decrease of anxiety is desirable whereas effects such as sedation are unwanted. The level of plasma concentration needed to achieve anxiolytic action varies greatly from one subject to another, removing the practicality of plasma concentration measurements as guidance to treatment. On the other hand some knowledge of pharmacokinetic parameters can help the clinician in predicting a maximal anxiolytic effect, once a steady-state plasma concentration is achieved.

The time required to reach a steady state concentration can be estimated from the elimination half-life of the drug. It is generally accepted that a period of time equivalent to five times the half-life of the drug is necessary to reach a steady-state concentration when taken at intervals equivalent to the drug's half-life (see Table I).

The rapid rate of absorption of some benzodiazepines, for instance clorazepate, can be equated with appearance of sedation soon after medication intake. In treating an anxious patient, the main goal is to produce a constant control of anxiety over time, with the minimum of adverse effects. Bearing in mind the rapid absorption rate of some drugs, it might be important to adopt schedules with multiple intakes of lower doses to reach tolerable peak effects. With such strategies, elimination half-lives play a more limited role in determining posologies. Additionally, it can be useful to administer a higher dose at bedtime to make use of the sedative effect, improving sleep in anxious patients.

It is difficult to estimate beforehand the anxiolytic dosage required for a particular patient. A wide range of dosage can be used to obtain anxiolytic effects and large inter-individual variations exist. Metabolic factors do not seem to play a major role in determining the proper anxiolytic dose. Predictive tables, taking into account body weight and severity of anxiety, have been established to help estimate necessary doses for a clinical effect. However, plasma concentrations have not been used to corroborate such tables.

Elimination half-lives must be considered when discontinuing treatment of benzodiazepines. It has been suggested that benzodiazepines with a short elimination half-life can result in a higher incidence of and more intense withdrawal reactions than benzodiazepines with a longer half-life.

3.4.2 Hypnotic use of benzodiazepine

Rapid absorption rates can result in sedation or hypnotic effects which are desirable for clinical indications such as insomnia. Rapid absorption rates are also desirable for use in pre-anaesthesia, midazolam having been used for such indications.

Elimination half-lives and volumes of distribution are also important parameters in these indications, especially for single dose administrations (Bourin et al. 1994).

In pre-anaesthetic conditions, factors such as pregnancy, renal deficiency, age, sex (female) and obesity increase time for distribution.

Chronic use of benzodiazepines for insomnia can lead to cumulative effects with compounds having long elimination half-lives (greater than 12-15 hours). Decreased psychomotor performance can be seen in the morning after intake. Such impairment can even be observed after single dose administration of benzodiazepines with half-lives of twenty-four hours or more (Bourin et al. 1989).

Unnecessarily high doses can be used with benzodiazepines like nitrazepam and flunitrazepam (5 mg and 2 mg respectively), in order to achieve sedative action. These molecules display long elimination half-lives which can be associated with cumulative effects.

It is interesting to note that the majority of benzodiazepines used as hypnotics, other than midazolam, are not biotransformed to active metabolites and their pharmacokinetic properties are not influenced by such factors as liver pathology.

3.4.3 Anticonvulsive use of benzodiazepines

Benzodiazepines such as diazepam, clobazam and clonazepam have demonstrated anticonvulsive action, especially on an acute basis. However, tolerance to this effect seems to occur after chronic administration over several months. Clonazepam is sometimes used in association with other anticonvulsive agents, especially in the chronic treatment of refractory epilepsy. It has been shown in one study that in epileptic patients receiving clonazepam monotherapy, the therapeutic blood concentration lies between 3 and 42 ng/ml. The only correlation found in the study was between side effects and given dosage. There was no comment in the study about drug plasma levels and toxicity (Naito, Wachi & Nishida, 1987).

3.5 Conclusion

We have discussed the usefulness of pharmacokinetic parameters in the clinical use of benzodiazepines. Notwithstanding their limits, their usefulness can be evident in reaching certain therapeutic goals. For example, knowledge of absorption rates can be useful in seeking or avoiding sedation, volumes of distribution and elimination half-lives can be useful in avoiding accumulation phenomena (Teboul & Chouinard, 1990). Also, elimination half-lives can be predictive of rebound and withdrawal phenomena upon discontinuation of treatment (Teboul & Chouinard, 1991).

Considering their cerebral activity profile, benzodiazepines differ:

a)   by their relative affinity to the receptors which influence the average therapeutic dose (Haefely 1991); and

b)   by their binding and release speed which influences rapidity and duration of action.

The fact that benzodiazepines bind on the same receptors has practical implications. First of all, it is necessary to avoid prescribing more than one benzodiazepine to the same patient because of their different affinities to the receptors. Some compounds are able to displace others, decreasing their activity.

Finally from a neurobiological point of view, the relationship between benzodiazepine receptors and anxiety can only be established by demonstrating the existence of endogenous ligands which might be anxiogenic or anxiolytic as it has been established to demonstrate the relationship between morphinomimetic receptors and pain.

TABLE I

PHARMACOKINETIC VALUES OF BENZODIAZEPINES

Generic name	Absorption time p.o. (t max) h	Elimination half-life (h)	Active metabolite with the longest t 1/2	Half-life (h)
Alprazolam	1 - 2	10 - 12		
Bromazepam	0,5 - 1,5	8 - 20		
Brotizolam		3-6	methylhydroxy brotizolam	2-4
Chlordiazepoxide	2 - 5	5 - 30	desmethyldiazepam	30 - 90
Clobazam	2 - 4	10 - 30	desmethylclobazam	36 - 46
Clonazepam	3-12	18-50		
Clorazepate	1 - 2		desmethyldiazepam	30 - 90
Clotiazepam	0,5 - 1,5	2 - 6		
Desmethyldiazepam	2	30 - 90		
Diazepam	0,5 - 1,5	15 - 60	desmethyldiazepam	30 - 90
Estazolam	1 - 1,5	18 - 24	numerous metabolites	
Flunitrazepam	1 - 1,5	20 - 30		
Halazepam			desmethyldiazepam	30 - 90
Loflazepate	1 - 2		desmethylflurazepam	70 - 120
Loprazolam	2 - 3	8 - 10		
Lorazepam	1 - 2	10 - 12		
Lormetazepam	1 - 1,2	10 - 12		
Nitrazepam	1,5 - 2	18 - 25		
Oxazepam	1 - 2	8 - 10		
Prazepam	3 - 6		desmethyldiazepam	30 - 90
Quazepam	1-1,5	40-60	N-desmethylflurazepam	70-120
Temazepam	0,3 - 0,7	5 - 15		
Tofizopam	?	6-8		
Triazolam	0,5 - 1	3 - 4	OH-triazolam	3 - 4

4.   INDICATIONS

The main indications for benzodiazepines are in the various forms of anxiety and in insomnia. This is reflected in the emphasis on these conditions in this chapter. Nevertheless, we have tried to be comprehensive in at least mentioning the other disorders in which benzodiazepines may be considered for use.

It was agreed that, where practicable, references to psychiatric diagnoses would be consistent with the ICD-10 classification (WHO, 1992). The relevant ICD-10 code is given in parentheses.

The use of non-benzodiazepine compounds and of non-pharmacological treatments will be considered in the chapter on strategy.

4.1   Psychiatric disorders

4.1.1   Anxiety disorders

Generalized anxiety disorder (F41.1) refers to:

a)   Psychological symptoms of anxiety or **apprehension** (e.g. "feeling on edge", difficulty in concentrating), the unpleasant emotion felt when a noxious event is feared in the future;

b)   **motor tension** (e.g. restless fidgeting, tension headaches, trembling); and

c)   **autonomic overactivity** (e.g. sweating, tachycardia and dry mouth). Although all these symptoms may occur in generalized anxiety disorder, they may occur in other psychiatric disorders as well, especially the acute functional mental illnesses.

These symptoms may also be found in anxiety disorder, unspecified (F41.9).

At the present time, benzodiazepines are still the most frequently used drugs when pharmacotherapy is indicated to treat anxiety disorders (Rifkin, 1990; Shader, Kennedy & Greenblatt, 1987).

Phobic symptoms

For specific, isolated phobia (F40.2), in the majority of cases there are a number of effective psychological (i.e. non-pharmaceutical) treatments available which have a more fundamental effect on the course of the disorder, and are thus preferred to benzodiazepines. The same also applies to agoraphobia (F40.00) where this is not accompanied by panic attacks (see below for the management of agoraphobia with panic attacks, F40.01).

The treatment of social phobias (F40.1) is complex and evolving, and the use of benzodiazepines may form part of the treatment programme.

Panic attacks

Panic attacks are characteristic of **panic disorder** (episodic paroxysmal anxiety, F41.0), but may occur in other disorders. Where the diagnosis is of panic disorder, and pharmacological treatment is indicated, opinions vary on the best approach, with some physicians favouring antidepressant compounds and others favouring benzodiazepines (typically in relatively high dose over many months), although both approaches are well established and accepted as effective and valid. Advantages of the benzodiazepines include their rapid onset of action and their low toxicity. The main advantage of antidepressants is their negligible tendency to produce dependence. Other factors to take into account are:

a) physical health of the patient;

b) presence or absence of other medications;

c) drug-taking compliance of the patient; and

d) differences in frequency and severity of adverse effects of each of the drugs.

Panic disorder (F41.0) should be diagnosed only in the absence of any of the phobias considered earlier. Thus agoraphobia with panic attacks would normally be diagnosed as a variety of agoraphobia (F40.01, agoraphobia with panic disorder). However, under these circumstances, depending on the clinical details, the physician may wish to treat the patient primarily as a case of agoraphobia or alternatively on the lines of the management of panic disorder.

4.1.2   Psychoses

Organic psychoses

a)   Acute organic brain syndrome

For many cases of delirium (e.g. F05.0), when psychotropic drugs are required, the neuroleptics are chosen. However, **delirium tremens**, a characteristic withdrawal syndrome occurring after an abrupt reduction of high input of alcohol and many sedative drugs, is treated with benzodiazepines (see Section 5 below). Benzodiazepines have been used in the treatment of psychosis induced by hallucinogens such as lysergide (LSD) (F16.04).

b)   Chronic organic brain syndrome

Benzodiazepines are not a treatment of dementia (e.g. F00.0) *per se*. In spite of the fact that they may impair the cognitive function still further, they may be considered for cautious use in the treatment of distressing symptoms in the demented patient.

Schizophrenia and related disorders

Some clinicians are cautious about using benzodiazepines in the adjunctive treatment of schizophrenia, for fear that a disinhibiting effect may release violent or unpredictable behaviour. However, others consider that benzodiazepines lower the dose of neuroleptic required to control violent behaviour in schizophrenia, and are interested in the possibility of a very rapid tranquillization.

Benzodiazepines alone are no substitute for neuroleptic drugs or mood stabilizers in the treatment of functional psychotic disorders (with rare exceptions, such as some patients with acute catatonic stupor). Combined treatment with benzodiazepines and antipsychotic drugs can allow a reduced dose of neuroleptic, but the effect of the benzodiazepines may be short lived (Dublin 1988).

In **catatonic schizophrenia** (F20.2) benzodiazepines have been used to attempt to bring a stuporous patient out of the mute state, sometimes with dramatic success.

Other psychoses

Their uses in drug withdrawal psychoses and in affective psychoses are considered below.

4.1.3 Mood disorders

Depression

When dealing with a depressive episode (F.31) antidepressant drugs, rather than benzodiazepines, are the treatment of choice when pharmacological intervention is indicated.

Since compliance with antidepressants can be a problem and there is a delay before their beneficial action is perceptible to the patient, benzodiazepines have been used as an adjunctive treatment in the initial phase, particularly when anxiety is a prominent clinical feature.

Mania

In manic episodes (F.30) benzodiazepines may be used adjunctively with mood stabilizers. Specifically, benzodiazepines will quickly promote sleep, foster calm, and reduce agitation, especially during the first several days of treatment while awaiting onset of action of the mood stabilizer (e.g. lithium, carbamazepine, valproate). The risk of tardive dyskinesia and neuroleptic malignant syndrome with neuroleptics makes benzodiazepines an attractive alternative. However, neuroleptics may be necessary in some patients, e.g. when extremely agitated or psychotic.

4.1.4 Drug and alcohol withdrawal syndromes

Benzodiazepines are of great value in the management of the withdrawal state ensuing on abstinence from alcohol (F10.3) or from use of sedatives or hypnotics (F13.3). Under these circumstances benzodiazepines are given in a very high dose initially, and the dose is tapered off gradually over a matter of days. Not all patients with high dose dependence on alcohol or other sedatives require such treatment, and many are able to taper their drug of dependence progressively without additional pharmacological help. However, where the withdrawal syndrome includes convulsions (e.g. F10.31) or delirium (e.g. F10.41, **delirium tremens**) or there is considered to be a danger of these complications, then benzodiazepines are entirely appropriate (Holloway et al., 1984).

Where it is anticipated that the withdrawal symptoms are likely to be minor or trivial, or the patient has a known tendency to misuse drugs, it may be considered better practice to rely instead on gradual withdrawal of the existing drug rather than to introduce the patient to a benzodiazepine.

Traditionally, chlordiazepoxide has been used with success for the management of alcohol and sedative withdrawal. If, however, there is known to be severe liver damage it should be borne in mind that chlordiazepoxide, diazepam and chlorazepate are all metabolized in the liver and may be cumulative on repeated dosing. Therefore, careful monitoring is required.

Chlormethiazole has been used as an alternative to benzodiazepines in drug withdrawal regimes. It has the advantage that a shorter programme of withdrawal can be employed (e.g. reducing the total number of days of hospitalization). However, chlormethiazole shares some of the properties of barbiturates, including high toxicity in overdose and a liability to produce itself a pattern of high dose dependence.

4.1.5 Personality disorder (F60.-) (See also section on ethical issues, chapter 7)

In general, benzodiazepines should be prescribed for patients with personality disorders only with great circumspection. This is particularly true when treating patients with **dependent personality disorder** (F60.7), **dissocial personality disorder** (F60.2) and **emotionally unstable personality disorder** (F60.3) where problems of dependence or misuse may occur. However benzodiazepines may be indicated for short-term use under circumstances of high levels of stress and anxiety, and in some patients with avoidant personality disorder (F60.6).

4.1.6 Suicidal patients (Z91.5)

The treatment of a suicidal patient is the management of the underlying disorder. Many clinicians will, however, be especially cautious in the use of benzodiazepines here for fear that disinhibition will tend to diminish the patient's control over suicidal impulses. In some patients, anxiety and tension may be considered to increase the risk of suicide. In such cases the adjunctive use of benzodiazepines can reduce anxiety and hence reduce the suicidal risk. Clearly the use of benzodiazepines in this way entails the careful monitoring of the patients' clinical state.

4.2 Other medical disorders

4.2.1 Seizure disorders (in psychiatric patients)

Where convulsions are purely psychogenic in nature (e.g. dissociative convulsions, F44.5) the treatment is of the underlying dissociative and conversion disorder, and benzodiazepines do not normally play a large part.

Benzodiazepines are used in the treatment of seizures of physical origin (G40), particularly in the treatment of status epilepticus (G41) or in other acute situations. The relative merits of the alternative anticonvulsants are not within the scope of this report.

4.2.2 Tardive dyskinesia and akathisia

Tardive dyskinesia is thought to be the result of chronic hypersensitivity of dopaminergic receptors, although this is not certain. The GABA-inhibiting effect on DA neurons provides the rationale that increasing GABA influences might successfully treat tardive dyskinesia. Benzodiazepines such as clonazepam, which may enhance GABA function, have either reduced or aggravated tardive dyskinesia (Casey, 1987).

The drug-induced restlessness of akathisia can be very distressing to patients. These symptoms must be distinguished from psychotic agitation and benzodiazepines will help to ease the distress.

4.2.3 Somatic presentations

In psychogenic autonomic dysfunction (the psychophysiological reaction to anxiety) (F45.3) treatment may be directed at the underlying cause or may be by non-pharmacological means.

Where symptomatic relief is indicated benzodiazepines may be used using the same general principles as apply to anxiety symptoms.

Where the somatic symptoms are part of a dissociative and conversion disorder (F44) the management is normally primarily with non-pharmaceutical therapy. When psychotropic drugs are indicated for psychogenic pain (F45.4) antidepressants are usually the treatment of choice.

Benzodiazepines are not normally ideal in the treatment of multiple somatization disorder (F45.0) since this condition is by definition chronic at the time that the diagnosis is made, and dependence on medication is a recognized complication of the disorder.

4.2.4 Muscle spasm

Benzodiazepines have a recognized place in the treatment of muscle spasm (e.g. spastic paraplegia).

4.2.5 Other indications

Benzodiazepines are used for a number of other medical indications, such as pre-operative sedation, anaesthesia and unpleasant investigation procedures. They are also used when chemotherapy for cancer is distressing and when patients are on artificial ventilation (e.g. in the treatment of tetanus). The use of benzodiazepines in the overall management of the distress resulting from physical illness must be considered on its merits according to the individual clinical features. In some cases it may be decided that benzodiazepines are indicated to reduce the excessive arousal induced by the disease process. Here the principles discussed above in Section 1 will again be relevant.

4.3 Symptomatic use

4.3.1 Sleep disorders

Insomnia (F51.0)

As with other symptomatic states, insomnia is best managed by treatment of the underlying cause. Where this is not known, or where the insomnia is isolated, it may respond to non-drug methods of management (i.e. sleep hygiene).

Where hypnotics are indicated, benzodiazepines have an advantage over most older compounds. In particular, barbiturates are much more likely to produce high dose dependence (with the possibility of convulsions or **delirium tremens** on withdrawal) and they are lethal in overdose. Compared with benzodiazepines, many other hypnotic compounds have a similarity to barbiturates in one or other of these respects, including alcohol, paraldehyde, chloralhydrate, glutethimide, methaqualone, methyprylone, meprobamate and chlormethiazole.

Where benzodiazepines are used for the treatment of insomnia, patients are often content to use a hypnotic on only alternate nights, or only one night in three, or at even greater intervals. This has two advantages. Firstly, it avoids even psychological dependence. Secondly, where the elimination half life of the benzodiazepine is long, an interrupted regime carries less risk of serious accumulation of the drug in the tissues. (Bryerley et al., 1984; Kales, 1990; Priest & Baldwin, 1992; Priest & Montgomery, 1988; Priest & Woolfson, 1986; Roehrs et al., 1990). This will be considered further in the chapter on strategy.

Disorders of arousal

Many benzodiazepines reduce the amount of deep sleep (slow wave sleep, sleep stages 3 and 4) by as much as 75 per cent. They are therefore potentially of use in those sleep disorders which arise in deep sleep, such as sleep-walking (F51.3) and sleep terrors (F51.4). However, it is rare that they will be in fact employed for this purpose since these sleep disorders occur most often in children, and treatment would probably require continuous long-term use.

4.4 Other situations

The appropriate use of benzodiazepines cannot always be linked systematically to specific definitive diagnoses. Often benzodiazepines are indicated for symptoms (e.g. insomnia) or syndromes (i.e. anxiety) that may be manifestations of a variety of disparate diagnoses. Thus benzodiazepines are often indicated in the management of adjustment disorders (F43.2) and in a variety of physical illnesses, including malignant disease, especially in the short term treatment of certain target symptoms.

Benzodiazepines are considered for the symptomatic relief of anxiety symptoms particularly when they are:

a)   disabling;
b)   severe; or
c)   subjecting the individual to unacceptable distress (Priest & Montgomery, 1988).

Ideally, benzodiazepines are intended to be prescribed for a period not exceeding one month, with a view to avoiding the development of a state in which drug discontinuation will result in the manifestation of physical withdrawal symptoms. Thus they are suitable for a situation which, although severe or disabling, is expected to be self-limiting. Alternatively, they may be used for symptomatic relief while a more definitive treatment of the underlying disorder gets under way.

It may be necessary to continue the prescription of benzodiazepines where the disorder, initially expected to be short lived, eventually turns out to be chronic, and the benzodiazepines continue to be required for relief of distress. Clearly the initiation of treatment with benzodiazepines is not ideal in a disorder which is already chronic at the time of presentation to the physician.

Finally, one or two doses of benzodiazepines are sometimes used for transient changes in the timing of daily activities (time zone change, shift work).

4.5   General comments

There are very few contraindications to the use of benzodiazepines. They cause hypoventilation, particularly during sleep. Thus neuromuscular disorders (e.g. myasthenia gravis), sleep apnoea and severe lung disease are among the few generally accepted contraindications.

As in other branches of medicine, the indication for a particular drug, or class of drugs, cannot be specified absolutely. With benzodiazepines in particular, the question of whether the compound should be prescribed for a particular individual relies heavily on the judgment of the physician, taking into account all the relevant clinical factors.

Further guidance is given in the chapter on Strategy.

5. ADVERSE EFFECTS

Compared to many other psychoactive drugs, benzodiazepines are safe, and are usually without any severe side effects which lead to discontinuation of the therapy. The acute toxicity of benzodiazepines is negligible in contrast with, for example, that of tricyclic antidepressants, and there is no risk of developing tardive dyskinesia as is the case for neuroleptics.

5.1 General adverse effects

The following table summarizes general adverse effects of benzodiazepines (Farmaceutiska Specialiteter i Sverige-FASS, 1996). As shown here, the commonest adverse effect is drowsiness which occurs in 10 to 15 per cent of those treated, but diminishes after a few days of treatment.

Common (1/100)	General: Drowsiness
Less common:	Allergic skin reactions Neurological: Ataxia, muscular weakness Psychiatric: Anterograde amnesia at high doses
Rare: (1/1000)	Skin: Allergic skin reactions Neurological: Respiratory depression Psychological: Insomnia, nightmares, paradoxical reactions, excitation states, aggression and hallucinations.

Adverse effects are largely dose dependent. This is particularly true with the elderly, who are slow metabolizers and are more susceptible to medication. Several types of adverse effects occur in the elderly including cognitive, hypnotic, psychomotor, and cerebellar toxicity. Cognitive impairment includes forgetfulness, altered attention, confusion, and anterograde amnesia. Hypnotic effects can occur, especially if medications are given during the day. Psychomotor impairment can be manifested in terms of poor hand-eye coordination, and slowed movements. Cerebellar toxicity includes dysarthria, poor coordination and ataxia. In elderly patients, there is a higher risk of falls resulting in fractures of the hip.

The effect of benzodiazepines on road safety is an issue of major importance and there is some evidence that people taking benzodiazepines are over-represented in crashes (van Laar et al., 1992).

There are some differences in the pattern of adverse effects amongst individual benzodiazepines. It is also probable that the heterogeneity of benzodiazepine receptors which is known today (Bell & Nutt, 1995), in combination with a variety of accompanying somatic and psychic disorders, may cause a substantial variation between different individuals in responding to benzodiazepines.

It can be difficult to distinguish some adverse effects from symptoms of underlying chronic diseases. Retrospective studies have shown that patients who claimed severe adverse effects from benzodiazepines had similar symptoms before the onset of benzodiazepine treatment (Franck et al., 1996; Romach et al., 1995).

5.2 Withdrawal syndrome and dependence

5.2.1 Withdrawal syndrome

During the 1960s, withdrawal symptoms were reported to occur upon discontinuation of long-term use of benzodiazepines at doses several times higher than the usual therapeutic dose. More recently, a number of studies have shown that withdrawal syndromes can occur even at therapeutic doses.

Benzodiazepine withdrawal symptoms reported include dissociative disorders, depression, insomnia, palpitations, agitation, confusion, gastrointestinal distress, persistent tinnitus, involuntary muscle twitching,

paresthesias, and seizures in rare cases. In general, the shorter the elimination half-life of the benzodiazepine, the sooner the withdrawal syndrome appears after cessation of the drug. Withdrawal syndromes due to the use of short-acting benzodiazepines may be more intense than withdrawal from benzodiazepines with longer durations of action (Woods, Katz & Winger, 1992, 1995; Woods & Winger, 1995).

Reported rates of occurrence of withdrawal syndromes among long-term therapeutic dose benzodiazepine users range from 5 to 75 per cent (Humphreys & Hallström, 1995), but these figures should be read with caution since there is a possibility that reported cases could include exaggerated, or even false-positive withdrawal syndromes induced by a notion of withdrawal rather than a real withdrawal ("nocebo" effects). It is also known that widespread knowledge of withdrawal symptoms can increase the sensitivity of patients to such effects (Tyrer, 1991). Furthermore, it is difficult to distinguish withdrawal syndromes from either a re-emergence of the original symptoms for which the drug was prescribed or a transient worsening of the original symptoms known as "rebound phenomena", both of which may occur after stopping the medication.

5.2.2   Dependence

The manifestation of withdrawal syndromes is often interpreted as evidence of "physical or physiological dependence", and "physical dependence" is commonly mistaken as a form of "drug dependence". This is wrong, because withdrawal syndromes do not necessarily lead to dependence. For example, when the withdrawal discomfort is mild and easy to tolerate, it will not be difficult for the patient to stop taking the drug, and those who can stop drug taking without much trouble are not dependent on the drug by definition. Since the term "physical dependence" invites confusion with the general term "dependence", it is preferable to avoid this term in clinical discussions (WHO 1993).

Among the long-term users experiencing withdrawal syndromes, some of those who have difficulty coming off the drug may be benzodiazepine-dependent. Studies on tapered discontinuation programmes for long-term benzodiazepine users show that 10 to 30 per cent dropout rates are not uncommon (Woods 1992). A substantial proportion of those who did not respond well to the discontinuation treatment may be taking benzodiazepine therapy as an appropriate medication for a chronic psychiatric condition (Romach et al., 1995). However, those who have resisted discontinuation treatment without having such a chronic condition can be considered to be truly dependent on benzodiazepines.

5.3   Overdose

Benzodiazepines are often taken in accidental and intentional self-poisonings, with or without suicidal intention. One benzodiazepine may be used more frequently in one country than in another. Flunitrazepam is a case in point. Lethal outcome, however, is extremely rare. Different benzodiazepines have been demonstrated in lethal cases, but their role in causality is unclear. Concomitant disease, use of other drugs and alcohol is abundant. It is not possible to define a lethal dose. Cardiac arrhythmias occur after benzodiazepines, but lethal arrhythmias are impossible to demonstrate.

Flumazenil is an effective antidote for benzodiazepine overdose. It rapidly displaces benzodiazepines at the receptor site to reverse their pharmacological action, but repeated dosage may be needed if the effect of the benzodiazepine persists.

6. STRATEGIES FOR PRESCRIBING BENZODIAZEPINES

6.1 Introduction

The optimal strategy for prescribing benzodiazepines is a multi-step process. It begins with a careful and thorough evaluation of the patient, including his or her familial and personal resources. Key factors to be determined in the evaluation are the primary diagnosis and comorbid conditions, severity of illness, duration of illness, and functional disability. This evaluation should include assessments of general, medical, psychiatric, social, and occupational status. Special attention should be given to suicidality, substance abuse, depression, and anxiety.

Following the establishment of the diagnosis and key factors, comes the selection of treatment. Alternative treatment approaches may exist, and should be explained and discussed thoroughly with the patient and his or her family. If a benzodiazepine is selected, it may be prescribed for a few days, a few weeks, or for an indefinite period, and it may be used intermittently or regularly.

The importance of establishing a good doctor-patient relationship cannot be overemphasized. Many of the illnesses for which benzodiazepines are prescribed are long lasting and will require return visits.

6.2 General approach

6.2.1 Evaluation of the patient

This section will be divided into recommended and optional aspects of the evaluation.

Recommended aspects

a) Use of Screening Instruments

Screening instruments can be utilized to increase efficiency (and perhaps shorten interview time) for use in primary care and psychiatric settings. These instruments can help to identify patients suffering from anxiety or other disorders relevant to benzodiazepine prescription. A list of recommended brief paper-and-pencil inventories is included in **Annex 4**.

b) The Clinical Interview

The clinical interview should focus on patients complaints and problems, and patients psychopathological symptoms, especially anxiety and depressive symptomatology. The severity and duration of the individual symptoms should be assessed. Suicide potential should also be assessed.

The interview should also include evaluation of important comorbid psychiatric disorders, including current and prior alcohol dependence and substance abuse, and, if possible, a history of personality disorders. A history of prior response to treatment is useful. The evaluation should include some assessment of occupational and familial functioning and impairment. For example, has the condition interfered with or prevented the individual from working? Has it interfered with marital, sexual, familial, and social relationships?

c) General Medical Evaluation

This evaluation should focus on general medical problem areas. In addition, it should include assessment of potential problem areas for prescription of benzodiazepines, such as a history of myasthenia gravis or allergies to benzodiazepines.

d)   Physical Examination

A physical examination should be performed, with particular focus on the patient's problem areas during the clinical psychiatric interview and the assessment of his or her general medical condition.

e)   Laboratory Procedures

Laboratory tests, when they are available, should be ordered as necessary on the basis of the prior interviews and physical exam. It is useful in general to obtain an assessment of thyroid, liver, and kidney function.

Optional Assessments

a)   Assessment of Family and Personal Resources

Management of the patient can be done much more effectively if the therapist knows of resources available to the individual and his or her family. These include stability of living situation, adequacy of living conditions, supportiveness of family members, presence of useful and satisfying role in life (occupational, student, etc), presence of other social supports, and social advocational life (including hobbies, religious groups in attendance, sports, etc).

Many patients, especially in rural areas, may have to travel considerable distances for medical and psychiatric treatment. Their treatment and management, therefore, will necessarily involve minimal follow-up and infrequent visits.

b)   Use of Additional Sources of Information

It is always useful to include the family and/or friends in the evaluation and gathering of information, of course with the permission of the patient. These other perspectives can often be very helpful because the patient may have minimized or ignored some aspects of the illness. In addition, examination of other sources of information, such as past medical records, school and work records, and forensic information can be very useful.

c)   Family History of Substance Abuse, Dependence, and Personality Disorders

Substance abuse and personality disorders may complicate the prescription of benzodiazepines. A family history of these problems can increase their risk for the individual patient.

Diagnosis

The evaluation process should lead to a primary diagnosis and a differential diagnosis, along with an assessment of the psychosocial situation and other pertinent information.

6.2.2   Selection of Treatment

General considerations

A variety of treatment modalities are available for many of the conditions and illnesses which are responsive to benzodiazepines. These include both pharmacological and psychological alternatives. It is important to present to the patient and his or her family various alternatives for the treatment of the condition, including the benefits and risks of each of the choices. The selection of the particular alternatives obviously is dependant upon an accurate and comprehensive diagnosis of the illness. This includes its

severity, duration, and comorbid psychiatric and medical conditions, as well as the assessment of psychosocial disability. Cultural traditions and patient preference must also be considered.

An important consideration is the availability of the various alternative treatments. For example, cognitive therapy may be extremely useful in the treatment of an individual patient, but there may be no trained cognitive therapist in the area. Furthermore, various psychotherapies or medications which need close monitoring may be impractical in rural areas where access to care and to follow-up is very limited.

Alternative treatments

Alternative pharmacotherapies include tricyclic and heterocyclic antidepressants, monoamine oxidase inhibitors (MAOIs), selective serotonin re-uptake inhibitors (SSRIs), neuroleptics, and non-benzodiazepine anxiolytics and hypnotics (e.g. zolpidem and zopiclone).

Psychotherapies include general brief psychotherapy, cognitive therapy, interpersonal therapy, behavioural therapy, and combined psychotherapy and pharmacotherapy.

Prescription of Benzodiazepines

The prescription of a benzodiazepine involves several considerations. First is the choice of a specific benzodiazepine. Second is whether a single medication is sufficient, or whether more than one is preferable. Third is the determination of duration of treatment. Finally is how and when to discontinue the medication.

a)   Choice of specific benzodiazepines

Key issues for the selection of a specific benzodiazepine for relief of anxiety include elimination half-life of the drug, rate of absorption of the drug, metabolism of the drug, and adverse effects.

Elimination half-life. The time required to reach a steady state concentration can be estimated from the elimination half-life of a drug. It is generally accepted that a period of time equivalent to five times the half-life of a drug (and active metabolites) is necessary to reach a steady-state concentration (see Table 1).

Rate of absorption. There is considerable variability in the rate of absorption among benzodiazepines, which influences the speed of both therapeutic response and onset of adverse effects. In general, rapid rate of onset is useful for hypnotic purposes and for treatment of acute anxiety.

Metabolism of the drug. As discussed in the pharmacology chapter, benzodiazepines are all metabolized in the liver. Most are oxidized and then conjugated. But three benzodiazepines (oxazepam, lorazepam, and temazepam) are directly conjugated. A number of factors can influence oxidation, including other drugs, age, and hepatic disease. Conjugation is less affected by these factors.

Adverse effects. Adverse effects are discussed in Chapter 5.

The clinician should keep in mind these issues when selecting a specific benzodiazepine for an individual patient.

Selection Strategy. In general, the very short acting benzodiazepines (such as triazolam) should be used primarily for inducing sleep, and not for anti-anxiety effects.

Whether continuous levels of medication are desirable or whether the levels should be episodic are important. Differences in rate of absorption and elimination half-life provide opportunities to achieve the desired effect. In general, people with anxiety disorders require continuous levels of medication in order

to reduce the level of anxiety, although there are patients who require episodic increases in medication for specific anxiety-provoking situations.

Medium duration benzodiazepines (such as alprazolam, lorazepam, and oxazepam) are preferred for most of the anxiety disorders, including panic disorder. Prescribed on a three to four times per day basis, they can provide fairly continuous levels of medication and resultant anti-anxiety effects. Accumulation is usually not a problem.

Medications with longer duration of action (such as clorazepate and diazepam) are also useful in treating anxiety disorders in that they require less frequent dosing, but may lead to accumulation, especially in the elderly.

Major benefits of the benzodiazepines include their rapid onset and low toxicity. However, they should be used with caution in patients with comorbid alcohol dependence, drug dependence, and personality disorders.

Selection of a particular benzodiazepine may be influenced by the presence of hepatic or renal problems. For example, diazepam, chlordiazepoxide, clorazepate, halazepam, and prazepam all have long-acting active metabolites. This may present a problem in elderly patients or those with liver problems. Other benzodiazepines such as oxazepam, lorazepam, and alprazolam, which are metabolized by conjugation or have minor active metabolites, are less of a problem in the elderly or those with impaired liver function, but may be more problematic in patients with kidney problems.

b)   Treatment with more than one medication

Conservatism is usually the best policy in medicine, and it is preferable to limit the number of medications, whenever possible. It is usually possible to do this for many of the indications for benzodiazepines, particularly the anxiety disorders. For example, an alternative to having one benzodiazepine during the day for anxiety symptoms and another in the evening for sleep would be to increase the dose in the evening to provide hypnotic effects so that only one drug would be needed.

There are situations in which more than one medication is necessary and/or desirable. Benzodiazepines are often useful as adjunctive treatment (usually short-term) with other psychotropic medications for depression, schizophrenia, and anxiety disorders. They may be used with lithium, tricyclic antidepressants, neuroleptics, anti-convulsants, and a variety of medications used in general medicine. They interact little with most other medications. However, sedative effects may be additive with those of other medications.

6.2.3   Management

In general it is advisable to begin with a low dose of a particular benzodiazepine, and to increase the dose slowly over one to two weeks or sometime longer until the desired effects are achieved. It is important to use sufficient dosing to achieve desired effects. For example, it may take a higher dose to prevent panic attacks and adequately treat panic disorder than to reduce anxiety symptoms.

Changes in dosage may be necessary to treat breakthroughs of anxiety or excessive drowsiness. They should usually be made slowly once an optimal dose level is achieved. The changes should be made in small amounts and usually not more than one to two adjustments per week.

6.2.4   Duration of treatment

Decisions regarding duration of treatment should be determined primarily by consideration of the basic problem being treated, and influenced by other factors such as severity, morbidity, and comorbidity of other illnesses. For transient stressful periods, for sleep problems, and for adjunctive treatment of medical

illnesses, treatment of anxiety symptoms in general should be several weeks or less. For more chronic problems, such as panic disorder and generalized anxiety disorder, long-term treatment is often necessary. In determining whether long-term treatment is warranted, the clinician should recognize that withdrawal may be a risk. Long-term treatment should be prescribed when benefits of treatment outweigh such risks.

6.2.5 Discontinuation

Discontinuation of treatment with benzodiazepines is an important issue. For those who have used benzodiazepines for several weeks or less, particularly in low doses, they may be tapered over a week or stopped abruptly without problems (Tyrer, Murphy & Riley, 1990). However, for patients who have taken higher doses for several months or longer, several clinical phenomena can occur including rebound, recurrence, and withdrawal syndrome.

Rebound symptoms refer to the return of the original symptoms for which the benzodiazepine was prescribed, in a more intense form. Rebound usually occurs within days of discontinuation and lasts for several days. Recurrence refers to a return of the original symptoms, following clearance of the benzodiazepine from the body. The severity of the symptoms is similar to that of the original ones. The symptoms usually begin gradually and persist.

Rebound, recurrence, and withdrawal symptoms may be difficult to distinguish and may co-exist. It is strongly advisable to follow a discontinuation programme with patients who have been taking benzodiazepines for longer than several months. The most widely used approach is to taper the medication slowly. If symptoms persist for many months, recurrence of the anxiety disorder is most likely the cause, not the benzodiazepine. Reduction of 50 per cent in daily dose can be done over several days, but the next 25 per cent may require several weeks, and the final 25 per cent may require one to six months (Ashton, 1991). For the shorter half-life high potency benzodiazepines, this is particularly important.

Some clinicians substitute long duration benzodiazepines (e.g. diazepam or clonazepam) while withdrawing fairly quickly from the short half-life benzodiazepines. Then the long half-life benzodiazepines are themselves tapered over several weeks or months. An example of this withdrawal scheme is shown in the next sub-section. A number of other medications have been used with varying degrees of success as substitutes (such as propranolol, clonidine, and carbamazepine).

For many patients the reduction presents no problems and goes smoothly, especially if the managing clinician maintains sufficient contact and is reassuring. However, patients with concomitant psychiatric comorbidity, particularly substance abuse and personality disorders, may require a slower taper and increased clinician patient interaction. For a few patients the discontinuation process may require hospitalisation.

6.2.6 Withdrawal management

Withdrawal treatment should be a combination of gradual dose reduction and anxiety management. The dosage reduction is by far the easiest but long-term psychological support is equally important for successful outcome, particularly for reducing the incidence and severity of post-withdrawal syndromes.

Because groups of benzodiazepine users differ there is not one single management approach. Age, indication and duration of use, all, will influence the ease with which benzodiazepines can be discontinued. For long-term benzodiazepine general practice, patients dependent on benzodiazepines who are willing to discontinue the drugs, the following rough guidelines can be considered.

In out-patient settings withdrawal programmes can take from 4 or 8 to 16 weeks. In general practice it is wise to use eight weeks to taper off the benzodiazepines so the period in which the post-withdrawal syndrome develops can be overseen. The tapering schedule can always be slowed if the patient is having difficulty coping with a particular dose reduction.

In a longer interview of an hour, the original reason why and for how long the benzodiazepines were prescribed is evaluated. The origin of the complaints are evaluated and a "baseline" of current complaints and symptoms are noted. Also, a baseline of patient specific symptoms (symptoms that occur during periods of fatigue, stress or general malaise, as well as subjective well being), and a benzodiazepine-withdrawal-symptom list is assessed. Whatever the benzodiazepine, it is wise to change to a long-half-life benzodiazepine such as diazepam. The patient is advised that during the first week of the withdrawal programme, the dosage of diazepam is the same, or slightly higher than, the last dose of the prescribed benzodiazepine. The patient is also advised to take the benzodiazepine at regular intervals. The patient should be informed of possible (withdrawal) problems during the eight week programme. Apart from the weekly evaluation when all the symptoms are assessed and difficulties will be discussed, support is given in the form of anxiety reduction, relaxation exercises (yoga and breathing) and sleeping courses . The patient can call the physician whenever necessary. The patients themselves keep a daily sleep diary and take notes that can be discussed during the weekly evaluation. Patients live from minute to minute, from day to day, and a diary can work well to keep a track of life. Good and bad days alternate. Instability becomes less, but in between, patients experience a relapse from week to week. Subjectively they feel sometimes worse than when they just stopped the benzodiazepines. Therefore, a comparison with baseline complaints and symptom checklists of previous weeks shows the patient the gradual increase in well-being over time.

Gradual withdrawal scheme:

Week 1	change to diazepam, equivalent dose of previous medication	
Week 2	7/8	dose
Week 3	6/8	dose
Week 4	5/8	dose
Week 5	4/8	dose
Week 6	3/8	dose
Week 7	2/8	dose
Week 8	1/8	dose

Withdrawal success rates:

In most programmes, long-term users in general practice are advised to join a withdrawal programme. The success rate of these patients discontinuing benzodiazepines for more than a year is about 50 per cent, 20 to 30 per cent will use a lower dose of benzodiazepines, and 20 to 30 per cent will fall back into their original use within a year. Most difficulties are encountered in long-term users and patients over 70 years of age. However, if patients decide themselves to stop for individual reasons (new partner, new physician, pregnancy, new environment), the rate of successful withdrawal is more than 60 per cent with a withdrawal programme as described above. Studies are hard to compare since social and cultural attitudes and medical conditions vary widely. For instance, in a UK study, long-term benzodiazepine-using patients received a letter from their general practitioner in which they were informed about adverse effects, dependence and the minimal long-term efficacy of benzodiazepines. As a consequence, 22 per cent of these patients stopped using benzodiazepines themselves (Cormack et al., 1994).

In all patients who managed to discontinue was the positive effect on their daily functioning, the feeling to be able to achieve, and therefore attack life with a higher self esteem (Salzman et al., 1993).

6.3 Special situations

Special attention must be given concerning the prescription of benzodiazepines to pregnant women, to children, to the elderly, to alcohol users, and to substance abusers.

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6.3.1 Benzodiazepines in children

Benzodiazepines may be useful in the treatment of childhood anxiety disorders, including separation anxiety disorder, over anxious disorder, avoidant disorder, and panic disorder. Benzodiazepines have been found to worsen psychoses in children and to be ineffective in the treatment of attention deficit/hyperactivity disorder.

There are no established guidelines for using benzodiazepines for the treatment of psychiatric disorders in children. Children have a faster rate of metabolism of benzodiazepines than adults, and it may be necessary to administer benzodiazepines more frequently than in adults. Benzodiazepines should be used for as brief a period as possible, generally for only a few weeks.

Common adverse effects of benzodiazepines in children are drowsiness and fatigue, which may be lessened by giving divided doses. It is important to watch for behavioural disinhibition with symptoms of aggression, rage, excitation and hostility, which may occur in some children taking benzodiazepines.

6.3.2 Benzodiazepines in the elderly

There are several special considerations which must be addressed in prescribing benzodiazepines to elderly populations including age, polypharmacy, and general medical comorbidity.

The central nervous system becomes more sensitive to the effects of anxiolytics as age increases. Metabolism and excretion of anxiolytics is slower in the elderly because hepatic metabolism becomes less efficient and the kidneys work less well with advancing age.

Older people are much more likely than younger people to be taking several medications at the same time. Some of these can cause or exacerbate anxiety, such as steroids or stimulants. Others, such as cimetidine and anti-convulsants, may alter blood levels of benzodiazepines.

General medical illnesses are much more likely in elderly patients, including central nervous system disorders, such as stroke, dementias, and Parkinson's Disease. These illnesses can increase sensitivity to anxiolytics.

Several types of toxic effects of benzodiazepines occur in the elderly including cognitive, hypnotic, psychomotor, and cerebellar toxicity. Cognitive impairments include forgetfulness, altered attention and anterograde amnesia. Hypnotic effects can occur, especially if medications are given during the day. Psychomotor impairment can be manifested in terms of poor hand-eye coordination, and slowed movements. The risk of hip fractures is increased. Cerebellar toxicity includes dysarthria, poor coordination, and ataxia.

Bearing in mind the special clinical factors present in the elderly and the potential toxic effects, prescription of benzodiazepines in the elderly should be employed cautiously and at minimal doses. In general, short and medium duration benzodiazepines such as oxazepam, lorazepam, and alprazolam are recommended because they are less likely to accumulate in the blood. Long-acting benzodiazepines, such as diazepam, should be used carefully, because of problems associated with accumulation.

6.3.3 Pregnancy and breast feeding

In general, use of medications during pregnancy should be avoided, if possible. However, benzodiazepines may be considered in certain situations. In such situations the clinician should discuss fully with the patient the benefits and risks for both the mother and the foetus, as well as suggesting alternative treatment.

In the 1970s, there was concern regarding possible teratogenic properties of benzodiazepines in humans and in experimental animals, but studies were not conclusive. In the latter 1980s, developmental abnormalities, including dysmorphism and mental retardation, were reported in seven Swedish children of selected mothers using high doses of benzodiazepines regularly during pregnancy (diazepam and/or oxazepam). This "embryopathy" resembles the foetal alcohol syndrome in that the doses used by the index women were far higher than the prescribed daily doses (PDD) - for diazepam 30 mg versus PDD 8 mg and for oxazepam 75 mg in the index group versus 27 mg as PDD. The high doses were doses of abuse rather than prescribed doses (Laegreid et al., 1992).

Available drug data bases in Sweden including 450,000 people, years of observation, and 4,600 pregnancies, were unable to identify a sufficient number of index pregnancies to confirm the hypothesis that chronic use of high doses of benzodiazepines during pregnancy causes abnormalities in children. However, the incidence of apparent regular benzodiazepine users during pregnancy in all Sweden (1.3 per 1000 live births) was lower than the 5.5/1000 in the data reported by Laegreid.

Benzodiazepine use during pregnancy was investigated in an existing file of 104,000 in-patient deliveries in the US Medicaid database between 1980 and 1983, and outcome assessed from the paediatric profiles linked to these mothers, six to nine years after delivery. There were no diagnoses of mental retardation in the exposed offspring. Two infants had diagnoses of eye movement or alignment problems. None of the 1,345 first trimester benzodiazepine exposures had a diagnosis of oral cleft. This long-term, longitudinal study does not support evidence of teratogenicity in use, even heavy use, of benzodiazepines during pregnancy. If a pregnant woman takes benzodiazepines during the last part of her pregnancy, there is a risk of the "floppy infant syndrome" developing in the neonate.

Some benzodiazepines pass into breast milk, in a concentration of 10 to 20 per cent than in plasma. There is no absolute contraindication to breast feeding, but infants should be watched for signs of sedation.

Benzodiazepines have been administered to large numbers of pregnant women, and there is no indication of increased risks of teratogenicity when used in therapeutic doses. However we cannot state definitively that benzodiazepine use during pregnancy is without risk of injury to the foetus. Therefore we would caution against its use in women during pregnancy, when possible (Bergman et al. 1992).

6.3.4   Alcohol

The frequency and quantity of alcohol consumption is a major consideration in patients who need treatment with benzodiazepines. Following Linnoila (1990) we will sub-divide the issue into four categories:

Use of benzodiazepines among social drinkers. There is no essential metabolic interaction between benzodiazepines and alcohol with regard to alcohol dehydrogenases, aldehyde dehydrogenases or cytochromes. Alcohol affects the benzodiazepine receptor complex and has an agonist-like action. In general there is a clinical potentiation between alcohol and benzodiazepines. However there are differences in the interaction between various benzodiazepines and alcohol which may have clinical relevance. In general, despite the frequent concomitant use of alcohol and benzodiazepines, the frequency of interactions of major consequence is low among social drinkers.

The use of benzodiazepines for treating alcohol withdrawal. The use of benzodiazepines in the treatment of alcohol withdrawal is covered in sub-section 4.1.4. Most clinicians and scientists recommend that their use should be kept to a minimum, and should only be used if the withdrawal is severe. Benzodiazepines can also prevent and treat withdrawal seizures and delirium tremens. Barbiturates have no use in treating alcohol withdrawal today.

The use of benzodiazepines in patients with alcohol dependence. Clinicians should try to recognize and treat anxiety disorders in alcoholic patients. Panic attacks with and without agoraphobia are common

among alcoholics and their relatives. Though much of the psychopathology present in early withdrawal disappears within a month (more than 40 per cent), there is a remaining group of at least 4 per cent of previously alcohol dependent patients who need further treatment with antidepressant and/or benzodiazepines for anxiety disorders or insomnia. The risk of suicide is considerable in this often neglected group.

Non-medical use of benzodiazepines in patients with alcohol dependence and/or drug dependence. Benzodiazepines are also abused by some alcoholic patients to potentiate the effects of alcohol or to produce euphoria, but the frequency, nature and severity is largely unknown.

6.3.5   Illicit drugs and benzodiazepines

In patients addicted to drugs, insomnia is a frequent and severe problem, which can be verified electrophysiologically with EEG. The ethics of giving a drug addict a hypnotic is often debated as are the rights of these patients to treatment compared with the non-addicted population. Not to hurt (non-nocere) is a good principle to follow, but in medicine we also want to give effective help (Navaratnam & Foong, 1990). Though there is some cross-tolerance between different dependence-producing drugs, there are no absolute indications for the use of benzodiazepines in withdrawal from illegal drugs.

7. SOCIAL AND ECONOMIC ISSUES

In discussing socioeconomic issues related to benzodiazepines, it is useful to be reminded that although benzodiazepines have several indications - discussed previously - the long-term treatment of chronic anxiety states constitute a real socioeconomic problem and, to a lesser degree, of insomnia. As an overall figure, benzodiazepine use for anxiety in the USA in the late 1970s amounted to almost 1.6 per cent of the population daily (Mellinger et al., 1978). With this is mind, let us explore some major issues concerning benzodiazepines and society.

7.1 Attitudes towards benzodiazepines

Despite their obvious usefulness in many cases, a negative attitude in relation to benzodiazepines from the general public and the media has appeared recently. Nagy (1987) has looked at this issue and proposes that at the root of these attitudes a series of misunderstandings lay, such as:

a)   confusion between long-term use and dependence;
b)   lack of information on the epidemiology of anxiety, responsible for benzodiazepine use;
c)   insufficient attention to undesirable alternatives (e.g. barbiturates, alcohol) when benzodiazepines are not available; and
d)   insufficient awareness of recent data on the physiology of anxiety.

In addition, the ever-growing coverage by the press of drug-related issues, which does not always make a distinction between illegal drugs and medicines, also contributes to a certain degree of hostility towards benzodiazepines, which are perceived more as a threat than as a drug which can be greatly beneficial to many people.

Although dependence to benzodiazepines is indeed limited - about one per cent of users according to Khan (1992) - such hostile attitudes as mentioned above are reinforced by some multiple drug users taking large quantities of benzodiazepines. In addition, the problem of chronic users taking moderate doses for many years adds to this notion.

One should also bear in mind the general public's attitude towards drug treatment when faced with less dramatic psychological problems: many believe that the use of medication in such circumstances is a sign of weakness, and therefore develop negative feelings in relation to medication in general.

The combination of justified fears and imaginary threats leads sometimes to radical action by drug regulatory authorities against benzodiazepines, which have been questioned on both pharmaceutical and psychotherapeutic grounds. Objective discussions, based upon reliable data, are necessary in order to avoid misguided judgements about this group of drugs, as well as about those patients who take them.

7.2 Ethical issues

The use of benzodiazepines raises a few ethical problems. First, there is the query on the use of drugs as a questionable solution to some life problems - trivial or not. A systematic prescription of benzodiazepines would deny the concerned person both the right and the obligation to face the problem and to cope with it, thus finding a personal answer to life problems, and thereby learning from his or her own experience. Admittedly this is a theoretical argument, considering that most of the users are people in a state of ill-health.

Second, since benzodiazepines can reduce tension, their prescription in some settings (such as prisons) could be seen as an instrument of social control. However, should we leave untreated a prisoner with a serious anxiety disorder, for instance claustrophobia? In such circumstances the most important ethical value lies in defending the person's best interests and his/her right to benefit from effective treatment. Only these,

and clinical considerations, should influence the decision whether or not to prescribe, and not our own personal feelings and attitudes toward prisoners and prisons.

Third, the estimation of beneficial and adverse effects of benzodiazepines should take into consideration their immediate and long-term consequences upon social, emotional and professional life. The potential development of dependence should be carefully estimated in connection with the person's life history and current conditions, in order to minimise that risk.

7.3 Regulations

Because of their abuse potential, 35 benzodiazepines are currently controlled internationally under the Convention on Psychotropic Substances, 1971. The Convention does not restrict therapeutic use of benzodiozepines but requires that they be dispensed only on prescription[1].

Some countries place some or all of these benzodiazepines under stricter national control systems, mostly in order to reduce abusive prescriptions of benzodiazepines and illicit use of such products. One of the most elaborate of such systems concerns the New York State Regulations (Schwartz & Blank, 1991). According to New York State Regulations, prescriptions must be written exclusively on the State's triplicate copy prescription forms; one of these copies is sent to the State Department of Health for computerized monitoring.

Regulations of this kind pose some problems. Perhaps the most serious consequence is the non-prescription of benzodiazepines to patients who could benefit from them. In addition to the reluctance of some doctors to prescribe benzodiazepines, patients themselves may refuse a prescription on the basis of the assumption that information on them would be given to health authorities and entered into a data system.

Another potential problem is related to the controlled drug - a benzodiazepine, in this case - being replaced by other non-controlled products, not exempt of adverse effects. An increase in alcohol or other substance consumption is always a potential risk, although not easy to be evaluated.

7.4 Economic issues

The evaluation of economic issues related to diseases must distinguish between direct and indirect costs. Direct costs are those related to diagnostic procedures (such as laboratory tests or radiological examinations) and to treatment procedures (such as medication and hospitalization bills). Indirect costs include absenteeism and/or the reduction of performance at work (due either to the disease itself or to the treatment), resulting in unemployment and frequently long-lasting work incapacities. More particularly, the estimation of costs associated with anxiety and its treatment must take into consideration at least three components:

a) the cost of untreated anxiety;
b) the cost of the treatment of anxiety; and
c) cost-effectiveness of benzodiazepines (Edlund, 1990).

As for the cost of untreated anxiety, precise data on the extent of anxiety in the overall population are lacking. One of the reasons for this lack lies in that, on the one hand an unknown proportion of anxious patients fail to seek medical help, and on the other hand, several general population surveys have recorded different types of anxiety disorders according to categories existing in different classification systems. Nevertheless, several authors have indicated that the costs associated with anxiety run in the range of billions

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Reflecting increased abuse mainly by multiple drug abusers, flunitrazepam was subjected to a stricter control regimen in 1995.

of dollars annually and that the costs of treating anxiety are smaller than the cost of untreated anxiety (Edlund & Swann, 1987).

One of the most important costs associated with anxiety disorders are those related to the extensive use of expensive laboratory tests or radiological examinations because their complaints are thought to be the physical manifestations of a somatic disease and not recognized as anxiety-related. It has furthermore been shown that medically ill patients in general hospitals entail higher costs if their disease is accompanied by a high degree of psychopathology among which anxiety plays a preponderant role (Levenson et al., 1990).

The costs of medication for anxiety disorders are usually estimated with reference to the expenditure on anxiolytics based on the yearly prescriptions of these compounds. Such estimations entail a certain degree of inaccuracy, as it cannot be excluded that an unknown number of these prescriptions were prepared for other reasons than anxiety. At any rate there is some evidence that in relation to other pharmacological agents, as well as to non-drug therapy strategies (e.g. acupuncture, massotherapy, homeopathy) benzodiazepines appeared to have the best global cost-benefit ratio (Le Pen et al., 1991).

These results must be interpreted with caution until data comparing long-term costs and outcomes of different therapeutic strategies (which are currently lacking) become available. This caution must also apply to the cost-benefit ratio of the various psychotherapeutic and behavioural treatments for anxiety. Nevertheless, the additional cost of treating benzodiazepine dependence must not be forgotten.

Regarding the treatment of sleep disturbances with benzodiazepines, available data lead to conclusions which are in agreement with those reached when estimating the cost-benefit ratio of these drugs in the treatment of anxiety states. At adequate dosage, benzodiazepines can avoid high indirect economic burden through their beneficial effects on well-being and on the improvement of the work capacity of people with sleep disorders, provided they are not prescribed as monotherapy for sleep disorders associated with underlying psychiatric disorders requiring specific treatments.

In addition to expenditures specifically associated with anxiety disorders as such, a significant number of patients suffering from anxiety disorders and sleep disorders as well seek alleviation of their suffering via alcohol, and some develop alcohol dependence (5 to 20 per cent of alcoholics have a prior or related history of anxiety disorder), which further reduces their capacity to work and may cause high direct costs related to hospitalization.

Evaluation of the cost/benefit for pharmacological treatments is dependent on a number of factors. First, one must establish the actual cost of the prescription of the drug under review and relate it to its benefits. One must also investigate what expenses would result from the non-prescription of the substance, and from under-treatment. In addition, it is necessary to obtain the costs and benefits of alternative treatments and compare these with those obtained for the appropriate prescription of the drug under consideration.

For substances possessing a certain dependence and/or abuse potential, it is furthermore, necessary to determine the degree of dependence and abuse in therapeutic doses and to have an exact estimate of their respective health care costs. These different facets of the cost benefit ratio depend partially on socio-cultural differences and may therefore vary between countries.

In relation to benzodiazepines, these data are currently limited. Studies referring to the cost benefit ratio of benzodiazepines have been carried out in different geographical areas and are based on differing assessment techniques (e.g. interview conducted by clinical or lay interviewers, applying different tests or rating scales to hospitalized or non-hospitalized population samples; questionnaires submitted to general practitioners, psychiatrists or other experts). What has been published so far suggests that benzodiazepines are essentially prescribed for the treatment of anxiety (Le Pen et al., 1991).

The establishment of a significant correlation between psychopathological co-morbidity and duration of hospital stay leads to the conclusion that psychiatric consultation-liaison programmes may have economic benefits in such cases (Saravay et al., 1991). It seems quite probable that these consultations would entail the prescription of benzodiazepines for a high proportion of suitable patients and thus reduce the costs caused by the absence of an appropriate treatment of the anxiety accompanying the patients medical illness.

In conclusion, according to data currently available, adequately prescribed benzodiazepines can be considered as showing a very satisfactory cost-benefit ratio. Further research however is necessary to clarify whether for some specific conditions other strategies, such as psychotherapy or behaviour therapy, may be more efficient and thus avoid long-term expenses.

7.5 Educational problems

The rational use of benzodiazepines has a long way to go which certainly includes training of general practitioners, and informing and educating the general public. Since this issue concerns society as a whole, the wide participation of health personnel (e.g. pharmacists, nurses) is needed, as well as an unbiased cooperation from the media. A doctor who is not well-informed about psychiatric disorders may easily resort to the prescription of a psychoactive drug even though it may not be indicated. Therefore, professional training would offer the doctor some alternatives to the prescription of an anxiolytic drug.

The use of alternative treatments - different types of psychotherapies, for example - would contribute to a reduction in the prescription of psychoactive drugs. In some countries, due to media and public pressure, doctors have "spontaneously" ceased prescribing benzodiazepines which for some patients might mean not receiving perhaps the best treatment for their condition.

8. NON-MEDICAL USE OF BENZODIAZEPINES

8.1 Introduction

In the past decade, the worldwide increase in the consumption of psychotropic drugs, particularly of anxiolytics and sedatives/hypnotics, has been a matter of concern to health professionals and the public. At the same time, an increasing group of polydrug users, opioid dependents and other injecting drug users are also using benzodiazepines for non-medical purposes as one part of a wider pattern of chaotic, illicit drug use (Busto et al., 1986). Although estimates of the extent of benzodiazepine use vary considerably depending on the population studied, definitions used and methodology adopted, more recent studies are beginning to understand the reasons and consequences of such use in these high risk populations.

8.2 Patterns of use

The available evidence concerning non-medical use of benzodiazepines by multiple drug users demonstrates that they match the drug harmful use model by escalating the dose, combining several types of benzodiazepines, administering the drugs intravenously and misusing a range of stimulant and opioid drugs. They may importune several family doctors concurrently for supplies of their favourite benzodiazepines. These substances are used to induce euphoria or to intensify the action of opioids, to ease the "crash" down from the euphoric peak of cocaine or amphetamine, or to reinforce alcohol effects (Lader, 1994). In a report on patients with benzodiazepine dependence attending a dependence research unit, polydrug users were younger, took higher daily doses and had a higher life-time exposure to benzodiazepines than patients who took benzodiazepines only. Of patients taking over 60mg of diazepam or its equivalent per day, 71 per cent were multiple drug users.

Several reports indicate that benzodiazepines are often abused by opioid dependent individuals, in and out of treatment settings (Iguchi et al., 1993; Woody et al., 1975a, 1975b; Kleber and Gold, 1978; Budd et al., 1979). The reason for consuming benzodiazepines may be associated with factors such as easy access and availability, to increase the effect of heroin or methadone, to produce a "high", to overcome insomnia, to strengthen the sensation of well-being, to reduce anxiety and withdrawal symptoms, or for selling to produce income (Iguchi et al., 1993; Forsyth et al., 1993).

In a study comparing methadone maintenance clients who used benzodiazepines and other drugs to those who did not use benzodiazepines (Darke et al., 1993), benzodiazepine users were more likely to have recently injected, to have used cocaine and amphetamines, and to have borrowed or lent used needles and syringes in the preceding month. The authors concluded that this sub-group of methadone maintenance patients are more dysfunctional and may require more clinical intervention than other patients.

In has been reported that almost three quarters of heroin users entering treatment reported using benzodiazepines in the previous year in the US (US Treatment and Outcome Prospective Study; TOPS). In Australia , between 37 and 50 per cent of injecting illicit drug users had used benzodiazepines for non-medical purposes, diazepam and temazepam being the most frequently used (Darke, Ross & Hall, 1995). In Great Britain, it was found as well that among dependents (mainly opioid dependents) in contact with services in Sheffield, more than 50 per cent reported regular use of benzodiazepines in the last year. In Glasgow, among an estimated population of 8,500 injecting drug users in 1990, heroin, benzodiazepines and buprenorphine (Temgesic) constitute the main types of drugs that have been injected in the last ten years (WHO, 1994; Forsyth et al., 1993). In Denmark and Norway, one third of all cases of fatal poisoning among illicit drug dependents in the 1980s involved alcohol and benzodiazepines, which demonstrates the frequency with which these substances are also used in these groups (Kaa & Teige, 1993).

It is difficult to ascertain whether pharmacological characteristics among the various benzodiazepines or differences in availability in countries account for variations in the use of one or another type of benzodiazepines. For example, more recent reports have drawn attention to the growing preference for

temazepam (Forsyth et al., 1993; Darke, Ross & Hall, 1995; Klee & Morris, 1995) in the UK. Of particular concern in the UK has been the recent phenomenon of intravenous use of gel-filled temazepam capsules[2]. Anecdotal reports have claimed that drug users take temazepam after their heroin injection to feel relaxed, or to be stupefied, by taking it at the same time as opioids or even prior to opioid injection.

On the other hand, according to official data from the "Brigada Central de Estupefacientes", flunitrazepam is the substance most often found in the possession of heroin addicts over the past 10 years (San et al., 1993). In other countries, flunitrazepam is widely used intra-nasally to achieve rapid absorption (Lader, 1994).

Despite the inherent risks, intravenous use of benzodiazepines appears to be increasing and has been related to HIV infection (Darke et al., 1992). In a study of opioid dependents attending clinics in seven cities in Great Britain, it was found that the proportion of patients injecting benzodiazepines ranged from a third to three-quarters, with temazepam being the most commonly injected benzodiazepine.

Research conducted to date indicates that benzodiazepine use among intravenous drug users is an extensive and serious problem (Hammersley et al., 1995). First, it would appear that medical practitioners should exercise extreme caution in prescribing benzodiazepines to intravenous drug users. While it may be thought that prescribing benzodiazepines reduces the chance of injecting, for instance if the patient is in withdrawal, the research data indicate that increased injecting frequency and needle sharing are associated with the use of benzodiazepines, especially intravenously.

Finally, it has been reported that benzodiazepine use is increasing among methadone maintenance patients (Iguchi et al., 1993). During a 2-year period prior to 1978, large increases in the use of diazepam were evident in a group of methadone maintenance patients, actually 72 per cent of all the patients. Clients reported that diazepam was used to "boost the high" associated with methadone administration. Another report study (Oyefeso, Ghodse & Williams, 1995) compared two separate samples of opioid dependents admitted to South West Thames Drug Dependency Treatment and Research Unit in London over two matched 12 month periods. The percentage of patients using benzodiazepines in the six weeks prior to admission rose from 12 per cent for the year 1988/9 to 36 per cent for the year 1992/3.

In conclusion, the results suggest that, in settings where benzodiazepines are to be prescribed for an individual with a drug use history, care should be taken to avoid prolonged use without a precise medical indication, and to prevent the non-medical use of these therapeutic agents. Studies are needed to better investigate the specific abuse liability of various benzodiazepines and their interactions with other psychoactive substances, as well as systematic epidemiological data on non-medical use of benzodiazepines among high-risk groups, such as opioid dependents, polydrug users and dependents, alcohol dependents, cocaine dependents, or intravenous drug users.

Initially available in a liquid-filled capsule which was easily injectable, the preparation was changed in 1989 to a (semi-solid) gel-filled capsule in an attempt to prevent further intravenous misuse. Dependents soon discovered that the gel could be liquified by heating it and then injected. Unfortunately once injected it resolidifies at body temperature with resultant severe physical complications including superficial and deep vein thrombosis. A number of cases of acute limb (ischaemia) involving necrosis of fingers and toes following inadvertent injection of temazepam gel into arteries have been reported (Williams 1995).

9. SUMMARY AND RECOMMENDATIONS

Benzodiazepines are a class of medications which have anxiolytic, hypnotic, muscle relaxing and anticonvulsant properties. They have been in wide clinical use throughout the world for over three decades in the treatment of anxiety symptoms and disorders, insomnia, and a variety of other medical uses.

Benzodiazepines are widely used by both men and women, and people of all ages. Women use them approximately twice as frequently, and use increases substantially among elderly populations. Use in children is relatively uncommon. Approximately one-half of benzodiazepine use is in the treatment of mental disorders, and approximately one-half for general medical problems.

With regard to pharmacology, benzodiazepines have similar mechanisms of action. Most are metabolized in the liver and excreted through the kidneys. Their half-life and duration of action vary widely, although onset of action from oral administration is usually rapid (i.e. within 30 minutes).

Benzodiazepines are indicated for treatment of anxiety symptoms, anxiety disorders, induction of sleep, muscle relaxation and alcohol withdrawal. In general such treatment should be short-term (i.e., less than thirty days). Benzodiazepines are effective treatments for several long-lasting (and sometimes chronic) anxiety disorders, including panic disorder and generalized anxiety disorder. In such cases long-term use may be necessary and desirable. Benzodiazepines as adjuncts to mood stabilizers are also very effective as in the treatment of anxiety, agitation and sleeplessness associated with acute mania. They may also be used adjunctively with antidepressants in the short-term treatment of anxiety, agitation, and insomnia associated with major depression.

In general, the side effect profile for benzodiazepines is benign, and fatalities in overdose are extremely rare when no other medications are involved. Common adverse effects include drowsiness and sedation, psychomotor impairment, and cognitive impairment. These effects can become serious problems among elderly populations where metabolism rates are slowed, other medications are often used, and increased vulnerability to cognitive and psychomotor impairment is heightened. Occasionally, patients may become disinhibited, and show increased agitation and confusion. In such situations, additional benzodiazepines will exacerbate, rather than alleviate, the symptoms.

Discontinuation of benzodiazepines requires attention, especially following long-term use at higher doses. Discontinuation reactions include withdrawal syndrome, rebound symptomatology, and relapse of the underlying condition. In some patients discontinuation from benzodiazepines can take weeks to months.

The strategy for prescription of benzodiazepines requires a thorough evaluation of the patient, including a clinical interview, a physical examination, and laboratory procedures. Screening inventories for anxiety and/or depression may help to identify people for whom benzodiazepines may be considered. After making the diagnosis, various treatment options (including psychotherapy) should be discussed with the patient. If benzodiazepine prescription is selected, in general, dosage should start low and be increased over days to several weeks. Except for chronic or relapsing anxiety disorders such as panic disorder, benzodiazepines should be prescribed for thirty days or less. The use of benzodiazepines in the overall management of acute distress, resulting from general medical illness or psychosocial problems, should be considered on a case-by-case fashion and should in general be short-term. Selection of a specific benzodiazepine should be influenced by duration of action, metabolic pathway, and rapidity of onset. In general, shorter acting benzodiazepines are more useful as hypnotics and longer-acting ones are better for anxiety symptoms and disorders. It is often useful for a clinician to obtain a good knowledge of just a few benzodiazepines, with differing half-lives and metabolic pathways. Benzodiazepines should be prescribed with caution or not at all to patients with comorbid substance abuse and personality disorders.

Benzodiazepines are not usually recommend for use during pregnancy, especially in the first trimester, and should be used only with strict indications.

Among elderly populations benzodiazepine prescriptions should be made more cautiously with a lower starting dose, slower titration, and lower final dose. Clinicians should be concerned about the possibility of accumulation of benzodiazepines.

In some countries and some jurisdictions within some countries, there are restrictions on the prescription and use of benzodiazepines. Clinicians should be cognizant of rules and regulations regarding the prescription and use of benzodiazepines in their particular area.

Benzodiazepines can be and are abused by some people, particularly drug abusers.

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TERMINOLOGY (ABUSE, MISUSE, NON-MEDICAL USE, DEPENDENCE, DEPENDENCE SYNDROME, WITHDRAWAL STATE)

Abuse (drug, alcohol, chemical, substance, or psychoactive substance). A group of terms in wide use but of varying meaning. The term "abuse" is sometimes used disapprovingly to refer to any use at all, particularly of **illicit drugs**. Because of its ambiguity, the term is not used in ICD-10 (except in the case of non-dependence-producing substances; **harmful use** and **hazardous use** are the equivalent terms in WHO usage, although they usually relate only to effects on health and not to social consequences).

In other contexts, abuse has referred to non-medical or unsanctioned patterns of use, irrespective of consequences. Thus the definition published in 1969 by the WHO Expert Committee on Drug Dependence was "persistent or sporadic excessive drug use inconsistent with or unrelated to acceptable medical practice".

Misuse (drug or alcohol). Use of a substance for a purpose not consistent with legal or medical guidelines, as in the **non-medical use** of prescription medications. The term is preferred by some to **abuse** in the belief that it is less judgemental.

Non-medical use. Use of a prescription drug, whether obtained by prescription or otherwise, other than in the manner or for the time period prescribed, or by a person for whom the drug was not prescribed. The term sometimes also covers the use of **illicit drugs**.

Dependence syndrome. A cluster of physiological, behavioural, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviours that once had greater value. A central descriptive characteristic of the dependence syndrome is the desire (often strong, sometimes overpowering) to take psychoactive drugs (which may or may not have been medically prescribed), alcohol, or tobacco. There may be evidence that return to substance use after a period of abstinence leads to a more rapid reappearance of other features of the syndrome than occurs with non-dependent individuals.

Withdrawal state. A group of symptoms of variable clustering and severity occurring on absolute or relative withdrawal of a substance after repeated, and usually prolonged and/or high-dose, use of that substance. Onset and course of the withdrawal state are time-limited and are related to the type of substance and the dose being used immediately before abstinence. The withdrawal state may be complicated by convulsions.

ICD-10 CLASSIFICATION OF ANXIETY DISORDERS
Neurotic, stress-related and somatoform disorders

F40 Phobic anxiety disorders

F40. 0	Agoraphobia	
.00	Without panic disorder	
.01	With panic disorder	
F40.1		Social phobias
F40.2		Specific (isolated) phobias
F40.8		Other phobic anxiety disorders
F40.9		Phobic anxiety disorder, unspecified

F41   Other anxiety disorders

F41.0	Panic disorder [episodic paroxysmal anxiety]
F41.1	Generalised anxiety disorder
F41.2	Mixed anxiety and depressive disorder
F41.3	Other mixed anxiety disorders
F41.8	Other specified anxiety disorders
F41.9	Anxiety disorder, unspecified

The ICD-10 classifies anxiety disorders under a large group of neurotic, stress-related and somatoform disorders and a subgroup of phobic and other anxiety disorders. The former disorders have been brought together in one large overall group because of their historical association with the concept of neurosis and the association of a substantial proportion of these disorders with psychological causation. In the phobic group of disorders, anxiety is evoked only, or predominantly, by certain well-defined situations or objects (external to the individual) which are currently dangerous. As a result, these situations or objects are characteristically avoided or endured with dread. Phobic anxiety is distinguishable subjectively, physiologically, and behaviourally from other types of anxiety and may vary in severity from mild unease to terror. The individual's concern may focus on individual symptoms such as palpitations or feeling faint and is often associated with secondary fears of dying, losing control, or going mad. The anxiety is not relieved by the knowledge that other people do not regard the situation in question as dangerous or threatening. Mere contemplation of entry to the phobic situation usually generates anticipatory anxiety.

Phobic anxiety often co-exists with depression. Pre-existing phobic anxiety almost invariably gets worse during an intercurrent depressive episode. Some depressive episodes are accompanied by temporary phobic anxiety and a depressive mood often accompanies some phobias, particularly agoraphobia [fears of open spaces, presence of crowds and the difficulty of immediate easy escape to a safe place (usually home)]. Whether two diagnoses, phobic anxiety and depressive episode, are needed or only one is determined by whether one disorder developed clearly before the other and by whether one is clearly predominant at the time of diagnosis. If the criteria for depressive disorder were met before the phobic symptoms first appeared, the former should be given diagnostic precedence.

Most phobic disorders other than social phobias are more common in women that in men.

Manifestations of anxiety are the major symptoms of "other anxiety disorders" and are not restricted to any particular environmental situation. Depressive and obsessional symptoms, and even some elements of phobic anxiety, may also be present, provided that they are clearly secondary or less severe.

Annex 4

SCREENING INSTRUMENTS

Instrument	Reference
Beck Depression Inventory (BDI)	Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Archives of General Psychiatry*, 1961, 4:561-571.
Beck Anxiety Scale	Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: Psychometric properties. *Journal of Consulting and Clinical Psychology*, 1988, 56:893-897.
Center for Epidemiologic Studies Depression scale (CES-D)	Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychology Measurement*, 1977, 1:385-401.
General Health Questionnaire (GHQ-12)	Goldberg DP, Williams P. *A user's guide to the General Health Questionnaire*. London, UK: NFER, 1988.

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