



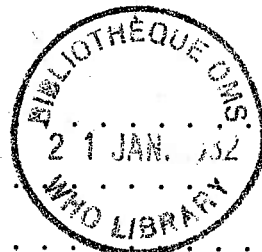
*Drug Abuse Control
Benzodiazepine tranquilizers*

5TH REVIEW OF PSYCHOACTIVE SUBSTANCES FOR INTERNATIONAL CONTROL INDEXED

Geneva, 16-20 November 1981

CONTENTS

	<u>Page</u>
1. Introduction	2
2. Basic Pharmacology	3
3. Dependence Studies in Animals	5
3.1 Physical Dependence	5
3.2 Self-Administration/Reinforcing Properties	6
4. Dependence Studies in Humans	7
4.1 Physical Dependence	7
4.2 Psychological Dependence/Reinforcing Properties	7
5. Availability of Substances and Their Preparations in Various Countries	8
6. Therapeutic Use of Benzodiazepines	8
7. Drug Utilization Data	9
8. Evidence of Abuse and Related Public Health Problems	10
9. Health and Social Consequences	12
9.1 Organ System Pathology	12
9.2 Behavioural Effects	12
9.3 WHO Initiatives	13
10. Selection of Topics for Future Review Groups	13
11. Recommendations	14
11.1 The Control of Benzodiazepines Under the 1971 Convention	14
11.2 Research, Information and Data Collection	15
11.3 - 11.6 Other Recommendations	16
12. List of Participants	17
13. List of Background Documents Available to the Group	18
Annex I - Discussion with Pharmaceutical Companies	22



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1. INTRODUCTION

The Group was welcomed by Dr Norman Sartorius, Director of the Division of Mental Health on behalf of Dr H. Mahler, Director-General of WHO. Dr Sartorius informed the Group that the decisions regarding the international regulation of drugs had been enlarged and made more complex by the Convention on Psychotropic Substances (1971)¹. The use and misuse of the benzodiazepines which this group is charged to review represents a particularly complex problem since there is no universal agreement among medical practitioners as to the clinical indications warranting the use of these drugs. Although it is clear that these drugs are safe and effective in the treatment of anxiety, insomnia and certain neuromuscular and convulsive disorders, their widespread availability has given rise to concerns of their being over-prescribed. Further, reports of illegal diversion of various benzodiazepines into street use has been reported by various countries. These problems have prompted WHO to consider this class of drugs for possible scheduling under the 1971 Convention.

Dr Sartorius specifically charged the Group to consider certain issues and to make recommendations on:

- How can WHO expand its collaborative efforts with the associated Non-governmental Organizations?
- How can WHO establish a relationship with the pharmaceutical industry; to promote the rational use of psychoactive drugs?
- How can WHO expand its activities in training and physician education?

Dr B. Sankaran, Director of the Division of Diagnostic, Therapeutic and Rehabilitative Technology, informed the Group that a meeting of experts was currently being held in his division to determine information for individual drugs included in the list of essential drugs. They will include in their deliberation information relating to dependence potential and abuse liability of the benzodiazepines and other psychoactive drugs.

WHO's initiatives in the area of psychotropic drug control were reviewed for the Group.

The Group was informed that WHO had recommended control of diazepam and chlordiazepoxide which was not accepted by the Plenipotentiary Conference held in Vienna in 1971.

WHO convened two Expert Committees which produced reports on the methods available for providing data on the dependence potential and actual abuse of psychoactive drugs (TRS 618 and 656). TRS 618 deals with methods for assessing the psychopharmacological properties of drugs and TRS 656 for assessing the public health and social problems associated with the use of psychotropic drugs. Since 1978, WHO has developed close collaboration with the United Nations Division of Narcotic Drugs and Interpol in seeking information concerning drug trafficking, clandestine laboratories, forensic laboratories and reports of illicit drug use.

In 1981, WHO in collaboration with the Government of Finland and UNFDAC, investigated in depth, certain aspects of the public health problems (mortality, morbidity and particularly intoxication and road traffic accidents) and the utilization of psychotropic drugs in a meeting with the participation of experts from 14 developing countries. A project has now been proposed which will seek information on the above-mentioned parameters from general hospitals with psychiatric beds in a number of developing countries. The role of alcohol as a cause of road traffic accidents is established but more work is needed to assess the role of drugs, alone and in combination with alcohol. Accordingly, WHO in collaboration with the National Institute on Drug Abuse (USA), has reviewed this area and a report will soon be available

¹ (later on referred to as the 1971 Convention)

The procedure provides information analogous to a human testing situation in which subjects categorize drugs with respect to their subjective effects. It has been possible to train animals to discriminate a benzodiazepine from saline, thus indicating the discriminability of the benzodiazepines. When other drugs have been substituted in chlordiazepoxide-trained animals, the drug-appropriate response has occurred for all other benzodiazepines tested for most other sedative-hypnotics, but not for neuroleptics; thus indicating some specificity of effect. Although pentobarbital and alcohol-trained animals also show generalization to benzodiazepines under the drug discrimination procedure, animals can be trained to discriminate chlordiazepoxide from pentobarbital. Thus, evidence exists for some differential, as well as common, stimulus attributes of the sedative hypnotic drugs, including the benzodiazepines.

Systematic comparison in monkeys of sixteen clinically used benzodiazepines in a series of behavioural-pharmacological tests (including, assessment of behavioural effects, anti-convulsant activity, potentiation of barbiturate induced sleeping time, physical dependence producing potential and reinforcing effects) has shown that the relative potency of any two compounds may vary widely depending on the test (Yanagita, 1981)¹. Although definitive conclusions await further research, these results suggest that there may be important differences among benzodiazepines in the degree of behavioural impairment they produce at therapeutic and/or self-administered dose levels.

Benzodiazepines decrease sleep latency, increase time spent in sleep, increase REM sleep latency and reduce REM sleep. Sleep is less restless. There is an increase in stage 2 sleep while stages 3 and 4 are usually shortened. Drug withdrawal rebound phenomenon usually associated with many hypnotics is less frequent with benzodiazepines.

In animals and humans benzodiazepines prevent the subcortical spread of seizure activity. They strongly inhibit pentylentetrazol and picrotoxin induced seizures, but are relatively less effective against the seizure activity induced by strychnine or electroshock. In experimental models of epilepsy, all benzodiazepines suppress the spread of seizure activity produced by epileptogenic foci in the cortex, thalamus and limbic structures but do not abolish the abnormal discharge of the focus. Benzodiazepines also suppress polysynaptic reflexes in the spinal cord and decrease neuronal activity in the mesencephalic reticular system.

Benzodiazepines, administered to humans in usual therapeutic doses by the oral route have no significant influence on respiration and cardiovascular function. By the intravenous route these drugs can cause respiratory depression. None of the benzodiazepines exert direct effects on the gastrointestinal tract.

Benzodiazepines are well absorbed from the gastrointestinal tract but vary in their rate of absorption and the rate at which they enter the brain. Most, but not all, benzodiazepines are highly bound to plasma proteins.

Benzodiazepines vary in their mode of elimination. Some such as diazepam are metabolized by N-desmethylation and hydroxylation; others such as oxazepam are conjugated with glucuronic acid to form water-soluble derivatives. Benzodiazepines vary widely in their elimination half-lives, diazepam having a half-life of 50 hours or more, triazolam having a half-life of a few hours. Furthermore, some have active metabolites, and others do not. The effect of benzodiazepines is usually prolonged in the elderly, usually due to slowed elimination.

¹This reference is contained in the background document prepared by Yanagita for this meeting.

It is of great theoretical importance that a close relation between benzodiazepines and the GABAergic system was discovered recently. A second important discovery was the demonstration of specific high-affinity binding sites for the benzodiazepines. Some, but by no means all of these binding sites are in close proximity to the GABAergic system and have a functional relationship with GABAergic receptor-chloride ionophores. These complexes may also contain binding sites for picrotoxin and barbiturates.

An important line of current research is that directed at isolating an endogenous ligand for the benzodiazepine receptor. A highly promising new tool for the investigations is now provided by the recently developed selective benzodiazepine antagonist, RO-15-1788, which is the first derivative of the family which inhibits potently ³H-diazepam binding and antagonizes the pharmacological effects of the benzodiazepines.

There is mutual potentiation between benzodiazepines and other CNS depressants, including alcohol. Other drug interactions are clinically unimportant except for the enhancement of effects of diazepam by cimetidine.

Tolerance to the anticonvulsant and muscle relaxant effects of the benzodiazepines was observed in both animal experiments and in humans in the clinic. The development of tolerance to the sleep inducing effects of the sedative-hypnotic benzodiazepines is very slow and practically no tolerance to the anti-anxiety effect of anxiolytic benzodiazepines has been observed.

3. DEPENDENCE STUDIES IN ANIMALS

3.1 Physical Dependence

Preclinical studies dealing with the physical dependence potential of benzodiazepines have been conducted primarily in three species: rat, dog, and monkey. In all three species a fairly consistent pattern has emerged, suggesting that benzodiazepines produce barbiturate-like physical dependence.

Two procedures have been used for testing the physical dependence potential of benzodiazepines and other sedative drugs: the substitution test and the physical dependence producing test (WHO TRS 618). Results from these procedures are summarized below.

Substitution test: In the substitution test, animals are first made physically dependent on a barbiturate (e.g., barbital), by means of repeated administration for days or weeks. The drug is then withdrawn, and once clear withdrawal signs are observed, a single dose or short-term repeated doses of a test drug are administered. The extent to which suppression of barbiturate withdrawal is observed defines the cross-physical dependence potential of the test drug.

Using this approach, studies in barbiturate dependent monkeys and rats have shown that all benzodiazepines tested to date partially or completely suppress the signs of barbiturate withdrawal¹.

The doses required for complete suppression varied from one drug to the other, and did not necessarily coincide with their recommended clinical dosages, nor pharmacological potencies.

¹ Benzodiazepines which have been tested in these experiments include: alprazolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, cloxazolam, diazepam, flunitrazepam, flurazepam, halazepam, lorazepam, nitrazepam, oxazolam, prazepam, temazepam and triazolam.

Physical dependence producing test: The physical dependence producing procedure involves administering the test drug to naïve animals once or more daily for several days or weeks. The drug is then withdrawn and the animals are observed for several days for signs of withdrawal. The cycle can be repeated using higher dose levels to obtain convincing negative or positive results. Physical dependence potential is established by grading the signs of withdrawal into several general categories: mild, intermediate or severe.

Using this approach, studies in monkeys, rats and dogs have shown that all benzodiazepines tested to date produce some degree of physical dependence. Benzodiazepines which have been tested include the same compounds that have been evaluated on the substitution test. Data collected to date indicate that there are some differences in the ability of different benzodiazepines in producing physical dependence which bear no systematic relationship to their pharmacological potencies. The range of differences between drugs in terms of their physical dependence potentials within the benzodiazepine class is much smaller than that found with the opioid analgesic class.

3.2 Self-Administration/Reinforcing Properties

One approach to studying dependence potential has been the development of experimental paradigms for controlled investigations of drug self-administration in laboratory animals (WHO TRS 618). Such experimental models can provide various types of information relevant to dependence potential of drugs, including comparative information about the relative reinforcing efficacy and dose level with which different drugs maintain drug self-administration. The validity of this approach is supported by the good correspondence between those drugs that are self-administered by laboratory animals and those self-administered and abused by humans.

Experimental studies with rats and nonhuman primates have examined self-administration of a variety of benzodiazepines via the intravenous, intragastric and oral routes.

Overall, studies of benzodiazepine self-administration in rats provide only limited evidence for drug reinforcement. While several studies in rats using intravenous, intragastric and oral routes have demonstrated higher levels of benzodiazepine intake over that seen for vehicle control, other studies have failed to demonstrate drug reinforcement.

Studies in nonhuman primates provide stronger evidence for the reinforcing properties of benzodiazepines. In these studies the percentage of animals self-administering the drug, the rate of drug self-administration, or drug choice performance are taken as indicators of the relative reinforcing efficacy of the drug. These studies showed that benzodiazepines as a class are more effective reinforcers than some other psychoactive drugs, including chlorpromazine, imipramine, haloperidol or perphenazine. The studies also showed, however, that benzodiazepines were clearly less effective reinforcers than a range of other drugs, including pentobarbital, alcohol, amobarbital, secobarbital and cocaine. On the whole, the data suggest that benzodiazepines can be considered to be weakly reinforcing. Several studies which have compared the self-administration of different benzodiazepines suggest that some of the rapidly absorbed and eliminated compounds may have a greater potential for maintaining self-administration than the more slowly absorbed and eliminated benzodiazepines.

Comparative data obtained from studies of the intragastric continuous self-administration of various benzodiazepines show that some susceptible rhesus monkeys self-administered large quantities (i.e. high daily doses) of some benzodiazepines relative to their minimum effective doses as determined by gross behavioural observation in normal rhesus monkeys. In contrast, the intake of other benzodiazepines was lower.

without histories of drug abuse. In interpreting these results, however, it should be recognized that other clinical studies have shown that development of psychological dependence in people without histories of drug abuse is also unusual with drugs such as amphetamine or morphine.

Experimental investigations and case reports on psychological dependence on several benzodiazepines do not provide an empirical basis for differentiating between these drugs.

5. AVAILABILITY OF SUBSTANCES AND THEIR PREPARATIONS IN VARIOUS COUNTRIES

The United Nations Division of Narcotic Drugs assisted the Director-General of WHO in obtaining certain data on the benzodiazepines. 52 countries of the 154 member states of the United Nations responded to a request for data on the substances to be reviewed in this meeting in order to determine whether any of them should be recommended for scheduling under the 1971 Convention. Analysis of the data indicates that benzodiazepines are widely available in most countries of the world. There was an indeterminate amount of illicit traffic and no clandestine laboratories were reported, perhaps because benzodiazepines are very difficult to synthesize. Instances were cited in which price differences for the same products resulted in unauthorized movement across national frontiers. On the other hand, products sold illicitly may occasionally be cheaper than the same products obtained through licit distribution channels.

Benzodiazepines have been reported as being seized along with illicit drugs in all geographic areas of the world, although the quantities varied widely. On occasions on which benzodiazepines have been seized by law enforcement agencies, they have generally been found in the process of arrests for other drugs.

Most industrialized countries exercise control over the manufacture and sale of benzodiazepines which are usually available only on a prescription basis. Many of the developing countries which import benzodiazepines licitly do not have sufficient control measures, for a number of reasons. Sometimes they may lack the administrative organization required; at times, detailed information on appropriate use and potential misuse is not provided by manufacturers and distributors; in most instances, different social and economic priorities have an overriding importance for these countries. Control measures in developing countries are often complicated by the clandestine appearance of benzodiazepines sometimes following importation under false pretense, such as mis-labelling of products. The vast majority of illicitly available benzodiazepines are presumed to be used for non-medical purposes.

The Group felt that the excessive number of benzodiazepine preparations often confused both physicians and other health care workers and strained the economies of many developing countries.

6. THERAPEUTIC USE OF BENZODIAZEPINES

Benzodiazepines are among the most widely used therapeutic agents available today. They are used to alleviate the symptoms which accompany numerous psychological, psychosomatic and somatic disorders. In many countries they have largely replaced the barbiturates as sedative-hypnotics and anxiolytics.

a. The most common use of the benzodiazepines is in the treatment of emotional disorders, particularly anxiety and stress-related reactions. Many trials attest to the efficacy, at least in the short term, of the benzodiazepines in lessening both the subjective feelings of unrest, tension and apprehension of the future and the bodily accompaniments such as palpitations, tremor and sweating, characteristic of anxiety. There seems little to choose among the benzodiazepines in their effectiveness at allaying anxiety. This use of the benzodiazepines is part of a general management for the patient which may include reassurance, support, formal psychotherapy, behavioural methods of treatment and social adjustment.

However, the evidence that benzodiazepines are effective beyond a few weeks of treatment with chronically anxious patients is not clear. Nevertheless, many such patients are maintained on benzodiazepines for many months or even years.

b. Another symptom for which the benzodiazepines are widely prescribed is insomnia. They are particularly used in patients in whom the insomnia is related to a general anxiety state. The benzodiazepines are effective hypnotics but alter the structure of sleep with implications which are unclear. Evidence for effectiveness beyond one month is limited. Diazepam is also used to treat sleep disorders such as sleep walking or night terrors because of its suppression of the stage of sleep in which this symptom commonly occurs.

c. The benzodiazepines are also widely used to treat neuromuscular disorders characterized by muscle spasticity. Such conditions include cerebral palsy, multiple sclerosis, cerebrovascular accidents and spinal cord lesions. However, effectiveness is greater against spasm emanating from traumatic causes such as "slipped disc" and sports injuries.

d. Intravenous diazepam is the treatment of choice in managing status epilepticus. Nitrazepam orally is used to prevent infantile spasms. Clonazepam is being increasingly used as an anticonvulsant, however, intermittent use is advised to prevent tolerance.

e. Other uses of benzodiazepines include as pre-operative medication and for minor therapeutic and operative procedures such as endoscopy and dental surgery because of their ability to produce deep sedation and amnesia. Benzodiazepines are used as adjuncts to relaxation therapy in phobic patients and used in the management of alcohol withdrawal.

Criticisms have been levelled that the widespread use of the benzodiazepines reflects indiscriminate prescribing by the doctor - general practitioner, psychiatrist, internist, orthopedic specialist, etc. This has prompted concern by authorities in many nations that the widespread use of benzodiazepines suggests inappropriate and overprescribing by medical practitioners. The group expressed the opinion that assessing the extent of medical misuse of these drugs is difficult to determine particularly in the treatment of anxiety. In part this difficulty stems from the fact that practitioners differ in their opinion as to the intensity of anxiety warranting the use of these drugs. The group suggested physician education programmes as the most appropriate means to ensure the appropriate use of these drugs.

7. DRUG UTILIZATION DATA

The most basic information on the use of any drug relates simply to its past and current total usage in a particular country. Surveillance of drug consumption in general, and the utilization of psychotropic drugs in particular, is in the interest of any health care system for the following reasons:

- To monitor the trends and variations of prescribing from time to time
- To evaluate if the extent of drug use is medically justified
- To find out if there does exist a risk of drug overuse or misuse or diversions from licit to illicit use
- To know the costs of drug treatment for health care
- To monitor what and how much is imported and exported and how drugs are distributed in a country (to hospitals, pharmacies, primary health care units, etc.)
- To assess the public health and social problems associated with the use of a particular psychotropic drug, it is essential that as a denominator one knows the total utilization figures of that particular drug in a community
- To measure how educational activities aimed at physicians and the regulatory actions taken by health authorities (e.g. warnings in medical journals, revision of promotional information, restrictions, withdrawals from the market, etc.) have influenced prescribing and whether or not additional actions may be needed.

Although drug consumption figures are most essential to know for any health authority, there is in most countries a lack of adequate information about the way in which and the extent to which drugs are used and misused.

In order to obtain reliable comparative data for drug consumption between different countries, between various drugs or drug groups and to observe changes that occur with time, it is necessary to have a common universally acceptable basis for drug classification, units of measurement and the same type of source from which data could be obtained. Even when data have been obtained, special techniques are required for their validation, correct analysis, and interpretation. These necessities have been thoroughly investigated and considered by a WHO Drug Utilization Research Group. Its recommendations as well as some practical applications from Nordic and some other European countries are now available (see WHO TRS 656 and Studies on Drug Utilization, WHO Regional Office Publication, European Series, No. 8 (1979) and the Nordic Statistics on Medicine del I and II, Helsinki and Oslo, 1979).

Using procedures designed to generate such utilization data, evidence suggesting over-prescribing of benzodiazepines prompted concern among certain national authorities in Nordic countries. After physician education efforts and the revision of drug prescribing regulations, the frequency of benzodiazepine prescriptions declined. This illustrates how such drug consumption surveillance systems can be used to detect a drug problem and thereby allow prompt intervention.

8. EVIDENCE OF ABUSE AND RELATED PUBLIC HEALTH PROBLEMS

The evidence that benzodiazepines are involved in abuse comes from several sources. Such use is not necessarily connected with a medical indication and the drug is not prescribed by a physician. The data do not permit an accurate quantitative estimate of the degree of the problem.

The Group felt that public health and social problems associated with benzodiazepines were as important as abuse liability and that attention needed to be paid to them. The Group considered the reports prepared by the UN Division of Narcotic Drugs (DND 421/12 (1) WHO, also addendum I and II dated 9 October and 10, 11 November 1981), the Report on Benzodiazepine Trafficking prepared by the Drug Enforcement Administration, Washington D.C., USA and the report by Interpol. The data contained in these reports permit the following observations:

Generally speaking most of the benzodiazepines were available worldwide. All geographic regions of the world reported that these substances were occasionally abused in widely varying degrees. Diazepam is the substance most widely prescribed, as well as abused and seized (Australia, Austria, Burma, Canada, Cyprus, France, New Zealand, Philippines, Portugal, South Africa and Sri Lanka). This substance is reported to be abused by opiate addicts in Burma, Canada, Cyprus, Federal Republic of Germany and Zambia when the primary drug of addiction is not available. It is reportedly used in combination with marijuana in the Philippines. Abuse of chlordiazepoxide was reported from Canada, Cyprus, France, Turkey and Zambia, and seizures were made in the Federal Republic of Germany, New Zealand, Philippines, South Africa and Turkey. Cases of nitrazepam dependence had increased recently in Burma and seizures were reported from Guatemala, New Zealand, Philippines and South Africa. The three preceding substances had been identified following analysis in government laboratories in Switzerland and the United Arab Emirates. The seizure and abuse of other benzodiazepines has been to a lesser extent.

There was good evidence that illicit traffic in these substances existed in many countries, the exact extent of which was difficult to establish. Evidence also suggested that organized illicit drug traffickers were expanding their operations to include benzodiazepines. This was, however, believed to be still on a small scale. Although accurate data was lacking, such traffic would seem to be increasing. It was noteworthy that seizures by law enforcement authorities were almost always incidental to investigations into, and seizures of, drugs already under national or international control. It was therefore principally through their activities in connexion with narcotic drugs and other psychotropic substances that authorities were able to supply some data on the abuse of benzodiazepines.

It was pointed out in the reports that illicit traffic in benzodiazepines originated from diversion from licit sources either in dosage form or in bulk which was subsequently processed and resold through questionable outlets. No clandestine laboratories as such were reported but the bulk products were subsequently formulated for sale in the streets. For example, tablets have even been made so as to imitate methaqualone tablets and sold at a higher price than that commanded by benzodiazepines.

Reports from other countries such as the Philippines, Australia and Malaysia do show a small but increasing use of benzodiazepines as the primary drug of abuse. In Thailand, diazepam abuse was first noted about 6 years ago and in 1980, that country reported 150 cases of primary diazepam dependence.

Surveys of patients in drug abuse treatment programmes in the United States indicate that diazepam is frequently used as a substitute drug when the primary drug of abuse cannot be obtained. Diazepam has also been found to be used by patients in methadone maintenance treatment programmes. Some of these individuals report that they achieve euphoria by combining diazepam with methadone. Urine testing of such patients in certain treatment programmes indicates that benzodiazepines are found in up to 65% of the cases. Several governments also report the abuse of benzodiazepines in combination with opioids.

Benzodiazepines are commonly used by poly-drug abusers in North America, but few use benzodiazepines as their primary drug of abuse. Users of drugs obtained illicitly have been found to take benzodiazepines for two basic reasons. First, the drug may be used with the intention of producing a state of euphoria. This may lead to escalation of intake so that persons utilizing over 1000 mg per day of diazepam have been reported. A second reason reported by users of illicit benzodiazepines is the self-medication of withdrawal symptoms occurring when the drug of choice (e.g., amphetamine, heroin, etc.) cannot be obtained.

It would appear, therefore, that benzodiazepines are the subject of abuse although it is not clear how widespread the problem is or how the problem compares with that of other drugs. However, drug utilization studies from Norway, Sweden, Finland and certain other countries have shown that physicians have increasingly replaced their prescribing of barbiturates with benzodiazepines. The Group recognized this as a positive contribution to public health because most of the benzodiazepines are less toxic and have lower abuse liability than the barbiturates.

9. HEALTH AND SOCIAL CONSEQUENCES

9.1 Organ System Pathology

With regard to respiratory function, it should be noted that although most benzodiazepines are potential respiratory depressants, only a minor degree of respiratory depression is produced in healthy subjects. However, reports exist that suggest that respiratory depression may occur after administration of most benzodiazepines to patients with existing pulmonary diseases.

Benzodiazepines have no marked effects upon gastro-intestinal function except as indirect consequences of central nervous system influences. Reports also exist which indicate adverse effects upon neonates due to the benzodiazepines used during labour. Benzodiazepines can cause a transient drop in temperature in infants following maternal drug administration. This temperature drop was associated with an increased incidence of assisted delivery and resuscitation.

The existence of teratogenic potential of benzodiazepines was also noted. Studies have suggested an association between benzodiazepine use during pregnancy and the incidence of oral clefts. Some studies indicate as high as four times the incidence of cleft lip with or without cleft palate in children born to mothers who used diazepam in the first trimester of pregnancy. Further, withdrawal signs have been observed in the infants born to mothers chronically receiving diazepam.

In general, as with organ system pathology, the lethality of benzodiazepines is extremely low. Fatalities due to benzodiazepine overdosage are exceedingly rare. In contrast to barbiturates, the benzodiazepines are relatively non-toxic compounds. Adverse effects such as ataxia, hypotonia, drowsiness, etc., have been noted. Aberrant responses including fine motor tremor in the upper extremities, apprehension and insomnia marked by severe nocturnal confusion, although rare, has been reported. These adverse effects are more frequent and severe in the elderly.

9.2 Behavioural Effects

Both psychomotor and cognitive deficits have been noted in commonly used tests of behavioural performances. Performance on a vigilance task, for example, was impaired in normal human subjects. It was also noted that the various studies were unable to clarify whether the impairment of psychomotor performance is a direct consequence of benzodiazepine action in the central nervous system or secondary to the sedative or muscle relaxant properties of these agents. Some studies indicate that chronic administration of benzodiazepines do seem to produce impairment in learning memory, and psychomotor functioning. Finally, signs of intoxication and behavioural impairment have been observed in people abusing high doses of these drugs.

In relation to the effects of benzodiazepines and driving, the studies based on driving simulators on healthy volunteers have shown that benzodiazepines alone and particularly in combination with alcohol, have deleterious effects on driving performance. These facts are mentioned in data sheets and health authorities in collaboration with drug manufacturers (Nordic Countries) have decided to label benzodiazepine preparations with a special warning symbol.

A variety of behavioural and mood disturbances have been associated with chronic diazepam administration in clinical situations, including increased hostility, depression, paranoid ideation and suicidal tendencies. Because the frequency of such observations has been relatively low, it has often been assumed that these effects represent idiosyncratic reactions to diazepam. However, a series of controlled experiments in non-anxious subjects with chlordiazepoxide and diazepam, suggests that increased hostility may represent a regular, rather than an idiosyncratic effect of some of these drugs in these subjects. Several studies have reported an aggravation of depressive symptoms by certain benzodiazepines in patients not treated with anti-depressants.

9.3 WHO Initiatives

The Group was also appraised of the efforts made by WHO headquarters and its regional offices to collect information about the imports, types, distribution and use as well as public health and social consequences of benzodiazepine use in the various countries.

The information gathered came from only a limited number of developing countries. In most instances the information was insufficient, incomplete and sometimes contradictory. The enquiry initiated by the Mental Health Division of WHO helped discover some interesting facts. Thailand for instance, has benzodiazepines marketed by numerous pharmaceutical companies, each of which market a bewildering number of benzodiazepine preparations. Regulations governing the use of benzodiazepines in different countries varied widely and the degree to which they were enforced presented even greater variations.

The Group felt that the pharmaceutical industry may prove to be a good source of information but at the same time it does recognize that these data will usually not include abuse liability and may occasionally be self-serving. Other sources of information, particularly the United Nations specialized agency reports, national drug control authorities data as well as information provided by Non-governmental Organizations are of utmost importance.

10. SELECTION OF TOPICS FOR FUTURE REVIEW GROUPS

The Group rediscussed the topics selected for future consideration of need for international control under the 1961 and 1971 Conventions proposed by a previous WHO Group¹ and adopted the list of topics contained in that Report. The Group, however, was of the opinion that because of the developments on the drug scene that can be briefly characterized by appearance in illicit traffic and in street abuse of a number of derivatives of substances already scheduled or reviewed, or proposed for scheduling (e.g. fenetylline, fenbutrazone, ethylamphetamine, isomeprobamate, phenoprobamate, methylfentanyl), a priority should be given by WHO to consider certain derivatives and congeners of analgesic, sedative, hypnotic, anxiolytic and stimulant substances already scheduled under 1961 and 1971 Conventions, as well as derivatives and congeners of such substances proposed for scheduling by WHO.

¹WHO Document MNH/81.26 - 4th Review of Psychoactive Substances for International Control.

Consequently, the following list of topics was adopted for review in the following order:

1. Derivatives and congeners of analgesic, sedative hypnotic, anxiolytic and stimulant substances already scheduled or proposed for scheduling under both 1961 and 1971 Conventions.
2. Analgesic drugs not subjected to international control.
3. Sedative, hypnotic and anxiolytic drugs not subjected to international control.
4. Precursors and intermediates of drugs listed in schedules of both Conventions.
5. Synthetic and natural stimulants already scheduled under the 1971 Convention.
6. Antipsychotic and antidepressant drugs with dependence potential and abuse liability.
7. Derivatives and congeners of tetrahydrocannabinols with regard to their dependence potential, abuse liability and therapeutic usefulness.

The Group also recommended that in preparation of the forthcoming review meetings, the United Nations Agencies concerned, and particularly the UNDND, were requested to indicate, additionally, that the substances:

- a) have been recently seized from illicit traffic, and
- b) have been put under national control because of their abuse potential and dependence liability.

11. RECOMMENDATIONS

11.1 The Control of Benzodiazepines Under the 1971 Convention

The Group reviewed the evidence available on diazepam as a prototype of the benzodiazepines. In accordance with Article 2, paragraph 4 (a)(i) and (b) of the Convention on Psychotropic Substances, the Group concluded that diazepam did meet the criteria for scheduling under that Convention and recommended that diazepam be placed in Schedule IV. The Group felt that the evidence reviewed so far is insufficient to allow differentiation among the various benzodiazepines as to dependence potential, abuse liability, and risk to public health and concluded that at this time all benzodiazepines should be scheduled similarly. The Group recognized that it was possible that in time evidence might be presented that would lead to rescheduling or descheduling of certain benzodiazepines. The Group also recognized that the list of benzodiazepines reviewed did not include all those available worldwide but concluded that on the basis of present knowledge all currently marketed benzodiazepines should be placed in Schedule IV of the 1971 Convention. The critical problem in connection with these substances in the developing countries and their imperative needs led the Group to reject the suggestion that formal scheduling recommendations of those drugs be considered by a subsequent WHO Review Group. The Group was of the opinion that it should continue to evaluate proposals to schedule, reschedule or deschedule benzodiazepines.

Therefore, the Group recommended that the following benzodiazepines be placed in Schedule IV of the Convention on Psychotropic Substances:

bromazepam, camazepam, clorazepate, chlordiazepoxide, clobazam, clonazepam, cloxazolam, estazolam, flunitrazepam, flurazepam, fludiazepam, lorazepam, medazepam, nordazepam, nimetazepam, nitrazepam, oxazepam, oxazolam, pinazepam, prazepam, temazepam, tetrazepam, triazolam.

The Group further recommended that WHO, at regular intervals, review the status of scheduling of these benzodiazepines (either to reschedule or to deschedule) and recognized that new derivatives of benzodiazepines may not share the pharmacological profile and dependence potential or therapeutic indications of currently marketed benzodiazepines such that these new compounds may not require scheduling.

11.2 Research, Information and Data Collection

The Group recommended that various types of clinical, laboratory and epidemiological research be encouraged:

1. Physical dependence testing in animals should be expanded to provide more information permitting comparison of drugs within the benzodiazepine class. Techniques which permit standardization of dosing in primary dependence studies based upon the production of a standardized level of drug effect should be used.
2. Future research in animals and humans should provide more comparative data about the reinforcing efficacy of different benzodiazepines. In these studies particular attention should be given to differences in rates of absorption, CNS penetration and duration of action as properties which may occur with reinforcing efficacy.
3. The animal research reviewed on oral or intragastric administration of benzodiazepines has been quite limited. Since the oral route is the most common route by which benzodiazepines are abused in humans, future research should be conducted to develop animal models involving oral and intragastric benzodiazepine administration.
4. Future research with both animals and humans should provide more basic experimental and epidemiological information on drug history and other population differences as potential determinants of benzodiazepine self-administration.
5. A balanced view of the abuse liability of psychoactive drugs must carefully consider their adverse consequences, e.g. memory deficits, sensory/motor impairment and other adverse changes in mood and behaviour. Animal and human research should determine the magnitude, prevalence and mechanism underlying such effects.
6. Prospective studies of patients given benzodiazepines should be conducted to determine the prevalence of the development of physical and psychological dependence under these therapeutic conditions.
7. The Group urgently requested that UNDND, possibly in cooperation with various international, intergovernmental and regional organizations, develop procedures to rapidly collect reliable data on the abuse of and illicit traffic in various psychoactive substances which WHO may wish to review, as well as the verification of the composition and identification of such substances.
8. The Group concluded that there is a pressing need for drug utilization data in view of their importance for the optimization of drug therapy and drug control. Therefore, a universally applicable and accepted procedure to collect drug consumption figures particularly in regard to psychotropic drugs, has to be established.

The Group recommended that methods and sources of such data collection should be standardized, insofar as possible, so that meaningful comparisons can be made between various countries, and drugs, to identify discrepancies and eventual problems.

Essential to the standardization of such surveys is the adoption of a uniform classification of drugs and of an international unit comparison system (e.g. the defined daily dose).

11.3 The Group recommended that data relevant to abuse and misuse as well as the social and public health consequences of controlled substances under review be collected in a standard fashion throughout member countries. Standard data are important for evaluating the effects of scheduling and to detect potential problems in the future. Examples of the type of data which could be collected include:

- i. Frequency of the drug discovered in seizures of illegal drugs (heroin, etc.)
- ii. Frequency of overdoses and drug dependency found in hospital/emergency room treated cases (a random sample in a given country could be checked).
- iii. Price of street samples compared to average price through retail licit channels.
- iv. Prescription practices:
 - a) Checking of a random sample of pharmacies to determine frequency of benzodiazepine prescriptions;
 - b) Amount of benzodiazepines prescribed in each prescription;
 - c) Duration of prescriptions (number of refills, weeks of therapy).

11.4 The Group also recommended that WHO should initiate certain other activities. The Group extensively discussed the overprescribing and inappropriate prescribing of benzodiazepines. The Group agreed that this topic was of major concern especially in the developing countries. It was concluded that overprescribing and inappropriate prescribing were difficult to define and assess since physician judgment was involved. For this reason, the Group recommends that WHO addresses the concerns relating to overprescribing and inappropriate prescribing by developing a physician educational programme that provides accurate and up to date information on the disease entities appropriately treated with benzodiazepines and the rational use of benzodiazepines for such diseases. Further, it was hoped that WHO could obtain the cooperation and participation of the manufacturers of benzodiazepines in this endeavour.

11.5 Concern was expressed that the scheduling of the benzodiazepines under the Convention on Psychotropic Substances may inadvertently have a negative impact on public health by influencing price and availability of benzodiazepines for legitimate medical use. Therefore, the Group recommended that WHO organize a programme to evaluate systematically these consequences of scheduling the benzodiazepines, especially in developing countries.

11.6 The Group discussed the role of the drug manufacturers in the review process of WHO. Despite the concerns that biased information might be received and inappropriate influences exerted, the Group concluded that, on the whole, the drug manufacturers had provided information useful to their deliberations. In many instances, this information was unobtainable from other sources. Therefore, the Group recommended that WHO continue to solicit information from drug manufacturers. This information, however, should only be provided upon the specific request of WHO. Meetings with the representatives of the drug manufacturers should involve the entire Group and should occur only at the specific request of WHO. To facilitate the acquisition of information from the drug manufacturers, the Group suggested that WHO explore the establishment of a liaison with international associations of drug manufacturers.

12. List of Participants

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Dr Inayat Khan, Senior Medical Officer, Division of Mental Health, WHO, Geneva,
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Observer

Dr C. O'Brien, Department of Psychiatry, University of Pennsylvania, Philadelphia.
(Member, Executive Committee, Committee on Problems of Drug Dependence, USA).

13. List of Background Documents Available to the Group

1. MNH/R5/81.1 - A Review of Benzodiazepines Dependence Studies in Animal and Man:
A background paper by Roland R. Griffiths, Nancy A. Ator and
Scott E. Lukas.
2. MNH/R5/81.2 - Evidence of the Inappropriate Prescription of Benzodiazepines
by Elina Hemminki.
3. MNH/R5/81.3 - Brief Summary of the Pharmacology of 1,4 Benzodiazepines
by J. Knoll.
4. MNH/R5/81.3 - Therapeutic Indications for Use of Benzodiazepines
by Malcolm Lader

*Invited but unable to attend

5. MNH/R5/81.5 - Benzodiazepines Dependence
by Malcolm Lader
(based on a paper given at CINP Symposium, Hong Kong, October 1981)
6. MNH/R5/81.6 - Benzodiazepines Availability and Uses in Nigeria
by O.O. Olayemi and O.O. Ogunremi
7. MNH/R5/81.7 - Tranquilizer Abuse - Results of a Nationwide Swiss Survey
by D. Ladewig, W. Bänziger and M. Löwenheck
8. MNH/R5/81.8 - Public Health and Social Problems Associated with the Use of
Benzodiazepines - Reports from Countries
by Inayat Khan.
9. MNH/R5/81.9 - Assessing the Impact on Public Health, Individual Deficit on
Organ System Damage Associated with use of Diazepam and Flurazepam
by C.R. Schuster and Jack Bergman
10. MNH/R5/81.10 - A comparison of the Dependence Potentials of Various Benzodiazepines
Assessed in Rhesus Monkeys
by Tomoji Yanagita.
11. MNH/R5/81.11 - Comparison of Some Pharmacological Characteristics of Various
Benzodiazepines
by Tomoji Yanagita.
12. MNH/R5/81.12 - Benzodiazepines in Pakistan
by K. Zaki Hasan.
13. MNH/R5/81.13 - Public Health and Social Problems - Data for South East Asia/Pacific
by V. Navaratnam.
14. MNH/R5/81.14 - Summary of Studies with Alprazolam
by J. Knoll.
15. MNH/R5/81.15 - Summary of Studies with Triazolam
by J. Knoll.
16. MNH/R5/81.16 - Drug Utilization Studies in the Nordic Countries: Benzodiazepines
by Juhana Idänpään-Heikkilä.
17. Assessment of Benzodiazepines for International Control -
F. Hoffmann-La Roche & Co.
18. Report from Interpol for the 5th Review of Psychoactive Substances for International
Control.

19. Nitrazepam -
F. Hoffmann-La Roche & Co.
20. Restoril (temazepam) -
Sandoz documentation submitted to the Food and Drug Administration on 10 November 1978 and subsequently presented at the Drug Abuse Advisory Committee meeting of 18 December 1978.
21. Clobazam -
Hoechst Aktiengesellschaft.
22. Assessment of Benzodiazepines for International Control -
F. Hoffmann-La Roche & Co.
23. Single Convention of Narcotic Drugs, 1961
24. Convention on Psychotropic Substances, 1971
25. Assessment of Public Health and Social Problems Associated with the Use of Psychotropic Drugs (TRS 656)
26. Report of the 3rd WHO Travelling Seminar in the USSR on the "Safe Use of Psychotropic and Narcotic Substances", Moscow and Tashkent, 5-17 October 1981 (MNH/81.34)
27. Prevalence and Patterns of Use of Psychotherapeutic Drugs: Results from a 1979 National Survey of American Adults
by Glen D. Mellinger and Mitchell B. Balter
28. Benzodiazepine Trafficking
by Drug Enforcement Administration, Office of Compliance and Regulatory Affairs, Washington D.C. (USA)
29. Report of the 4th Review of Psychoactive Substances for International Control. (MNH/81.26)
30. WHO Features No. 71, July 1981 - Drugs and Driving.
31. Drugs and their Available Pharmaceutical Dosage Forms.
32. Information Relative to Dependency Potential of Lorazepam as Contained in NDA No. 17-94
Wyeth Laboratories
33. Tranxene (Chlorazepate)
Abbott Laboratories
34. The Benzodiazepines, Evaluation of Abuse Liability - Volumes I-VIII
F. Hoffmann-La Roche Laboratories
(covers chlordiazepoxide, diazepam, clorazepam, flurazepam, nitrazepam)

35. Alprazolam - Summary of Dependence Liability Studies
36. Halazepam - Schering Laboratories
37. Centrax - Prazepam
Parke-Davis Laboratories
38. Therapeutic Monograph - Sedative Drugs
Canadian Authorities
39. Benzodiazepines -
Department of Health and Human Services, U.S. Government, 1981
40. Report on the Use and Misuse of Benzodiazepines in Argentina
by Dr G. Fernandez, 1981.
41. DND 421/12(1) WHO - Report compiled by the United Nations Division of Narcotic
Drugs for use at the WHO Meeting for the Review of Benzodiazepines,
16-20 November 1981. (Addendum)

3. Corporation

CNS Disease Research,
The Upjohn Company, Kalamazoo, Michigan, USA.

and

The Upjohn Company
Rue de Genève, Brussels
Belgium.

Products

Triazolam and alprazolam

Representatives

Robert N. Straw, Research Head, Medical, (Kalamazoo),
Philip C. Carra, Corporate Affairs Consultant, (Brussels).

4. Corporation

Abbott Laboratories, North Chicago, Illinois, USA.

Product

clorazepate

Representative

Michael J. Foley, Director of United States Regulatory Operations.

5. Corporation

Sanofi Recherches, Avenue Pierre 1^{er} de Service, Paris, France.

Product

clorazepate

Representatives

Dr Michele Bousquet
Dr Jean-Pierre Lombard

6. Corporation

Wyeth International Ltd,
Philadelphia, USA.

and

American Home Products Corporation
New York, USA.

Products

Oxazepam, lorazepam and temazepam.

Representatives

Thomas Christie, M.D., Vice President (Philadelphia)
John H. Wood, Senior Attorney (New York)
David Richards, M.D., Director, Special Projects (Philadelphia)

7. Corporation

Sandoz Pharmaceutical Company, East Hanover, New Jersey, USA.

Product

Temazepam

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