IMPACT OF SCHEDULING DRUGS UNDER THE 1971 CONVENTION ON PSYCHOTROPIC SUBSTANCES – THE BENZODIAZEPINES REAPPRAISED*

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MINDEN, PENANG
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* A study funded by the United Nations Fund for Drug Abuse Control

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edited by:
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1. PREFACE

Concern over the abuse of psychoactive substances, particularly amphetamines and barbiturates, emerged early in the 50's. In an attempt to bring about unified action for the control of these psychoactive substances a special international control instrument – the 1971 Convention on Psychotropic Substances – was introduced. *The major aims of the Psychotropic Convention* are to control the production, marketing (sale on prescription only), exportation and importation of psychotropic substances which have dependence producing liability.

The criteria for the inclusion of a psychoactive substance in the 1971 Convention is contained in Article 2, Section 4 and 5, of the said Convention which also clearly identifies the responsible organs to undertake the evaluative functions. The article mentioned above require that:-

"If the World Health Organisation finds:

a. That the substance has the capacity to produce

   i. (1) A state of dependence, and
      (2) Central nervous system stimulation or depression, resulting in hallucination or disturbances in motor function or thinking or behaviour or perception or mood, or

   ii. Similar abuse and similar ill effects as a substance in Schedule I, II, III or IV and

b. That there is sufficient evidence that the substance is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control, the World Health Organisation shall communicate to the Commission an assessment of the substance, including the extent or likehood of abuse, the degree of seriousness of the public health and social problem and the degree of usefulness of the substance in medical therapy, together with recommendations on control measures, if any, that would be appropriate in the light of its assessment.

The Commission, taking into account the communication from the World Health Organisation, whose assessments shall be determinative as to medical and scientific matters and bearing in mind the economic social, legal, administrative and other factors it may consider relevant, may add the substance to Schedule, I, II, III or IV. The Commission may seek further information from the World Health Organisation or from other appropriate sources".

During the meeting of the Seventh Special Session of the United Nations Commission on Narcotic Drugs held in Vienna from 2-8 February 1982, the Commission adopted a Resolution 2(S-VII) on Procedure to be followed by the Commission on Narcotic Drugs in matters of scheduling of narcotic drugs and psychotropic substances. The Resolution apart from identifying the types of information that should be considered by the World Health Organisation also requested Member State for "information on the economic, social, legal and administrative factors related to the abuse of substances being considered for possible scheduling, and to supply as complete data as possible on any illicit trafficking in the substances in question".

Subsequent to the meeting of the Commission, interested Member States, scientists and the Secretariat of the Commission held extensive discussions to address the request of the Commission. It was noted that the National Drug Research Centre, University of Science of Malaysia, a designated United Nations/World Health Organisation Research and Training Centre in Drug Control, was already undertaking an UNFDAC supported study on similar lines. Hence it was considered that the centre should expand the existing study and undertake appropriate analysis in collaboration with UNDND and prepare a report on its findings.

Based on the discussions, a questionnaire was developed by a panel of researchers and circulated to selected scientists for comments, and based on the suggestions a final questionnaire was prepared. It was originally envisaged that the questionnaire would be circulated to all Member States by the UNDND; however, due to technical and administrative difficulties, it was decided to reduce the "additional" data gathering activity to a sample of fifteen anglophone countries. This study shall be called throughout this report the IMPACT – study because one of its objectives was to gather data on the IMPACT of scheduling substances under the 1971 Convention.

Data gathered by the United Nations, through the normal procedure of Annual Reports etc. was also available to the researchers who undertook extensive analysis. Concurrently with this data gathering/analysis activity, a literature survey of published report etc. was undertaken.

Initially, the objective of this report was to limit the review only to the economic, social, legal and administrative factors related to the abuse and illicit traffic as well as to assess the impact of scheduling substances

under the 1971 Convention. However, early in the project, it became very apparent to the research team that data on the diverse elements of required information exist in different isolated packets. In order to provide a comprehensive picture it was decided that this Report should present an analysis of the current understanding (knowledge) on all elements of information requested in the 1971 Convention. Hence it is essential that this Report is considered as being complementary and supplementary to WHO and other reports.

Further, since the Commission decided to consider the benzodiazepine group of substances for possible scheduling in 1983, this group of substances have been chosen for our review. The methodology developed in this project, obviously could be and should be applied for all future substances considered for scheduling.

The report presented here has assembled and analyzed data from various sources including information from the IMPACT – study, and reviewed the literature in order to address the following issues with regard to the benzodiazepines:

i. The pharmacology, toxicity and therapeutic use;

ii. Overuse, abuse potential and the extent of abuse and their consequence, social and public problems, as well as illicit drug traffic. Existing data, as well as new data are critically examined in relation to the general problem of drug abuse to ascertain the real extent to which it causes social and public health problem;

iii. The extent to which national legislation can effectively address the problems of benzodiazepine abuse and the effectiveness and usefulness of international control in addressing these same problems;

iv. The economic, social, legal and administrative aspects as well as the impact of controlling the benzodiazepines internationally was assessed.

2. BENZODIAZEPINES – WHAT ARE THEY?

HISTORY

The first members of the family of the 4,5-benzo(hept)-1,2,6-oxidiazines were synthesised by Sternbach in Poland in 1933. In 1955, this group of compounds were taken up at the Hoffmann La Roche Laboratories in Nutley, N.J., by Sternbach. These research efforts led to the discovery and development of Chlordiazepoxide (Librium) as the first of a group of clinically useful and pharmacologically unique anxiolytic agents (Sternbach, 1973). Since then thousands of benzodiazepine compounds have been synthesized and tested pharmacologically and many have been used clinically.

CHEMISTRY

The 1,4-benzodiazepines all have the following basic structure: R_1 is usually an electron-withdrawing

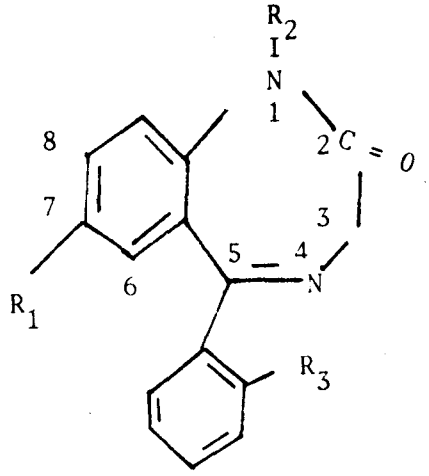


FIGURE 1

substitutent, R_2 is usually an alkyl group (or hydrogen). All important CNS-depressant benzodiazepines contain a 5-aryl or a 5-cyclohexyl group. Other than that, the structure-activity relationship is not stringent. Electron-withdrawing substituents at position 7 enhance and electron-releasing as well as large substituent groups suppress pharmacological activity. Substitution with a 7-nitro group enhances anticonvulsant activity. Substitution at position R_3 with electron-withdrawing groups enhances potency (Harvey, 1980).

With the exception of chlordiazepoxide hydrochloride and flurazepam hydrochloride which are salts and thus exhibit good solubility in water, most of the other benzodiazepines are usually present as free bases and are thus poorly soluble in water but easily soluble in methanol and chloroform. Solutions of benzodiazepines in methanol and absolute ethanol are very stable. However aqueous solutions decompose under acid and alkali conditions (Clifford, 1974).

BASIC PHARMACOLOGY AND MECHANISM OF ACTION

It is usually assumed that the benzodiazepines as a class of drugs all exert the same qualitative actions and possess the same mechanisms of action, even though there are quantitative differences in their pharmacodynamic activity. Clinically, however, diazepam, chlordiazepoxide, oxazepam are used as anxiolytics as well as sedative/hynotics whereas other cogeners like flurazepam and nitrazepam are used principally as sedative/hypnotics.

The most characteristic and specific action of the benzodiazepines is the disinhibition or the normalization of behavioural responses suppressed previously by punishment or by absence of reward. This is clearly exhibited in experimental conflict situations where behavioural responses inhibited by punishment reappear after the administration of benzodiazepines. Such conflict experiments are used in the screening of anxiolytics.

The benzodiazepines also increase behaviour responses in non-reward situations. Whereas the release of behavioural responses suppressed by punishment is considered due to a reduction of fear, the increase in non-rewarded behaviour indicates an anti-frustration activity. The benzodiazepines also increase exploratory activity and this is thought to be due to the reduction in the fear of novelty.

This specific activity is usually not exhibited by other groups of psychotropic drugs, with minor exceptions e.g. alcohol, barbiturates, meprobamate, valproate etc. However, the latter drugs exhibit a very narrow range of dissociation between anticonflict and unspecific "sedative" effects.

Anti-aggressive activity of the benzodiazepines has been demonstrated in spontaneously aggressive monkeys and wild animals, in mice made aggressive by isolation or by foot shock, and in affective defensive behaviour induced by brain stimulation in cats, monkeys and rats. However, the benzodiazepines did not affect muricidal activity and brain lesion induced aggressiveness, in fact, they even enhanced aggressive activity in grouped male mice (Knoll et. al., 1980).

Benzodiazepines produce various effects which are categorised clinically as "sedative" effects but in experimental pharmacology are termed "reduced arousal". This effect is manifested clinically as an increase in amount of sleep, reduction of sleep latency, decrease in wakefulness and restlessness during sleeping, thereby increasing sleep comfort.

The benzodiazepines are quite potent in blocking convulsions and epileptiform EEG activity induced by chemical agents like pentylenetetrazol, pictrotoxin, bicuculline and 3 mercaptopropionic acid. Strychnine and electroshock induced seizures are suppressed at somewhat higher doses. The mode of action by which this effect is attained is via the prevention of the subcortical spread of the seizure activity. The benzodiazepines do not abolish or arrest the discharge of the seizure focus. They also block seizures occuring during ethanol or barbiturate withdrawal and also photic seizures in baboons. Recently, it has been reported that the benzodiazepines are effective for controlling seizures induced by pyrogens. Flunitrazepam, tirazolam, clonazepam, nitrazepam and bromazepam are pronounced in their anticonvulsant effects as compared to the other benzodiazepine derivatives. In man diazepam is especially useful in controlling status epilepticus.

The benzodiazepines produce muscle-relaxant effects in experimental animals as well as in intact animals i.e. with normal muscle tone. The muscle-relaxant effect appears at doses which are far below those needed for an overt CNS depression. However, this seems in general not to be the case in man. Although the benzodiazepines in therapeutic doses do not exhibit a direct action on peripheral autonomic functions, they reduce the autonomic responses to direct electrical stimulation of the hypothalamus and other brain structures, and autonomic reflexes induced by peripheral stimuli. This is the rationale for the use of the benzodiazepines in various psychosomatic, cardiovascular, gastrointestinal, urogenital and endocrinological disorders. Benzodiazepines enhance primary afferent depolarization subserving presynaptic inhibition and reduce gamma-motoneurone activity and mono – and polysynaptic reflexes in the spinal cord. They depress the spontaneous and evoked neuronal activity in various brain areas. In high intravenous doses, the benzodiazepines produce anterograde amnesia (Haefely, 1980; Haefely, et. al., 1981; Knoll, 1980; Harvey, 1980).

The mechanism of action of the benzodiazepines is postulated to be in some way related to the action of GABA (Haefely et. al., 1981). In 1977, Squires and Braestrup and Mohler and Okada initiated binding studies which led the way for research on benzodiazepine receptors. They discovered that ^{3}H-diazepam was specifically bound to a protein in crude rat brain membranes. These benzodiazepine receptors were not found outside the Central Nervous System. The presently accepted hypothesis on the relationship between GABA and benzodiazepine receptors is that the GABA receptor-chloride ionophore complexes contain in addition receptor sites for benzodiazepines (and also for picrotoxin and barbiturates). Evidence indicates that all benzodiazepine receptor sites are associated with GABA receptor-chloride ionophore complexes but the latter may exist in a form independent of the benzodiazepine receptor. The suggestion that these GABA receptor-chloride ionophore complexes also contain picrotoxin/barbiturate recognition sites is borne out by picrotoxin binding studies and by the fact that barbiturates enhance both GABA and benzodiazepine binding to their receptor sites. Present emphasis of research is focussed on the search for a freely diffusable extracellular endogenous ligand. At present, inosine, hypoxanthine, nicotinamide, thromboxane H_2 and betacarboline esters have been implicated as putative endogenous ligands (Knoll, 1981).

The benzodiazepine receptors are unevenly distributed in the brain regions. The cerebral and cerebellar cortical areas as well as the limbic areas have higher densities of benzodiazepine receptors, while other areas have lower levels (Squires and Braestrup, 1977; Mohler and Okada, 1977; Speth et. al., 1978). The regional variations in receptor density is species dependent in some instances.

Current evidence points to the fact that the sensivity of the receptors may be increased by various chemical agents, especially GABA and its agonists. Also the number of binding sites may be altered after seizures by pretreatment by chemical agents like diphenylhydantoin (Tallman, J.F. 1980). An interesting observation made during these binding studies is that complete occupancy of these binding sites is not necessary to protect against seizure activity.

PHARMACOKINETICS

As a class the benzodiazepines are rapidly and almost completely absorbed from the gastro-intestinal tract,

reaching peak blood concentration shortly after administration (Kaplan, 1980). For example, diazepam, one of the most rapidly absorbed compounds, reaches peak blood concentrations within one hour. The extent of protein binding in the plasma varies with the compound concerned. Generally, it falls within the range of 85-95%. An exception is flurazepam, which is minimally protein bound. The plasma concentration kinetic patterns of the benzodiazepines are consistent with the two/three compartment open pharmacokinetic model, the three compartment model being more appropriate for more lipid soluble derivatives. Enterohepatic circulation may cause a secondary surge in plasma concentration hours after drug administration (Harvey, 1980). Most biotransformation occurs in the liver and excretion is mainly in the form of conjugated glucuronides. Many pharmacologically active metabolites may be formed as a result of biotransformation on the 1,4-diazepine ring. For example, diazepam has three principal active metabolites, namely N-desmethyldiazepam, oxazepam and temazepam.

BENZODIAZEPINE ANTAGONISTS

While working on a series of imidazodiazepines, potent inhibitors of benzodiazepines were discovered recently in the Roche laboratories. From a large group of these compounds, the compound Ro 15-1788 has been selected and tested clinically. This antagonist inhibits the specific binding of ^{3}H-diazepam to the receptors and antagonises, antipunishment, anticonvulsant, muscle-relaxant and the polysynaptic depressant effects of benzodiazepines. The antagonistic activity is specific for benzodiazepine effects mediated by the central benzodiazepine receptor. The structure of the antagonist, Ro 15-1788 is as shown in Figure 2 (Hunkeler et. al., 1981).

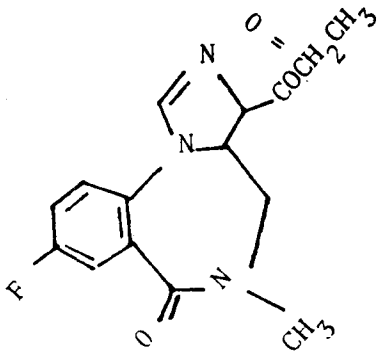


FIGURE 2: Structure of Benzodiazepine Antagonist, Ro 15-1788

TOXICITY

The commonly observed side effects include drowsiness, confusion, ataxia, excitement, vertigo, transient hypotension, gastrointestinal distress and skin rashes (Bellantuono et. al., 1980).

The major side effect is sedation. However, tolerance or adaptation occurs and the initial drowsiness if experienced, usually abates over time with repeated administration. Serious intoxication and death due to the ingestion of benzodiazepines alone are extremely rare. Serious sequelae of sucidal attempt or death usually occur in association with concomitant intake of alcohol/other drugs. Most authors are of the opinion that the benzodiazepines are very safe drugs and death as a consequence to benzodiazepines alone is almost impossible.

THERAPEUTIC USE

By the introduction of the first benzodiazepine (chlordiazepoxide) in 1960 a major change in therapeutic practice was initiated. Four main actions characterise this class of drugs:

- anxiolytic
- muscle-relaxant
- antiepileptic
- sedative-hypnotic

These four action components are present in all benzodiazepines so far on the market; however they may differ from each other in the relative strength of the four components. Research is still on going to find benzodiazepines that have a more selective action e.g. anxiolytic without the sedative-hypnotic component. Since the* discovery of antagonists and – more important from this point – of partial antagonists this hope does not seem totally unrealistic.

The main indication at introduction was *anxiolysis,* and this has remained a major indication for these drugs, as anxiety is widespread in most of modern societies. Anxiety neurosis is a wide field, and many patients who have difficulties of coping with their life problems because they are anxious benefit from this sort of medication. This was demonstrated by a great number of studies again and again, many of which were well controlled and fulfilled the criteria of the most stringent regulatory authorities. In this field the benzodiazepines are considered a major innovation, not only because they were better anxiolytics than the then widely used barbiturates but also because they are much less toxic and by that fact curbed the number of barbiturate intoxications often lethal. It was soon discovered that anxiety present in somatic and psychosomatic conditions responded well to these anxiolytics; this widened the field of indication to a great extent. Finally the anxiolytic action of benzodiazepines made them a useful adjunct in the treatment of depression when anxiety was a prominent feature of it. Though strictly controlled clinical trials over long periods (a year or longer) are not available, there is good clinical evidence that anxiety can be relieved for long periods (years) by the benzodiazepines. This evidence is based on the reappearance of anxiety after withdrawal of treatment for long periods (Rickels, 1982). It has to be stressed that benzodiazepines should be reserved for the treatment of pathological anxiety; they are not indicated to cope better with everyday stress. The question to what extent overprescription and overuse in this respect have been practiced will be treated in a later chapter.

The muscle relaxing action of benzodiazepines was only discovered in the second preparation on the market, diazepam, as it showed this property in a more pronounced way than chlordiazepoxide. It has found a wide field of indication, quantitatively the most important being muscle spasms accompanying rheumatic disease in the wider sense of the word. Clinically of little importance is the relief from muscle tension in decerebrate rigidity, impressive as the demonstration of this may be in experimental animals. However in tetanus which leads to reflex muscle spasm, the muscle relaxing activity of benzodiazepines can be *life saving.* Before the advent of the benzodiazepines a few cases of severe tetanus could be saved by curarization and artificial respiration of the patient for weeks, a procedure that needs all the facilities of a modern, well equipped intensive care unit with a large staff of highly skilled personnel. This method is available in industrialized countries only in highly sophisticated hospitals and rarely at the disposal of patients in developing countries. All the more important for them is treatment by benzodiazepines, especially because tetanus of the new born is not infrequent in developing countries.

The *antiepileptic activity* of the benzodiazepines was known from the experimental screening since the development of chlordiazepoxide, the first benzodiazepines introduced into therapy. This activity is still used as a screening procedure for new products. However the great hopes set into the benzodiazepines for the treatment of the average epileptic patient have not been fulfilled. Some preparations with experimentally pronounced antiepileptic medication already known and used, but none of the benzodiazepines was able to replace the former antiepileptics (phenobarbitone, hydantoins etc.) to any relevant extent. Furthermore there is some evidence that the antiepileptic efficiency of benzodiazepines diminishes in the course of weeks or months in many cases, in contrast to what has been experienced with the anxiolytic action of these drugs. This is all the more disappointing as epileptics are for the most part in need of life long treatment. However there is one epileptic condition in which benzodiazepines have brought on a major advantage. This is *status epilepticus,* life-threatening, a condition seen e.g. in acute cerebral trauma, in severe meningitis (with encephalitis), in malaria, and in chloroquine and cocaine intoxication. 20 years ago treatment of status epilepticus was a cauchemar for the clinician because no reliably efficient medication was available. Since about 15 years intravenous diazepam has become the treatment of choice since by this measure status epilepticus can be stopped in almost every case. It is then a *life saving* drug. Malaria and chloroquine intoxication (mostly voluntary with the objective of abortion) are frequent in developing countries. There this life saving antiepileptic activity is of special importance. In an African study mortality of chloroquine intoxications has been reduced from 35% to 5% by the introduction of intravenous diazepam in status epilepticus.

The sedative *hypnotic action* of the benzodiazepines has led to the introduction of a series of substances of that class as hypnotic drugs. They have soon replaced former hypnotic drugs like barbiturates to a large extent in the prescription practice and thereby also in the market. One major advantage over the barbiturates is the high safety margin of the benzodiazepines. Voluntary or accidental intoxication by benzodiazepines is almost never lethal, in contrast to the barbiturates. There is also a definitely smaller dependence producing potential of benzodiazepines as compared to the barbiturates in experimental studies (Yanagita, 1973). However, the decisive factor in the acceptance of benzodiazepine hypnotics may have been, that the sleep induced by them is of better quality, nearer to natural sleep, than the sleep brought on by barbiturates, as can be judged from clinical as well as from electro-physiological data (e.g. lesser disturbance of REM sleep).

The sedative and sleep-inducing properties of benzodiazepines have been taken advantage of by anaesthesiologists. Several of these hypnotics (including diazepam) have found large application as premedication and as induction agents for narcosis. As they produce amnesia without putting the patient in deep narcosis they are used extensively in diagnostic procedures, in minor surgery and in dentistry, in hospital as well as in ambulatory practice. The advantages of benzodiazepines in the anaesthetic problems of developing countries have been stressed by several authors (Aderoju, Nigeria, 1978, Yanov and Kujan, Ethiopia, 1981).

It may be fit at this point to mention two clinical studies that relate to *social issues* of the therapeutic use of benzodiazepines. The usual objective of clinical investigations is to determine efficacy and side effects. These studies go further and investigate social effects of diazepam, the aim of a psychotherapeutic action being not only relief of the patient but also his integration in his surroundings. The WHO Expert Committee on drug dependence has stated that true drug abuse characteristically gives rise to adverse social effects not only on the individual abusing the drug but also on the abuser's immediate social surrounding, family, friends, work situation and society as a whole. Proctor, (1981) compared the effects on work place parameters of psychoactive versus non-psychoactive medication with special emphasis to diazepam. He found that diazepam is not associated with any difference in performance or in accident or absentee rate above that observed in patients taking *any* other type of medication. The results from this study showed no negative effects in the work place associated with diazepam use. Whybrow, Matlins and Greenberg investigated the social impact of psychoactive drugs in a survey of the perceptions of prescribing and non-prescribing health practitioners. Three categories of drugs had a beneficial effect on anti-social behaviour.

major tranquillizers
anti-depressants
minor tranquillizers

Practitioners singled out minor tranquillizers for being most effective in ameliorating behaviour disruptive of family life, verbal and physical abuse of family members, and neglect of family. Practitioners identified minor tranquillizers as the drug they most often prescribed or saw prescribed in order to reduce dependence on alcohol (by easing the symptoms of withdrawal). While the above three drug categories were judged in over 90% to contribute to improved quality of life, stimulants, barbiturates and alcohol in the majority of cases did not improve quality of life.

Starting from these data the Institute for Social Research of Michigan University has started an extensive study on the effects of benzodiazepines in the social context. Preliminary results show a conservative use of benzodiazepines by prescribing physicians and by patients and a beneficial effect on factors decisive in quality of life.

DEPENDENCE

In studies of drug abuse and dependence, two distinct types of dependence can be distinguished, i.e. physiological (physical) dependence and psychological dependence. *Physiological* dependence manifests itself by the fact that on discontinuation of drug treatment a time limited withdrawal reaction follows; this however is prevented by continued drug treatment. *Psychological* dependence is manifested by a tendency of a subject to repeatedly seek and self-administer a drug (Woods et. al., 1982).

Experimental studies of dependence usually involve laboratory animals (usually rats, monkeys, baboons) as well as observation on humans through clinical case studies or controlled trials.

PHYSIOLOGICAL DEPENDENCE

Experimental animal studies on physiological dependence are of two major types, i.e. primary dependence studies and cross dependence studies.

In *primary dependence studies,* the test drug is repeatedly administered for a period of time and then suddenly discontinued. The withdrawal signs, if any, are then observed and recorded. Studies of this nature have been widely performed using various benzodiazepines.

In *cross dependence studies,* dependence is developed to some prototype compound of known dependence capacity and the capacity of the test drug to prevent or reverse withdrawal from the prototype compound is examined. The assumption is made that a drug that completely reverses the withdrawal symptoms of a prototype compound will produce a similar type of dependence when repeatedly administered. This assumption holds true with the narcotic group of drugs but with regards to sedative-hypnotic compounds it has not been fully validated. For the benzodiazepines, the prototype compound is usually barbital or phenobarbitone. Cross dependence studies in rodents as well as monkeys indicate that all of the benzodiazepines examined so far suppress barbital withdrawal similarly and only differ in their potency (Yanagita, 1981).

In regard to *benzodiazepines,* comparison of data is made difficult by the fact that varying dose levels have been used and the dosing regimens used vary with respect to the frequency of administration, the duration of administration and whether the dose is kept constant throughout the duration or whether the dose is increased in some specified manner. In addition, the doses used are usually many times higher than normal therapeutic doses. In spite of this, most studies are equivocal whether physiological dependence can develop in experimental animals. A study by Boisse et. al., (1981) has shown that the physiological dependence phenomenon is dependent on the dose level as well as the duration of administration using chlordiazepoxide in rats. A comparison of the

dependence producing effect of chlordiazepoxide and phenobarbital using the chronically equivalent dosing technique Boisse et. al., (1981) as well as Martin et. al., (1982) have found that the withdrawal symptoms observed are qualitatively different. There is no compelling evidence to date to demonstrate any difference in the dependence producing effect of the various benzodiazepine agents (Woods et. al., 1982). The newly developed benzodiazepine antagonist Ro 15-1788 has been used successfully to precipitate withdrawal in benzodiazepine dependent animals (Lucas and Griffiths, 1982b, c,; Rosenberg and Chiu, 1982 and McNicholas and Martin, 1982).

In humans, case reports and controlled studies provide evidence that physiological dependence can develop, especially at higher daily dose levels and with longer duration of drug treatment (Rickels, 1980). Some evidence is also available for the development of physiological dependence in patients on benzodiazepine therapy using therapeutic doses, although the incidence of this is small (Woods, 1982).

PSYCHOLOGICAL DEPENDENCE

Experimental studies on psychological dependence using animals involve the self-administration technique using oral, intragastric and intravenous routes of administration. In summarizing available studies using oral benzodiazepine intake *Woods* (1982) concludes that none of them has shown a substantial preference of drug solution over vehicle solution. In studies involving the intravenous or intragastric self-administration of drug solutions, drug delivery is used as a reinforcer for a certain response performed by the animal, such as pressing a lever. Comparison with the rate of self-administration of the control vehicle provides a measure to evaluate the drug reinforcement activity. The procedures used for these self-administration studies may vary from a simple one response/one injection ration at any time to a more complicated program like a fixed ratio of ten responses to one injection schedule, limited to a certain duration of experimental session. The majority of experiments in which there is unlimited access to the drug solution has been performed on monkeys. Yanagita and Takahashi (1973), Yanagita et. al., (1975), Yanagita and Kiyohira (1976), Yanagita et. al., (1981), reported somewhat various degrees of reinforcing properties for diazepam, chlordiazepoxide, halazepam, fludiazepam, medazepam and other benzodiazepines. Gotestam (1973) using experimental rats provided some evidence of the reinforcing properties of medazepam. However, these findings are not universally accepted. Weawer (1975) and Altshuler and Philips (1978), using a model with intragastric administration, found that diazepam did not maintain self-administration. Hackett and Hall, (1977) found the same lack of maintained self-administration for intravenous diazepam. Many of these studies however suffer from various experimental limitations and make their interpretation difficult.

In experimental studies using more complex and intermittent self-administration schedules, diazepam (Griffiths et. al., 1981; Yanagita and Oinura, 1982), chlordiazepoxide (Findley et. al., 1982), clonazepam, flurazepam (Griffiths, et. al., 1981) have been shown to be able to maintain self-administration rates above that of the control vehicle, although only marginally in some cases.

Some of the studies performed compared response rates of benzodiazepines with those maintained by other drugs. As a class, the benzodiazepines were more efficacious reinforcers than chlopromazine, imipramine, haloperidol and perphenazine, but were less efficacious reinforcers than pentobarbital, alcohol, secobarbital, cocaine and codeine (Griffiths et. al., 1980). Thus the results of experimental studies in animals indicate that the benzodiazepines have reinforcing properties although generally less than other sedative hypnotic agents or alcohol.

Studies on the reinforcing properties of benzodiazepine in *humans* may take a variety of approaches. Generally, studies show that while the benzodiazepines can maintain self-administration their efficacy appears to depend on the type of population studied, among other procedural factors. Studies by Johnston and Ulenhuth (1980) using normal population and by De Witt et. al., (1982) using anxious subjects show no preference for diazepam over placebo. However, Fabre et. al., (1976) and Jick et. al., (1966) reported that insomniacs may prefer benzodiazepines over placebo which is understandable. Griffiths et. al., (1979, 1980) used pentobarbital and diazepam on human subjects at doses that produced equivalent subjective effects and reported that sedative-hypnotic abusers prefer pentobarbitone over diazepam while the high doses of diazepam were preferred over control vehicle. Higher doses of pentobarbital are associated with more regular self-administration as compared with high doses of diazepam. In a study by Krypsin – Exner (1975) it is suggested that subjects with a past history of hypnotic and narcotic abuse are more likely to self-administer higher levels of benzodiazepines than alcoholics. In another study, Rothstein (1976) expressed the opinion that benzodiazepine use in alcoholics is quite safe. Studies using subjects suffering from various psychotic and affective disorders (Winstead et. al., 1974; Balmer et. al., 1981; Hubbard and Kripki, 1976) suggest that benzodiazepines are self-administered at a low frequency when available on demand and the frequency tends to decline over time.

The results in general, would indicate that benzodiazepines at normal therapeutic level are not preferential reinforcers and the rates are lower than for many other sedative-hypnotics. Obviously at higher dose levels – above therapeutic levels the benzodiazepines do demonstrate a reinforcing property which is higher than the control vehicle. Current evidence from reinforcement studies do not allow one to distinguish between the different

benzodiazepines and even the suggestive evidence which is frequently quoted is contradictory.

Several factors have been considered in order to explain apparent differences in clinical observations of dependence.

Lipid solubility at physiological pH has been invoked on an a-priori-base assuming that higher lipid solubility might correspond to a higher dependence potential. However the values for lipid solubility as available are scattered over a rather wide range in an unsystematic way so that this value does not seem to be a major factor in producing dependence liability.

Pharmacokinetic factors may be more important. Half-life and speed of absorption may be factors influencing dependence liability. Griffiths et. al., (1981) and Griffiths and Lucas, (1982) have shown that benzodiazepines with short half-lives like midazolam and triazolam maintain higher rates of self-administration as compared with drug with longer elimination half-lives like diazepam, clonazepam, clorazepate, flurazepam and medazepam. Bliding (1974) found that diazepam, a more rapidly absorbed but longer half-life benzodiazepine, demonstrated greater subjective effects (including euphoria and dysphoria) than oxazepam, a less rapidly absorbed and shorter half-life benzodiazepine, but with chronic administration of diazepam, these subjective effect disappeared. On the basis of these results the authors concluded that the more rapidly absorbed benzodiazepines would tend to have greater dependence potential. Pharmacokinetic studies (Greenblatt and Shader, 1978) have shown that these subjective drug effects depend more on the rate of increase of blood concentrations than on the blood concentrations itself; this is in agreement with the report by Bliding (1974).

However these factors cannot be decisive because different countries have problems with different benzodiazepines.

While Thailand reports some abuse problems with diazepam and Singapore with flunitrazepam, Mauritus has no problem with diazepam but with lorazepam and Australia with oxazepam. A recent study from Switzerland by Ladewig (1981) shows an abuse prevalence which is in a very narrow range the same for the five most frequently prescribed benzodiazepines in this country, without correlation to half-life. The Ladewig study is reported more extensively in the Chapter on Abuse Liability.

One factor which emerges from these findings as most important is market penetration and probably (as a basis for this) prescribing habits of practicing physicians. At the same time these figures do not allow to differentiate between individual benzodiazepines as to their abuse potential. One could – on a-priori-basis again – assume, that relatively high dose recommendations might parallel a relatively higher dependence risk. However there is so far no evidence for such an assumption.

Data on seizures and street abuse indicate that benzodiazepines of long and short half-lives and of various degrees of lipid solubility are equally abused. Thus the pharmacological, pharmacokinetics and abuse data on the dependence potential of the benzodiazepines are inconsistent and often contradictory. On the basis of the current data available, it is not possible to arrive at any distinction as to the relative dependence potential of the individual benzodiazepines.

One fundamental basis of physiological dependence is the development of physical withdrawal symptoms on sudden cessation of drug administration. The mechanism of the development of withdrawal symptoms is practically unknown. Assuming the existence of endogenous benzodiazepine-receptor-ligands Kales et. al., (1978) have proposed a highly speculative hypothesis. The abrupt interruption of benzodiazepine administration causes a time-lag in production of endogenous benzodiazepine-receptor-ligands suppressed by the exogenously administered benzodiazepine; this time-lag would be responsible for the appearance of withdrawal symptoms. Based on this, drugs with plasma half-lives of 6-24 hours would tend to produce severe withdrawal symptoms; those drugs with plasma half-lives of 36 hours or more are likely to have a mild but longer withdrawal syndrome. Drugs with a very long half-life may not present any symptoms at all, whereas in drugs with ultrashort half-lives physical dependence is difficult, if not impossible to develop (Hollister, 1980).

THE 1,5 – BENZODIAZEPINES

In contrast to the other benzodiazepines, Clobazam (Frisium) is structurally different, being a 1,5-benzodiazepine with the nitrogen in 1,5-position of the diazepine ring rather than at the 1,4 position. Therapeutic trials indicate that the antianxiety effect of clobazam is comparable to diazepam. Clobazam is claimed to have minimal muscle-relaxant and hypnotic activity and to cause less objectively measurable sedation or psychomotor impairment than diazepam, chlordiazepoxide or lorazepam. Studies on epileptic patients have shown clobazam to be initially effective against all forms of epilepsy but it loses it efficacy within a few days or weeks in more than one-third of the patients.

Like the other benzodiazepines, clobazam is well absorbed orally, reaching peak blood levels 1-4 hours after oral administration. Clobazam undergoes dealkylation to form N-desmethylclobasam as its principal active

metabolite. In contrast to the 1,4-benzodiazepines, clobazam does not undergo hydroxylation at the 3-position of the diazepine ring but rather at the 4-position to form 4-hydroxyclobazam (Brogden, 1980).

Experience so far has shown that clobazam is not exempt from abuse liability similar to the 1,4-benzodiazepines.

3. BENZODIAZEPINES – SUBSTANCES OF OVERUSE?

Benzodiazepines have had an extraordinary success since their introduction some 20 years ago. Diazepam was for 10 years or so the most widely prescribed drug in the United States. Benzodiazepines as a class still are among the most widely used drugs the world over. This fact alone has drawn attention and provoked discussion. Are they overused?

This question proves to be difficult at a closer look. First exact consumption figures are not easy to get in many countries. In the United States and in Great Britain the possibility exists to check prescription frequency, but there is a gap in knowledge between these figures and consumption pattern. Some countries, mainly from the developing world, have import figures which should (roughly) parallel consumption. But worldwide drug consumption studies are not available for this class of drugs (nor for other classes).

Some figures, often quoted, may be recalled here. The U.S.-figures as presented e.g. by Hollister show a steady rise up to the early 70ies and then (since 1973) a steady fall, which has continued into the eighties. (Figure 3a).

In 1981 Blaha and Bruckmann presented figures for several European countries, stressing at the same time the difficulty of gathering reliable figures. With their reservations on the reliability of these figures they are reproduced here. Their figures have been drawn as a graph (Figure 3b). The figures can be found in the Annex Table 3(i).

A similar time course of the benzodiazepine consumption as in the U.S. has been found in Finland, the highest peak being reached in 1970 i.e. earlier than in the U.S., while in other European countries there is on the whole stabilization of consumption figures in the seventies. Czechoslovakia and Iceland which are still climbing, have the lowest and the highest absolute consumption among these countries.

Consumption figures for developing countries and Australia have been gathered in the course of the IMPACT study, tables are given in the Annex. (Table 3(ii)).

A comparison between *Indonesia* and *Malaysia* shows that absolute figures are roughly 100 times lower in Indonesia. Taking into account the population number they may be more than 1000 times lower per population head in Indonesia. Indonesia shows a rather stable consumption over the investigated 3 years, while in Malaysia there is a marked downward trend, the 1981 figures being at least 50% lower than the 1978 figures for the more important products.

Hong Kong's figures of consumption differs in their trend from one drug to another. The total consumption seems rather stable, probably with a slight upward trend since 1978. Taking into account the total population, Hong Kong's consumption is at least 10 times higher than Malaysia's (and by that about 10,000 times higher than Indonesia's). *Singapore* shows a definite diminution of benzodiazepine consumption from 1978 to 1981, the latter figures being about 50% of the former. In the *Philippines* there may be on the whole a slight upward trend of consumption. *Australia* shows a marked increase from 1967/7 to 1980/1, mainly due to the doubling of the consumption of oxazepam, which in this country is clearly the leading market product. Taking into account DDD the Australian consumption may be around 50 times higher than in Malaysia.

A comparison of consumption figures of Australia (Figure 3c) with those of Malaysia (Figure 3d) shows a sharp contrast. While the Australian total consumption figure is climbing the Malaysian figures are coming down, inspite of the fact that no overall special control for benzodiazepines has been instituted in Malaysia. This fall of consumption figures has to be attributed to an educational campaign for critical prescription practices among Malaysian prescribers.

This play with numbers raises more questions than it answers. It has a very limited value as we do not know to what segment of the population benzodiazepines are available. Thorough drug utilisation studies would be needed, along with epidemiological studies of morbidity prevalence and doctors' prescribing habits.

Based on these consumption figures alone and comparing them with those from U.S. and Europe there is no support for the hypothesis of overconsumption in these developing countries.

To answer the question whether there is overconsumption the fact that consumption figures are high is not a sufficient basis. These figures must be seen in relation with the number of people who are in need of the drug. This second field is still less explored than the consumption in absolute numbers. Prevalence of psychic disturbances, anxiety in particular, and the usual means of coping with them is known only in a very imprecise manner. Some epidemiological studies have been undertaken starting mainly from the U.S.

FIGURE 3a: Trend in Prescription for Antianxiety Drugs Adapted from Hollister

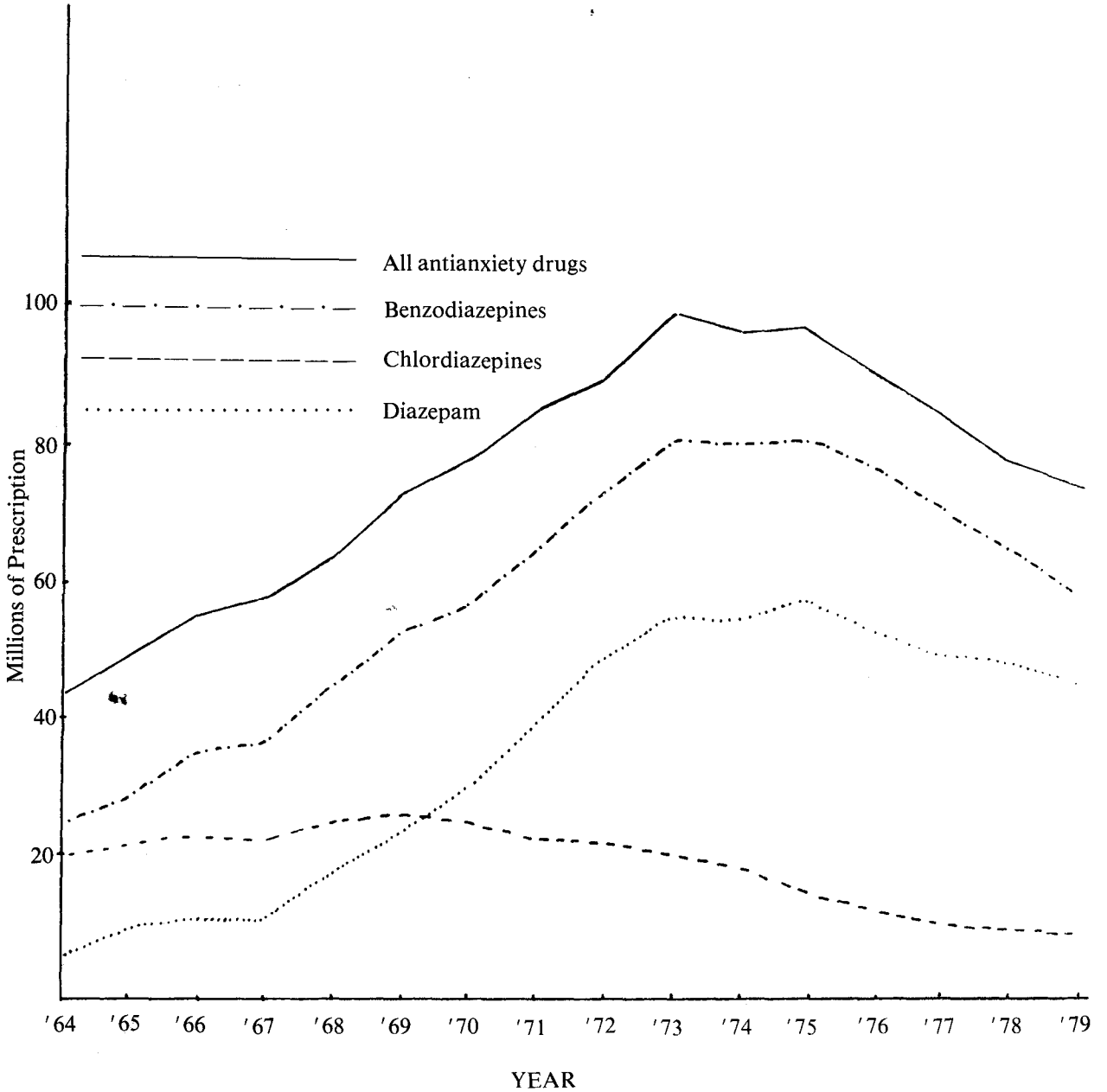


FIGURE 3b: Consumption of Benzodiazepines Anxiolytics (in DDD/1000 inhabitants/day)

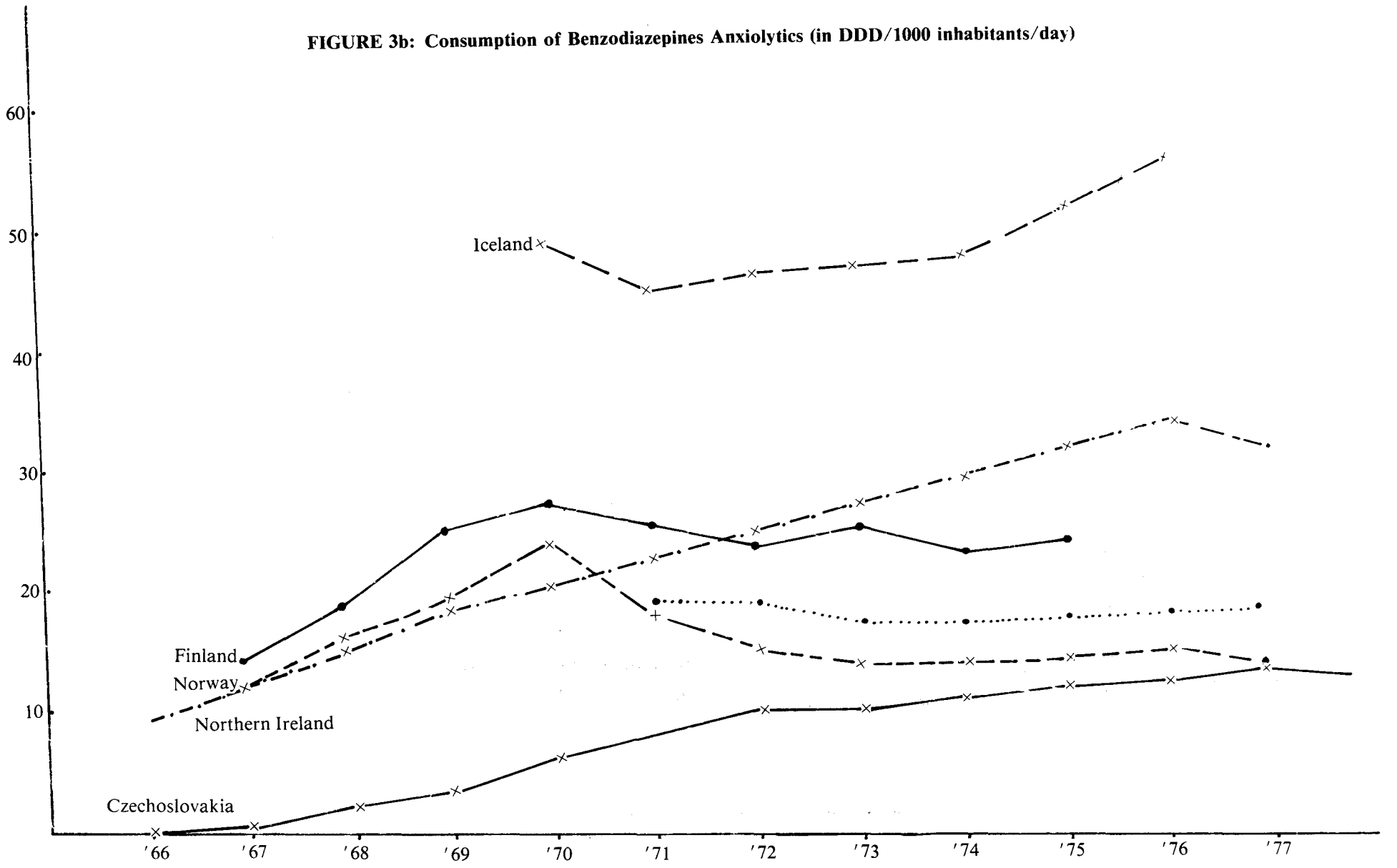


FIGURE 3c: Use of Benzodiazepines on the Pharmaceutical Benefits Scheme Expressed as DDD/1000/Day in Australia

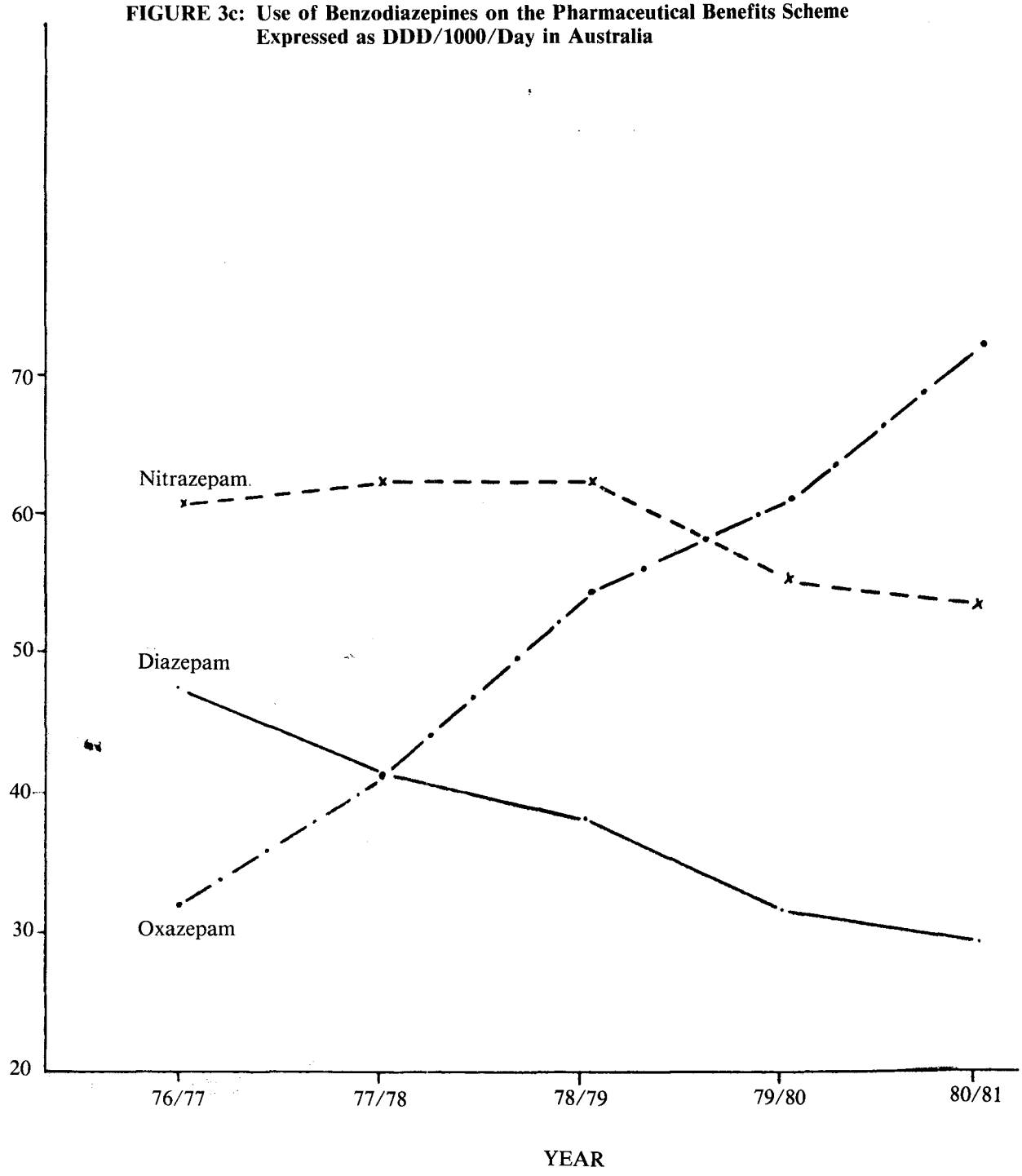
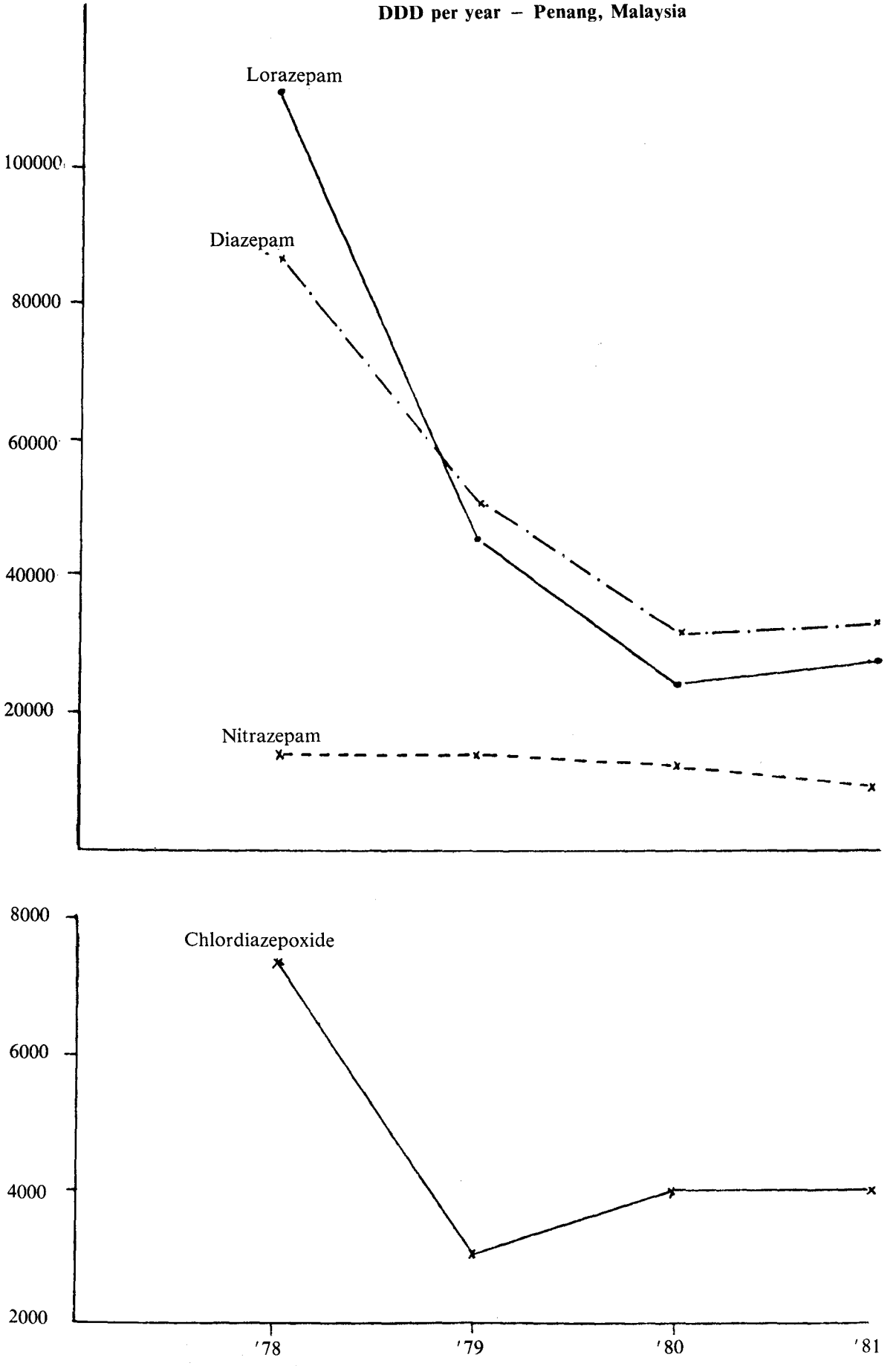


FIGURE 3d: Total Use of Benzodiazepines in Terms of DDD per year – Penang, Malaysia



In 1973 when benzodiazepine consumption was peaking in the U.S. the National Institute of Mental Health sponsored a survey to get more precise data about how antianxiety drugs were used. In a large random sample of adults in the U.S. it was found (Parry, Balter, Mellinger, et. al., 1973) that about 15% had taken at least one dose of an antianxiety drug, and about 6% had taken them for (at least) as long as one month. There was, however, no means of checking whether this extent of use was appropriate or not. So the study was extended into nine countries of Europe. This showed (Balter et. al., 1974) that Belgium and France were highest, Spain lowest and U.S. the average in sedative-hypnotic consumption. The numbers however show a rather narrow range, neither "any use" nor "regular use" numbers scattering by a factor bigger than 2 among highest and lowest consumption.

A comparison of these figures with the few data obtained from developing country presents several major difficulties. But also by themselves these figures show just a similarity between U.S. and some European countries. They do not say anything on the justification of the benzodiazepine medication. Here epidemiological studies on the incidence of emotional disorders come in.

Epidemiological evidence points to a point prevalence of about 15% of the general adult population having mental health and severe emotional problems, the overall prevalence being at least 20% (Regier et. al., 1978; Pardes, 1979; Kohn and White, 1976; Dohrenwend, et. al.,). In patient populations similar or higher rates are found (Shepherd, et. al., 1966).

It was again the Balter, Mellinger, group who undertook a survey on the incidence of psychic distress and life crisis in the U.S. population, these being main indications for the prescription of anxiolytic drugs. At the same time alcohol consumption in this population was investigated. This investigation (Mellinger, Balter et. al., 1978) showed that most of the regular users of psychotherapeutic drugs reported some psychic distress or life crisis.

Table 3a: Sedative-Hypnotic Drug Use in U.S. and Europe adapted from Hollister

Country	Percentage of Respondants	
	Any Use	Regular Use
Belgium	17	8
France	17	7
Sweden	15	6
Denmark	15	8
U.S.A.	15	6
West Germany	14	6
Great Britain	14	8
Netherlands	13	8
Italy	11	3
Spain	10	4

The more serious they were the greater was the fraction of patients treated with drugs. However, even of those reporting a high level of emotional distress and of life crisis only 35% of the women and 21% of the men had used any psychoactive medication at anytime in the previous year. It is interesting to see that alcohol use increases and is three to five times more frequent than regular use of psychotherapeutic drugs. In June 1981 Mellinger reported at a meeting in Milan, a follow-up done in 1979 of the quoted study. The follow-up confirmed the earlier views that "the prescription practices of physicians, as well as the attitudes and drug using behaviour of the general public, tends to be moderate and conservative". This is confirmed by other studies of the frequency with which tranquillizers are used. Kohn and White (1976) have established a point prevalence of use of about

Table 3b: Psychotherapeutic Drug and Alcohol Use in Relation to Psychic Distress and Life Crisis adapted from Hollister

	Any drug use past yr. (%)	Regular drug use (%)	Alcohol use (%)	Total persons (%)
Psychic Distress				
Low	9	3	34	1126
Medium	18	4	33	688
High	31	13	37	714
Life Crisis				
Low	11	3	28	647
Medium	16	5	34	1061
High	21	8	41	820

2% of the adult population and an annual prevalence of just under 15% for the U.S. and several other countries.

Studies by Uhlenhuth et. al., (1978) and by Hesbacher et. al., (1976) examining how well treatment was fitted to the treated illness point in the same direction that physicians do not unaccountably prescribe psychotherapeutic medication for emotionally healthy patients.

Allgulander from the Karolinska Institute found no evidence for over-prescription of benzodiazepines in Sweden in 1978.

These painstaking (and costly) studies come from highly industrialized countries. Similar data have not yet been gathered for developing countries. However, from recent WHO sponsored studies (Johnson 1976; Harding et. al., 1980; Busnello 1980) the (tentative) conclusion has to be drawn that there is not conspicuous difference in prevalence of emotional disturbances from industrialized countries. Consumption figures for benzodiazepines are however, very much lower per population head. Several factors may be hypothetically involved to explain these facts. First only a minority of the developing countries' population may have access to benzodiazepines (and other drugs). Second, financial aspects may be important. At first glance drug consumption (overall) roughly parallels national income. Third, these countries may have other (non-drug) sources to deal with emotional disorders (traditional healers, witch doctors). Fourth, there may be underprescription and underconsumption in relation to the total population, while some small segments of the population may get adequate or even exaggerated amounts of psychotherapeutic drugs. Only indepth drug utilisation studies will allow to answer these questions in the future.

Some of the criticisms that are current (but probably not founded on sound facts) and have given rise to the assumption that benzodiazepines are overused should be mentioned here. The recent book of Ruth Cooperstock (1982), "The Effects of Tranquillization: Benzodiazepine Use in Canada" may serve as an example. She argues that many stress situations derive from the social settings in which the patient is living, and recommends that the right answer would be an alteration of the social condition, not a tranquillizer drug. She may be right in theory but the practicability for the physician who is confronted with the problem may be questionable. There is no doubt however, that here is a large field for education of physicians on how to deal with psychological disturbances. Physical exercise was recommended by Hollister as an alternative to anxiolytic drugs. Alternatives have to be weighed carefully; alcohol would not seem to be a good answer.

4. BENZODIAZEPINES – ABUSE LIABILITY AND ACTUAL ABUSE

Practically since the introduction of the benzodiazepines it was known that they can produce physical dependence. HOLLISTER, in 1961, published that by giving psychotic patients over months very high doses of chlordiazepoxide and then stopping treatment suddenly, he was able to produce a withdrawal syndrome, two of the eleven patients having epileptic fits.

So the scientific community was aware of the possibility of physical dependence with protracted high doses. However, it was mainly in the second half of the seventies that attention was focussed on abuse and dependence problems connected with benzodiazepines. Surely the public media had an influence so that this aspect was brought to attention, be it for the better or worse.

One of the main difficulties in resolving this question was stressed in the report of the 5th WHO REVIEW COMMITTEE ON PSYCHOTROPIC DRUGS (Nov. 1981). It is the fact that compared to the wealth of anecodotal unsubstantiated evidence there are only scarce hard scientific data to form a decision basis, as the report states.

"... 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".

As a consequence of this the IMPACT study was carried out in order to get more precise data at least on the numbers of abuse cases in a few countries.

First a question of nomenclature should be clarified. Abuse and dependence are by no means synonymous.

Abuse should be defined as use outside prescribed therapy, or use in higher doses or for a longer time than prescribed. Even here arise difficulties. Is a Bangkok taxi driver who loses a days work in going to an ambulatory and gets a prescription for a minor tranquillizer abusing the substance if he buys a second package without a second prescription because the first package was beneficial? How far can an attempt to self-medication be qualified as abuse? How should the patient be classified who gets over a prolonged period of time report prescription for his tranquillizer from the receptionist of his doctor without the latter seeing him again, as it seems to happen frequently in the U.K. Marks, (1981) calculated, out of several studies, a mean of 50%, and the U.K. is probably not the only country where this happens – it is just in the U.K. that these studies have been done.

True dependence, physical and psychological, is known to occur, but the frequency of this phenomenon is debated. A first distinction is necessary, primary benzodiazepines dependence and benzodiazepines dependence within the frame of polydrug abuse.

In *polydrug abuse* numerous cases seem to be known. Many of them can be qualified as *iatrogenic;* this is the patient who was withdrawn from another drug with the help of a benzodiazepine and then became dependent on benzodiazepine. Benzodiazepine were for a number of years recommended in alcohol withdrawal, and also found rather safe in this indicator (i.e. Rothstein, Kryspin, 1976; Exner, 1975). However, there are enough authors who would not agree with this (e.g. D. Smith, 1981) so that the validity of benzodiazepines in alcohol withdrawal seems questionable. The same holds true for withdrawal from opiates, particularly heroin. But it must also be seen that this may often be, from a drug stand point, a no win situation. Well controlled prospective studies on this subject are lacking so far. In order to avoid difficulties for their benzodiazepines some drug manufacturers go as far as to warn against the use of benzodiazepines in detoxification of dependence patients. It may be questioned whether this is in their own or in societies interest.

One consequence that must be drawn from this is that prescription of a benzodiazepine to a dependence prone individual (that is an individual who has already a drug or alcohol problem, the role of smoking having not yet been elucidated) must be very carefully weighed by the prescribing physician. Will the prescription bring a benefit that is worth the risk of dependence? Treatment should be closely monitored and terminated as early as possible. To evaluate the risk it should be routine to take a careful drug history of the patient. However, neither this nor the close monitoring is routine – far from it.

It is safe to say that in the therapeutic setting dependence is rare. Its danger is increased with higher dose and with prolonged treatment. Pure benzodiazepine dependence stemming from the therapeutic situation has been looked for by several authors in prospective studies and not found (i.e. Balmer, et. al., 1981). However, as its incidence is rare it would be surprising to find them is such studies. Few data are available to calculate some sort of incidence of pure benzodiazepine dependence. The admission figures of the THANYARAK hospital in Bangkok illustrates the problem – where less than 1% of the addiction admissions were for benzodiazepines.

TABLE 4(a)

15366	Total Admissions	100%
14977	Narcotics	97.47%
277	Analgesics	1.48%
119	Benzodiazepines	0.77%
25	Other Sedative-Hypnotics	0.16%
18	Volatile Substances	0.12%

This table draws also attention to the fact that analgesics are more often abused than benzodiazepines. There are data from Thailand that salicylic acid preparations are the most commonly abused drugs among those who are not in the dangerous drug register. The use does not always seem to be rational. It is said that about 70% of the hill tribe people mix opium with salicylic acid preparations before smoking.

Similar figures on the relative abuse potential for analgesics and benzodiazepines have been reported from Switzerland. Kielholz (1968) compared the dependence producing potential of different substances. Allocating analgesics a risk quotient of 1, hypnotics were ranked 2.7, cerebral stimulants of the amine group 3.8 and tranquillizers 0.2. Prescott (1975) quotes that in New England there was a striking correlation in high-school children between the use of aspirin and the taking of non-medical psychoactive drugs such as marijuana, hallucinogens, amphetamines and barbiturates. It has to be borne in mind that salicylates have a much higher toxicity than benzodiazepines (see Social Issues).

Another group of substances that is increasingly abused are the volatiles. In Mexico volatile substance abuse has become more frequent than the abuse of tranquillizers (Hughes et. al., 1980). Recent reports from Singapore indicate that there have been a few cases of volatile abuse including one that culminated in a lethal overdose.

To our knowledge the only careful and extensive review of tranquillizer abuse was done by Ladewig (1981) in Switzerland. He interviewed all practicing physicians of his country by questionnaire concerning use of benzodiazepines, long term treatment (more than 10 weeks) and observations of inappropriate use during the last 5 years. He received replies from 72.9% of the questioned physicians. All those who reported observations of abuse were contacted by telephone and interviewed following a structured questionnaire. He found 180 patients for the 5 years period that seemed to be *isolated benzodiazepines abuse*. In this group there were positive and negative consequences of abuse. Positive consequences were ability to work and social stabilization. Negative consequences were irritability, increased fatigability and loss of interest. "In both the "switch-over" group and in those patients misusing benzodiazepines in combination with alcohol, hard drugs or other psychotropic drugs, significantly more negative consequences are listed. Particular mention is made of the markedly increased risk of accidents in traffic and at work".

Ladewig calculated a risk of two dependence cases per 100,000 prescriptions for benzodiazepines; for the five most frequently used benzodiazepines (only for these five such a calculation was meaningful) the incidence of dependence cases per 100,000 prescription was scattered over a very narrow range, 1.6 to 2.1. *"It was not possible to identify any increase in the inappropriate use of a particular compound. Among those found to be misused were both drugs with short half-life and those with long half-life, so that, from the epidemiological point of view, it is not possible to establish a connection between half-life and abuse risk".

It must be stressed that Ladewig is strictly speaking of "abuse". It can be assumed that quite a portion of these patients were also dependent. To find out this portion it would have been necessary to stop the benzodiazepine treatment abruptly and see what happened. This had been done on some cases by the treating physician as Ladewig reports. Typical or atypical withdrawal symptoms had been seen in 48 patients and no withdrawal symptoms in 55. For 77 cases no data were available.

Within the frame of polydrug abuse (alcohol included), one should distinguish drug experimenters from habitual drug abusers. Here even less is known about incidence and frequencies. In the Ladewig study the number of the polydrug abuser amounts to 254. However, in many studies the proportion of the polydrug abusers with benzodiazepines is much higher than 2 (approximate figure of Ladewig's study).

* The five most frequently used benzodiazepines in Switzerland are: bromazepam, diazepam, flunitrazepam, lorazepam, oxazepam.

What is the benzodiazepine's role in the field of *polydrug abuse*? Already here opinion is not unanimous. In the industrialized countries the benzodiazepines seem rarely to be a drug of primary abuse. David Smith (1981) is unequivocal in his statement, that benzodiazepines are not "primary drugs of abuse". Claims to the contrary (Woody, Patch, both quoted in Greenblatt and Shader) have not been substantiated by reliable documentation (Greenblatt and Shader, 1981). However, many dependents on heroin and amphetamines carry benzodiazepines in their pockets to get down from a bad trip that has provoked an anxiety state. How often they use this medication is a matter of guess. Urine analysis has given contradictory results. PRIMM (1981) reported in the U.S. FDA expert panel a very low incidence of benzodiazepine finding in random urine samples of a population of heroin addicts in Harlem. However, Poshychinda (1982) has recently reported that in Thailand diazepam use among the opiate dependents changed its role from being the supportive drug suppressing withdrawal signs and symptoms to being the synergistic drug used in combination with the opiate to potentiate the effects. 1.4% of the opium dependents and 3.5% of the heroin dependents were using the opiates in combination with diazepam. In amphetamine dependents the use of diazepam was even higher (around 20%). However, Poshychinda states at the same time, that the current data and information on diazepam abuse and dependence "by far fall short of presenting a clear pattern of the status of the situation".

The same author (1979) warns against "inappropriate and untimely control of a drug" because this "can actually lead to the aggravation of the drug dependence problem as evident in this country when opium was replaced by heroin". Here again more data would be needed to evaluate the situation.

What do the data from other sources, including the IMPACT study, show for *illicit drug traffic and abuse*?

Article 4(b) of the 1971 Convention on Psychotropic Substances requires "that there is sufficient evidence that the substance is being or likely to be abused ... warranting the placing of the substance under international control".

Traditionally the type of evidence that has been reviewed included not only public health problems, extent of abuse, etc. but also evidence of illicit traffic in that substance. This approach is in consonance and acknowledgement of the theory that illicit supply and illicit demand are intimately interlinked. The question whether illicit supply induces illicit demand or whether illicit demand stimulates illicit availability has been debated for many decades, and undoubtedly this will continue for several years in the future.

In keeping with the accepted practice, existing data of illicit availability and extent of abuse was reviewed. Country Reports to the United Nation Secretary-General, as well as Reports to Interpol were used as the information base.

ILLICIT TRAFFIC

Thirty-three countries reported the existence of illicit traffic with the benzodiazepines. Since the countries reporting are scattered throughout the world, it would be appropriate to conclude that illicit traffic in benzodiazepines exists in all regions of the world (Table 4(i), see Annex).

Of the 27 benzodiazepine substances reviewed, evidence of illicit traffic was reported for nineteen of these substances for the period 1979-1981. The benzodiazepine substances for which no evidence of illicit traffic was presented included alprazolam, camazepam, fludiazepam, nordiazepam, oxazolam, pinazepam, tetrazepam and halazepam. Table 4(i), Annex shows the analysis of various benzodiazepine substances found in illicit drug traffic by the various countries. Careful study of the data indicated that those benzodiazepine substances not reported or infrequently reported correlated very closely with those benzodiazepines which were less widely marketed globally.

An attempt was made to quantify the amount of the various benzodiazepines intercepted in the illicit drug traffic. Nineteen countries reported to the United Nations amounts of benzodiazepine seized in illicit drug traffic. Table 4(ii), Annex provides the analysis. Since the seizures were reported in various manners i.e. in weight, tablets/capsules or dosage units, it was not possible to do a more indepth analysis of reported consumption, importation and amount detected in illicit traffic. Actual seizure data was available for 17 benzodiazepine substances. The amounts seized varied widely and again it was apparent that the more widely the substances were marketed, the greater was the quantities that were likely to be intercepted in illicit drug traffic.

ABUSE DATA

Based on data reported to the United Nations for 1981/1982 it was found that twenty-two out of fifty-seven countries indicated the existence of benzodiazepine abuse (Table 4(iii), Annex). Interestingly only 16 of the 57 involved countries reported that they were experiencing a benzodiazepine problem which was causing public health concern. Twenty countries, including six countries who reported existence of benzodiazepine substances being abuse do not present any public health problems. Table 4(iv) in the Annex presents the relevant data.

An analysis of the reported abuse data with the various benzodiazepine substances was carried out (Table 4(iv), Annex). Here it was noted that nineteen benzodiazepine substances were reported as being abused. Interestingly, it was noted that three substances – alprazolam, camazepam and fludiazepam – for which no illicit traffic data was reported were being reported to be abused. Similarly three substances for which the existences of illicit traffic was reported did not have abuse indications.

Combining both the illicit traffic information and the abuse indication, one reaches the general conclusion that evidence existed which associated 22 out of the 27 benzodiazepine substances with illegal availability and/or abuse.

An attempt to quantify the extent and severity of the benzodiazepine problem was made. It was obvious from the very beginning that it was close to impossible to assess the exact (actual) extent of benzodiazepine abuse. Only nine countries were in a position to give a "head count" – where benzodiazepine abuse was the primary factor. Table 4(v) shown in the Annex provides a breakdown of actual cases of abusers and the type of benzodiazepine substance abused. A total of 1438 cases were reported by the nine countries, and these involved eleven benzodiazepine substances. Since it is acknowledged that data on actual benzodiazepine abuse is not only scanty and that specific diagnosis of benzodiazepine dependence is extremely complex, great caution is advocated in the use and interpretation of this data. From a methodological view point, it would be accurate to state that the reporting here may well not represent the actual extent of abuse. However, one could conclude that benzodiazepine substances are being abused and obviously have the potential to be abused. From this data one cannot draw an immediate conclusion that benzodiazepines on their own, are causing a significant social and public health problem. What is needed is more precise studies, particularly epidemiological and clinical, to determine the real extent of abuse and the associated problems.

An attempt was made to examine the extent to which benzodiazepine abuse contributed to the national/international drug abuse problem. Data reported primarily to the United Nations, as well as other sources were compiled as shown in Table 4(vi). This table compares for the different countries the number of persons arrested for drug abuse, with number of persons arrested for opiate abuse and reported cases of benzodiazepine abuse. Out of 85 countries that were reviewed for the drug abuse situation in 1980, it was noted that only eleven countries did not report the existence of a drug abuse problem. German Federal Republic, Canada, Australia, Japan, South Africa reported drug related arrests of over 20,000 for 1980. The total number of drug related arrests amounted to 3,344,110. Of this population 32,073 were arrested because of association with opiate abuse and 346 with benzodiazepine abuse.

The data tend to indicate that benzodiazepine abuse is minor compared to the general drug abuse problem or even opiate abuse. This is partially accurate since several countries stressed that benzodiazepine abuse was a secondary problem component to the problems associated with narcotic drugs. However, it must also be appreciated that the absence or insignificant reporting of benzodiazepine abuse, in almost all countries may be a bias as most nations have developed good monitoring systems for narcotic drugs specifically but not for benzodiazepines. The occurence of benzodiazepine abuse tends to be reported peripherally through the narcotic reporting systems.

In view of the inadequacy of data, it is extremely difficult to arrive at any conclusive statements on the abuse of benzodiazepines. It should be pointed out here that at least in two countries, Cyprus and Kuwait, benzodiazepine abuse represents a significant proportion of the drug abuse problem and is equivalent to if not greater than, in one country, the opiate abuse problem, though the incidence is small. Here again one is drawn to the general conclusion that benzodiazepine substances cause or possess the potential to cause an abuse problem. The difficulty that exists, is in determining whether they are causing social and public health problems to an extent that it is affecting the social fabric of society. This is one of the important questions that the UN Commission must take into consideration in its decision making process.

In this context the Commentary on the Convention on Psychotropic Substances is of interest; it reads (page 47, para 8.).

> "If the substance is abused or likely to be abuse in more than one country so as to constitute a public health and social problem in those countries, the problem is "international", but *this international character alone does not warrant "international control"*. What is required is that controls of the 1971 Convention are suitable to solve or at least to alleviate the problem ...".

The Commission will have to consider whether these requirements for international control are met by the data available for benzodiazepines. These have been decisions on similar issues previously. One such substance that has been brought to the attention of the Commission as a problem drug was pentazozine. Several countries since about 1980 have reported a significant abuse by its nationals. During the 1982 Session of the Commission, the Commission in concurrence with WHO recommendation did not schedule pentazozine under the 1961 Single Convention in spite of the fact that the substance had demonstrated evidence of dependence liability and significant data of abuse.

5. BENZODIAZEPINES – PUBLIC HEALTH AND SOCIAL ISSUES

In view of Article 2 in the 1971 Convention, mentioning public health and social problems expressedly for the consideration of scheduling substances, these issues will be considered here.

Mortality from overdosage of benzodiazepines is extremely rare. Finkle et. al., (1979) surveyed all drug induced deaths covering a total population of 79 million people in U.S. and Canada. Among 1239 fatal cases involving diazepam, only two could be attributed to diazepam itself. Similar results were reported by Prescott from Edinburgh in 1981, his main conclusion being that "death from benzodiazepam poisoning alone is extremely rare, ... in only one case in 8000 could death reasonably be attributed directly to benzodiazepine poisoning .... Since they have replaced the barbiturates the management of sedative-hypnotic poisoning has been transformed with much less frequent need for the full resources of intensive care".

This is set into perspective by the comparison with aspirin. This drug is "most commonly involved in paedeatric poisoning in the USA and some 500 children die there annually from this cause" (Prescott, 1975).

The incidence of overdosage of psychoactive drugs is largely related to the general levels of medical use and of availability. Alcohol is the most often used psychoactive substance in most societies, and also the most often abused. The great number of cases of benzodiazepine overdosage cases seems proportional to their wide therapeutic use. This is also confirmed by the Dawn data as presented by Rootman and Hughes (1980). Among the estimated emergency room visits monitored by the Dawn system, diazepam is top of the benzodiazepines and ranks high among the substances mentioned. However Rootman and Hughes have already added to the Dawn – data prescription information "to put these statistics in perspective". If viewed in relation with the prescription figures these numbers show indeed a different aspect. Diazepam comes down to the level of non-dependence producing substances like amitriptyline and chlorpromazine, methaqualone standing out; the same holds true when the emergency room figures are related to the total number of pills prescribed.

TABLE 5(a)

Emergency Room Admissions – adapted from Rootman et. al.,

	per 1000 prescription	per 100,000 tablet prescribed
Diazepam	0.95	2.47
Flurazepam	0.90	2.86
Chlordiazepoxide	0.61	1.01
Amitriptyline	0.85	1.54
Chlorpromazine	1.28	2.25
Pentobarbital	1.70	3.54
Methaqualone	4.15	11.00

Another indicator which would support the hypothesis that availability is an important, if not decisive factor; is that diazepam mentions have shown a consistent downward trend in Dawn mentions over the last few years, in parallel to the consistent decline of prescription its frequency.

Finally it must be seen clearly that Dawn data represent acute intoxications; they mirror abuse of drugs mainly, with and only in much smaller percentage dependence could be found as a motivation for drug taking. With all the "caveats" that are inherent in the Dawn recording its data have to be interpreted with great caution.

It might be added here that the number of suicidal attempts has not be influenced by the replacement of barbiturates by benzodiazepines. However the success rate of such attempts with benzodiazepines is certainly much lower than with barbiturates and the treatment cost will be lower too, because as Prescott (and others) states much less intensive care facilities are needed. The symptomatology of benzodiazepine intoxications alone even in high overdosage is usually not life threatening, nor do they produce systemic toxicological effects in acute overdose or in chronic use or abuse (see Toxicology section).

As with all CNS depressant drugs the combined effect of a benzodiazepine together with alcohol can result in an increased risk to the patient. This has led to the warning against taking benzodiazepines and consuming alcoholic beverages at the same time. However Prescott (1982) has encountered "drivers of double decker buses, of heavy goods vehicles and even the operator of a very large crane who stated that they had been prescribed benzodiazepines without any warning and restrictions".

This is of special importance in *traffic safety*. This highly complex issue is far from clear. It seems rather certain from laboratory studies that psychoactive drugs can produce impairment of performance even at a therapeutic dose (Linnoila, 1978; Nicholson, 1982). However, none of these laboratory parameters has been validated as a predictor of impaired (or unimpaired) traffic safety, nor are there, at present, epidemiological studies that establish the role benzodiazepines play in road accidents (Laudaner, 1981). This has however remained a controversial issue, as has the validity of predicting traffic safety from laboratory tests and from benzodiazepine blood levels. Certainly more research is needed in this field. Most experts however agree, that alcohol is a more important factor than benzodiazepines, and that the combination of the two should be avoided by all means when driving. All the more serious is the statement of Prescott quoted above; still better information on this issue to and by all physicians prescribing a benzodiazepine is desirable. A reservation has further to be made on studies of normal subjects under the influence of benzodiazepines; anxious or sleepless patients would be the valid subject selection, with or without benzodiazepine treatment.

The studies most needed in this field are of epidemiological nature, and their difficulties have been stressed in a recent WHO report (Techn. Rep. Series 656). In view of the important toll traffic accidents demand in human suffering and in financial losses this is an issue of high priority.

Within the social issues of benzodiazepines use and abuse, referral is made to the chapter on therapeutic use where studies of some social effects have been reported.

There is no reliable evidence that benzodiazepine use leads to *criminal behaviour*, (Tinklenberg, et. al., 1981). Thefts of benzodiazepines, with subsequent resale through normal channels have been reported. This type of criminal activity is, however, nor limited to benzodiazepines, but concerns many other pharmaceuticals, including antibiotics. Prescott's (1982) statement about benzodiazepines may be quoted here: "They are not "fun" drugs .... In Edinburgh drug takers and pushers often break into chemists' shops (drug stores). They are very discriminating and clear out all the narcotics, barbiturates, methaqualone and amphetamines but leave the benzodiazepines behind". Another factor to be taken into account in the evaluation of psychoactive substances is their *potential mode of spread* (WHO Techn. Report Series 407). There is no evidence that benzodiazepine users act as agents for spread of misuse of these drugs. Benzodiazepines have a low preference rating among drug abusers. However according to some reports benzodiazepines besides many other substances seem to be popular among group experimenters. No data are available on the quantitative importance of this, nor are there data to assess their dependence potential in these circumstances.

6. LEGAL IMPLICATIONS OF SCHEDULING PSYCHOACTIVE SUBSTANCES IN THE 1971 CONVENTION

RATIONALE AND MAJOR AIMS OF THE CONVENTION

The Convention on Psychotropic Substances is an international and multilateral agreement designed to prevent and combat the abuse of any psychoactive substance, natural or synthetic, that fulfills the criteria of a psychotropic substance as defined by the 1971 Convention. The *major aims* of the Psychotropic Convention are to control the production, exportation and importation of such substances and to restrict their use to medical and scientific purposes through a system of coordinated national and international measures. They are in essence conceived after the model of the 1961 Single Convention on Narcotic Substances.

Drugs are classified into four schedules according to actual or potential abuse, and therapeutic usefulness. The decision to schedule has also to take into account some rather vague general criteria ("economic, social, legal, administrative and other factors") referred to in Article 2.

In its *preamble* the Convention refers to "the public health and social problems which result from the abuse of certain psychotropic substances". The parties are "determined to prevent and combat abuse of such substances and the illicit traffic to which it gives rise". They recognize "that the use of psychotropic substances for medical and scientific purposes is indispensable and that their availability for such purposes should not be unduly restricted". The underlying objective of the Convention is to minimize availability of psychotropic substances for abuse without unduly restricting their availability for legitimate therapeutic purposes. This is a basic difference to the 1961 Convention.

The Convention entered into force on 16th August, 1976, that is, when 40 states had ratified it according to Article 26. As of early 1981, 68 nations out of 152 UN member states have ratified the Psychotropic Convention whereas 113 nations have ratified the Single Convention. There still seems to be considerable *reluctance* on the part of a number of nations, being drug manufacturing and drug importing, *to ratify this treaty*.

PROBLEMS OF SCHEDULING CRITERIA AND TERMINOLOGY

The treaty itself does not contain guidelines to indicate on which schedule a drug should be controlled. The decision to employ only *general criteria* stems from the fact that WHO's determinative role was restricted to the assessment of medical and scientific matters (Article 2, Section 5 of Convention). The generality of the criteria however may lead to ambiguities. The interpretation of scheduling criteria may be arbitrary, consequently the scope of control might be extended or modified in unexpected ways *(Report of the International Working Group on the Convention on Psychotropic Substances, 1971, September 8-12, 1982, Addiction Research Foundation, Toronto, Canada – Toronto-Report)*.

Finally terminologies of the Conventions have been subject to criticism. In particular, there is a discrepancy between the terminology of the Conventions and of medical and pharmaceutical literature. The Conventions do not adequately present scientific criteria of classification for different dependence types. Also the lines are not clearly drawn between drug misuse, abuse and dependence. If control is to be international in nature rather than national, then it would be important to clarify these definitions. Furthermore, the 1971 Convention does not address the problem of drug overuse by inadequate prescription.

ADVANTAGES AND DISADVANTAGES OF THE CONVENTION

The *need for control* of psychoactive substances has been recognized by many nations since about 30 years. However, the need for an international treaty has a shorter history and fewer supporters. Many nations felt – and still feel – that national control systems are sufficient and more adequate to deal with these problems. Any legislation concerning the complex field of drug abuse must fit within the general framework of national public health policy.

International treaties at the global level result from a compromise between largely diverging opinions between different states of different cultural and socio-economic background on objectives to reach and measures to apply. However such treaties are only one component affecting prevention, education, treatment, rehabilitation, reintegration and legal measures at the national level. The *implementation* of appropriate measures against substance abuse falls primarily in the sphere of national sovereignty.

The 1971 Convention brought a major advance over previous international legislation since it took into account the balance of social benefit, social and medical cost, and cost of legislation. Ideally the advantages in joining the Convention consist in a *shared responsibility* for the international solution of a difficult problem. The real value of the Convention however depends on the care with which States transform and implement the international treaty in their national legislation. Under these conditions, the following major benefits can result

for a country from ratifying the Convention:-

- The Convention assists governments to prevent easy availability of Schedule I substances which have limited or no medical use (Toronto-Report). The existence of an international treaty provides some form of moral pressure on government.

- Implementation of the control measures required by the Convention may necessitate the revision and updating of the national drug control mechanisms (Toronto-Report).

- The system of reporting has proved to be useful not only as a control measure but as a tool for policy-making.

- Article 13 allows a country to notify all other parties through the Secretary General that it prohibits the import of a substance in Schedules II-IV. But Article 13 cannot prohibit the transshipment of substances through third countries which are not parties to the Convention. The benefits of Article 13 can therefore easily be annihilated until the acceptance of the Convention has become worldwide.

Some of the criticisms that can be addressed to the Convention are implicit in the above considerations. There are however further limitations.

International treaties offer the potential for strengthening national legislation. If such legislation, e.g. availability on prescription only, is not in existence, or not implemented, international treaties will have little positive impact. New or additional control mechanisms can be very costly and require supplementary administrative work. However many developing countries are handicapped by the very limited number of physicians, pharmacists and pharmacies in their countries. They do not have enough professionals to assure an appropriate drug distribution network.

Some developing countries are not in a position to comply with prescription obligations as required by the Convention. The strict fulfilment of these obligations could therefore lead to the restricted availability of important therapeutic agents and hinder the medication of a relatively significant proportion of the countries' population (*Toronto-Report*, 1981).

Morever the adverse effects of regulation on the availability of medically needed drug in different developing countries was commented upon by different authors (Soueif, 1981; Supnet, 1980; Zarco and Almonte, 1977; Gamez, 1982; Comlavi, 1980).

Another undesirable effect of control can be the development of *black markets* in drugs and the *criminalization of users* (John C. Kramer). In this context it has to be stressed that the Convention does not envisage the *problems of imitation and counterfeits* and it does not affect street level abuse. Therefore the Convention is unable to deal with illicit trafficking of licitly or illicitly produced substances. Another fear seems to be that if larger numbers of substances are brought under control, *development of new drugs may be hindered* (Psychotropic Substances and Their International Control, Toronto 1981).

Finally inadequate availability as a consequence of international control can cause many people to *switch to undesirable alternatives, e.g. alcohol.* The WHO Expert Committee Report on the Assessment of Public Health and Social Problems associated with the use of psychotropic drugs noted that the net result of placing a drug under control may be positive, neutral or negative, depending in part, on the substitution of other drugs. If the controlled drug is replaced by another of equal or more deleterious effects the goal is not attained.

CONCLUSIONS

Several questions about the benefits of the Convention on Psychotropic Substances as an effective meansto combat drug abuse especially in developing countries remain unanswered.

In particular, Article 13 does not affect illicit trade nor does it cover the problems of counterfeit and falsification. The scheduling of substances hampers licit trade and might have negative effects on the availability for therapeutic use, especially in developing countries.

As there is often no uniform pattern of abuse for individual substances throughout the world, local and regional aspects have to be taken into consideration. It must be carefully assessed whether there is a need for international control as opposed to national or regional measures. Some authors point out that strategies patterned after western models have been found to be ineffective and counter-productive in developing countries.

Most scientific information on use and abuse patterns of psychotropic and other psychoactive substances has been gathered in industrialised countries. For the developing countries information is scarce and mostly

anecdotal. Reliable data on use and abuse patterns as well as on level and effects of control in developed as well as developing countries should form the decision basis for measures of international control.

The international substance control system should not be burdened by the control of substances which constitute mainly a local or regional problem. The problems vary from one country to another and it is a complex and difficult process to shift out from national experiences the factors relevant for the common benefit of the international community. Only such substances or groups of substances should be put under international control the abuse of which has a significant negative impact on the state of public health at the international level. However, from a preventive consideration, substances that have reliable data as causing social and public health problems, though not global in proportion should be evaluated for control.

7. BENZODIAZEPINES – ASSESSMENT OF THE IMPACT OF SCHEDULING

Many countries have expressed concern over the past few years about the effectiveness of the 1971 Convention on Psychotropic Substances as well as the problems associated with drugs scheduled under this Convention. The report of the International Working Group on the Convention on Psychotropic Substances, – September 8-12, 1981, Addiction Research Foundation, Toronto, Canada, reviewed many of these concerns. This same concern was reexpressed during previous Commission meetings in particular the last special session of the United Nations Commission on Narcotic Drugs, during the debate on proposals for scheduling substances under international treaties (Agenda Item 3). During the discussion of the Commission, some delegations indicated the need for international control while others noted that at present time there was a lack of knowledge on the real situation as it existed. Similarly several delegates were of the view that a careful evaluation should be undertaken to more thoroughly examining the existing evidence as well as evaluating the effect of scheduling substances under the 1971 Convention on Psychotropic Substances prior to any decision being taken by the Commission.

Reflecting on the criteria that need to be examined and fulfilled before any substance can be scheduled under the 1971 Convention, one notes that guides are provided in Article 2, Sections 4 and 5 of the said Convention. These two sections required that:

If the World Health Organisation finds:-

(a) That the substance has the capacity to produce

(i) (1) A state of dependence, and
(2) Central nervous system stimulation or depression resulting in hallucination or disturbances in motor function or thinking or behaviour or perception or mood, or

(ii) Similar abuse and similar ill effects as a substance in Schedule I, II, III or IV and

(iii) That there is sufficient evidence that the substance is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control, the World Health Organisation shall communicate to the Commission an assessment of the substance, including the extent or likelihood of abuse, the degree of seriousness of the public health and social problem and the degree of usefulness of the substance in medical therapy, together with recommendations on control measures, if any, that would be appropriate in the light of its assessment.

The Commission, taking into account the communication from the World Health Organisation, whose assessments shall be determinative as to medical and scientific matters and bearing in mind the economic, social, legal, administrative and other factors it may consider relevant, may add the substance to Schedule I, II, III or IV. The Commission may seek further information from the World Health Organisation or from other appropriate sources.

In order to assess the impact of scheduling drugs under the 1971 Convention, a study was developed by the National Drug Research Centre, University of Science Malaysia, which is a United Nations Collaborating Centre for research and training in Drug Dependence. Based on extensive discussions with scientists from various regional countries, it was decided that the most effective means of obtaining the necessary information was by undertaking a questionnaire survey.

The survey instrument was designed by a team of researchers and aimed at eliciting information on:-

(i) The adequacies and/or inadequacies of national controls in the various countries;

(ii) The effect of scheduling drugs under the 1971 Convention on the related drug abuse problem.

Specific information was also gathered on:

(i) the extent of drug abuse including benzodiazepine abuse;

(ii) the effect of national (legislative) control on the legal and illegal availability of benzodiazepines within the various countries;

(iii) the impact of international control.

METHODOLOGY

The original research proposal envisaged that the questionnaire instrument would be circulated to all member countries of the United Nations; however, this approach had to be modified because of technical difficulties. The survey was altered to study mainly the Anglophone countries in East Asia with one European, two North American and one African countries. Fifteen countries were finally selected and every effort was made to obtain a representative distribution of countries reporting varying levels is of problems associated with abuse of psychotropic and other psychoactive substances.

As this part of the study – the IMPACT study – only addresses issues relating to the economic, social, legal and administrative aspects, the information in these areas is discussed has Data obtained on other related areas such as abuse levels etc. are dealt with in other sections of this report. Further, since the information obtained was voluminous and represented an invaluable resource information for policy planners, the research team decided to undertake a detailed analysis of the gathered data and this will be published as a full monograph in the future. In this section, a summary of the major findings is given.

RESULT

Of the fifteen countries invited to participate in this study, eleven countries completed the necessary questionnaire instrument ('participating' countries, underlined):

1. Australia
2. Burma
3. Canada
4. Germany
5. Hong Kong
6. India
7. Indonesia
8. Malaysia
9. New Zealand
10. Nigeria
11. Pakistan
12. Philippines
13. Singapore
14. Thailand
15. United States of America

Five out of the eleven countries were signatories to the 1971 Convention, the remaining six had not yet acceded to it.

(a) Impact of the 1971 Convention

In regards to the actual implementation of the 1971 Convention non-signatory countries envisaged greater difficulties than signatories. The most commonly reported problem was in relation to administration, where many countries expressed the view that they had undertaken or will have to carry out extensive changes in their administrative procedures to implement the Convention effectively.

In many instances it was reported that they would have to redesign their information gathering and drug monitoring system. Further to ensure uniformity and prevent discrepancies at the national level on drug control, some scheduling activities would have to be carried out. Several countries, even some who were signatories, indicated that they did not have adequate resources to implement the 1971 Convention properly.

Some countries indicated that they would have to make several amendments to their existing legal acts, ordinances and regulations to ensure effective implementation.

Participating countries were asked to assess their national control measures with regards to the problems associated with abuse of psychotropic and other psychoactive substances. All except two countries (Pakistan and Thailand) reported that their existing national controls were adequate to deal with the existing problems caused by psychotropic and other psychoactive substances. Both in Thailand and Pakistan the problems experienced were associated with illegal availability, particularly the barbiturate hypnotics, methaqualone and amphetamines. Pakistan also indicated that they were currently involved in revising their national laws and with their enactment these controls should be adequate. Thailand reported that, partly due to the lack of medical per-

Note: "Psychotropic substances" means substances that are listed in the 1971 Convention. "Psychoactive substances" are all CNS – active substances.

sonnel and partly due to the widespread availability of psychotropic and other psychoactive substances which could easily be obtained through several retail outlets without prescription, additional national control measures were desirable to deal with the easy availability and abuse problem.

All the participating countries had legislative measures for the control of psychoactive substances. In all the countries, except for Thailand, psychotropic and other psychoactive substances which were used therapeutically were available only on prescription. Further national control existed for importation and exportation of these substances. The degree of monitoring/record keeping and inspection procedures varied among the different countries, though all the participating countries reported having the necessary mechanisms, but not necessarily the means for implementation.

The participating countries were requested to indicate whether international control would assist them in resolving their national problems associated with psychoactive substances. Rather surprisingly only three countries indicated affirmatively. Review of the reasons why the majority of countries felt that international control would have little or no effect on their national psychoactive drug problems indicated the following: –

i. The existing national controls were considered adequate and in most instances, the level of national control were more stringent that those called for in the 1971 Convention;

ii. For psychotropic substances in Schedule 1 and 2 of the 1971 Convention, it was opined that national control still remained the most effective way of dealing with their availability in the respective countries. International control at the level of Schedule 1 and 2 was stringent, had little if any impact and it was opined that the 1971 Convention was unable to address the main problem, that of illegal traffic. Methaqualone and amphetamine were cited as examples.

iii. For psychotropic and other psychoactive substances which are currently used in therapy the problems of misuse and illegal availability were a consequence of diversion and bad prescribing practices of a minority of physicians. They were considered to be best dealt with at the national level through drug enforcement and clinician education.

iv. Several countries, particularly those in the South-East Asian region (Thailand, Malaysia, Indonesia, Singapore and Hong Kong) considered that their problems associated with psychotropic substances and other psychoactive drugs were more closely related to the illegal availability and abuse of counterfeit products which could not be controlled by the 1971 Convention.

Those countries that considered that International Control, had assisted them in dealing with the related psychotropic substance abuse problem, indicated that: –

i. Placing a substance under International Control, enabled them to regulate the amount of a particular psychotropic substance being imported into their respective countries. It was pointed out that the 1971 Convention provides the necessary control procedures for importing and exporting countries, thereby not hampering trade while maintaining the necessary security among the signatory countries.

ii. Scheduling a substance under the 1971 Convention, will alert national authorities to the actual or potential danger of that substance and hence stimulate the authorities to enforce necessary control measures.

With regards to the 1971 Convention itself, it was the general consensus that the current Convention was inadequate in many respects and due to the insufficiencies, the 1971 Convention was unable to act as an international control instrument.

(b) **Potential Impact of Scheduling the Benzodiazepines**

Participating countries were asked to describe the national controls that were being applied to control benzodiazepines.

All countries except Thailand reported that benzodiazepines were available only on medical prescription. In Thailand, with the exception of diazepam injections and nitrazepam, all benzodiazepines could be purchased easily. In some countries, the purchase, possession and use without medical directive is considered an offence under their national law. Further, the importation and distribution could be carried out only by authorised agents. Some countries required the maintainence of sales records for the benzodiazepines.

Countries were asked to assess the effect of current national control measures on the medical use and illicit use of benzodiazepines. It should be pointed out at this juncture that some of the participating countries, i.e. Singapore, Malaysia, Philippines, Thailand, had controlled a small number of benzodiazepines under the

Dangerous Drug Act over and above the normal legislative control for psychoactive substances. The listing of any psychoactive substance in the Dangerous Drug Act, due to the stringent control measures, invariably diminished legal availability and obviously, due to enhanced legislative enforcement powers, reduced illegal availability wherever it existed.

In all countries, the normal legislative measures did not hamper legal availability of benzodiazepines at hospitals and in medical practice. Further, since in these countries national controls required the benzodiazepines to be available only on prescriptions, the legal outlet will be restricted to medical practices and pharmacies. Pharmacies were also required to maintain records of sales, though in some of the countries, these records represented minimal information.

With regards to illicit availability and use, these countries were unanimous in the view that national laws were adequate to control the diversion of legally imported benzodiazepines and non-medical use. Several of the countries reported that wherever illegal traffic or misuse of benzodiazepines existed, national control measures have had significant impact in reducing illegal availability and use.

Thailand on the other hand reported that current national control was inadequate for controlling the problems associated with benzodiazepines. Since the majority of benzodiazepines were NON PRESCRIPTION DRUGS, they were readily available from various retail outlets including pharmacies. Further, it was opined that, since this was a useful therapeutic agent, and that due to a lack of medical personnel especially in the remote areas, numerous difficulties will be generated by restricting the availability of these substances. It was fully acknowledged that additional national control was desirable.

Pakistan reported it has adequate national controls to manage the problems associated with the legally imported benzodiazepines. However, in consonance with several other South-East Asian countries, they reported severe problems stemming from illegally imported benzodiazepines. These illegally imported products, often brought into the countries by deliberate mislabelling, is sold cheaply to some unethical business outlets. Some of the countries reported that these illegally imported benzodiazepines have in certain instances proven to not even contain benzodiazepines but phenobarbitone and/or placebo substrate.

The national authorities of the participating countries were asked to review the effect of placing the benzodiazepines under international control and the impact of it of the national level. All the participant countries except Thailand, Philippines and Pakistan, reported that national controls were adequate and that international control would have no significant impact and hence be unnecessary. Several countries opined that, based on past experience, international control would have little impact on the illicit use (abuse) of benzodiazepines. Further, several countries reported that the current level of their national control were more stringent than those being consequential to international control. Some countries argued that international control would be a burden and may hamper health care practices in their countries. It was opined that placing the benzodiazepines on international control would place an additional administrative burden of having to report import/export and use figures to the International Narcotics Control Board. Also it was stated that international control may be restrictive in that their dispensation by health care workers will not be permitted and in several of these countries, health care workers were the backbone of the health delivery services.

The general consensus of these countries would appear to be that since benzodiazepines were already controlled nationally as prescription drugs, international control would not in anyway significantly enhance control measures. On the other hand it will impose some financial and certainly additional administrative burden for all member states. It must be pointed out here, that these countries did not view benzodiazepines as causing a major drug abuse or public health problem, especially in relation to their own national drug abuse problems. Some authorities opined that, in their countries where the problem of benzodiazepines abuse was associated with the use of these substances as secondary drugs of abuse with opiates and also when there were shortages of opiate supply, too tight a control of the benzodiazepines may cause these abusers to turn to other substitute drugs which could turn out to be more harmful to the user. All authorities acknowledged that the benzodiazepines if left totally uncontrolled did have the potential to cause an abuse problem; however, it was emphasised that national control was the best and most appropriate mechanism for controlling a group of substances which had wide therapeutic use that *did not*, in their view, constitute a global problem.

Three countries who called for international control, viewed the need for international control as a means to reducing availability by restricting the exportation of benzodiazepines by manufacturing countries. Philippines and Pakistan, whilst claiming that national control was adequate to deal with diversion of legally imported benzodiazepines, felt that international control was necessary to reduce illicit benzodiazepine traffic into their respective countries and their consequence availability in the illicit market. Thailand, whilst concurring with the above view, also felt International Control will enhance its law enforcement activities.

8. SUMMARY, SPECIAL ISSUES AND UNANSWERED QUESTIONS

INTRODUCTION AND BACKGROUND

The 1971 Convention on Psychotropic Substance was designed to facilitate the control of production, marketing (sales on prescription only), exportation and importation of psychotropic substances which have dependence producing liability. The Convention specifies the criteria which need to be fulfilled before a psychoactive substance can be included in the said Convention.

The 1971 Convention states that "the United Nations Commission on Narcotic Drugs, taking into account the communication from the World Health Organisation, whose assessment shall be determinative as to medical and scientific matters and bearing in mind the economic, social, legal, administrative and other factors it may consider relevant, may add the substance to Schedule I, II, III or IV. The Commission may seek further information from the World Health Organisation or other appropriate sources".

At its Seventh Special Session the Commission on Narcotic Drugs, adopted a Resolution 2(S-VII) on Procedures to be followed in matters of scheduling of narcotic drugs and psychotropic substances. As part of that resolution, the Commission requested Member States for "information on the economic, social, legal and administrative factors related to the abuse of substances being considered for possible scheduling, and to supply as complete data as possible on any illicit trafficking in the substances in question".

METHODOLOGY AND OBJECTIVES

Interested Member States and Scientists, and the Secretariat of the Commission held discussions on possible avenues for addressing the request of the Commission. The National Drug Research Centre, University of Science, Malaysia also was already undertaking an UNFDAC supported study on similar lines, and the Centre was encouraged to expand the scope and extent of its existing study.

An appropriate survey instrument was designed, sent to concerned scientists for their evaluation and modified according to comments received. Fifteen anglophone countries were selected for the study and every effort was made to ensure participation of signatory and non-signatory countries; of countries involved in the production and consumption of psychotropic substances as well as countries reporting problems associated with Psychotropic Substance Abuse. Existing information available from United Nations reports was also analysed and where appropriate was included in the study.

The *main objective* of the study was to design a data gathering instrument which would facilitate the comprehensive gathering of relevant information which interalia the Commission might carefully consider in fulfilling its functions as envisaged by the 1971 Convention.

The *secondary objective* was to apply the finalised data gathering instrument to single substance or groups of substances being considered for possible scheduling by the Commission. As the substance for consideration by the CND at its 30th Session in February 1983 was to be the benzodiazepines, this procedure was applied to these psychoactive substances.

In the development of the study it was suggested that this report should be limited to a review of the economic, social, legal and administrative factors related to the abuse and illicit traffic as well as to assessment of the impact of scheduling benzodiazepines under the 1971 Convention. During this study it became clear that, at present, data on the elements of information required according to 1971 Convention, for consideration by the Commission existed in several isolated packages. To provide comprehensiveness of information and understanding it was decided that this *Report should present an analysis of the current knowledge on all elements of information requested in the 1971 Convention.*

In accordance with the 1971 Convention this report should be considered as another "appropriate source" which is complementary and supplementary to reports of the World Health Organisation as well as other national and international agencies.

SUBSTANCES UNDER REVIEW – The Benzodiazepine Group

Several difficulties were encountered in reviewing these substances, mainly because they have extensive therapeutic application and as such, the balance between the therapeutic value and the social and public health risks involved with these drugs needed carefully assessment. The extensive therapeutic usefulness of the benzodiazepines is well documented; however, this information on the misuse and abuse of these drugs is in marked contrast poorly documented. This is probably due to fact that either the effect of abuse is minimal or due to a general lack of information or both. This inbalance of available information affected the assessment process.

The benzodiazepine drugs belong to the family of the 4,5-benzo(hept)-1,2,6-oxidiazines. The individual

substances in this group are chemically very similar, but minor differences exist in their potency, therapeutic usefulness and in the profile of their main actions.

Benzodiazepines as a class are among the most widely used drugs globally. The extensive use of the benzodiazepines has raised the question of overprescription. The evidence in this area is often contradictory. Some epidemiological studies indicate that there is significant overprescribing of this group of drugs. Other studies have demonstrated that the benzodiazepines were underprescribed. Irrespective of these contradictions, it has been suggested that the prescription habits of practising physicians could be improved by appropriate educational and informational measures.

Consumption figures indicate that the level of consumption in developing countries is much lower than in industrialised ones. This lower level of consumption may be due to several factors, such as the extent of the health care facilities that use these drugs and their availability. It is important to note that, in spite of lower levels of consumption in these countries, overprescription of benzodiazepines has been reported. More data is needed to clarify the situation.

The abuse of benzodiazepines is a fact, but the extent of this abuse is not clear. True dependence, physical and psychological, is known to occur with the benzodiazepines, but the frequency of this phenomenon is debated. There is at present *inadequate* evidence to enable conclusive differentiation of the dependence potential between any of the 27 benzodiazepines being considered for possible control. However, in concurrence with the 1982 WHO Panel on the scheduling of psychoactive substance for international control, it is opined that halazepam has a *potential* to demonstrate a *possible* difference; at present the supporting evidence is lacking.

An attempt has also been made to assemble data on the extent of abuse and illicit traffic from different sources. The existing evidence does not permit a precise conclusion. Nevertheless the following generalisations may be made.

(a) Several countries are aware and concerned of a benzodiazepine abuse problem, however, few of these countries (9 in this study) are able to report hard data on the actual number of persons associated with benzodiazepine abuse;

(b) In those countries where hard data was available, (with the exception of Cyprus and Kuwait), the proportion to which benzodiazepines contributed to the overall general drug abuse problem was not significant;

(c) In relation to the different benzodiazepine substances, 19 of the 27 substances have been reported to be associated with abuse problems. Similarly in relation to illicit traffic, several countries have reported seizures of various benzodiazepine substances;

(d) Combining available elements of information on the abuse and illicit traffic; a general conclusion reached is that 22 out of the 27 benzodiazepines substances had some association with the problem of abuse and illicit traffic.

The question that should be considered is "what does all this information mean and to what extent does information on abuse and illicit traffic reflect the abuse liability of benzodiazepines".

One conclusion that could be drawn from international reports was that the number of reports related to abuse and amounts of these substances intercepted in illicit traffic had a direct correlation to the availability of these substances. The Commission has to carefully evaluate this information.

Reviewing responses of countries on the effectiveness of national control and the need for international control, it appears that more than two-thirds of the countries that participated in the IMPACT study indicated that national controls were adequate and effective, at the present time, in dealing with benzodiazepine abuse problems. Several of these countries raised doubts as to the usefulness and value of international control. However, their main sources of concern were not directed at the substances under consideration, but rather at the 1971 Convention in general. The major concerns expressed were:-

(i) Inefficiency and/or ineffectiveness of the 1971 Convention on Psychotropic Substances;

(ii) Increase in burden of administrative and financial resources to implement and fulfill properly the requirements of the Convention;

(iii) Perceived restrictions imposed by the Convention on the therapeutic availability of these substances nationally and particularly to para-medical and health care workers.

To schedule a particular or all the benzodiazepine substances is the prerogative of the Commission on Narcotic Drugs. Reflecting on the available evidence it is possible to examine the options available to the Commission.

There is adequate evidence that all the benzodiazepines have a potential to produce dependence. Further, current evidence does not allow one to differentiate the dependence potential between any of the 27 benzodiazepines.

Existing information indicates that nearly all of the benzodiazepines (22 out of 27) have been associated with abuse and/or illicit traffic.

Hence, combining both these elements of information, irrespective of whether the Commission decides to schedule or not schedule these substances, *logic dictates that the benzodiazepines should be considered as a group*. The only possible exception is halazepam which, despite the lack of substantive evidence at present, is opined as having the *potential* to demonstrate a *possible* difference. Similarly, irrespective of the decision, it is essential that the responsible agencies assess and monitor the benzodiazepines abuse situation. This is important and would indicate any situation change which may necessitate action. A collective effort involving all interested parties including pharmaceutical industries is advocated.

Should the Commission concur with the above view, then the Commission has to decide, on the basis of available evidence whether to: –

(i) schedule all the 27 benzodiazepines, and defer consideration of halazepam, as recommended by the World Health Organisation;

(ii) defer the decision to schedule all 27 benzodiazepines, but continue to monitor on a biannual or annual basis the extent of benzodiazepine abuse;

(iii) not to schedule the benzodiazepines under the 1971 Convention.

Several elements of information should be reviewed by the Commission carefully in reaching its final decision, including whether the current extent of benzodiazepine abuse constituted a global problem, needing international control. Several countries have indicated that, at present, national controls are adequate. Others feel that a situation has been reached necessitating international control. In addressing this issue the Commission should also take into account that many countries reported that benzodiazepine abuse was closely associated with illegal products/counterfeits and their illicit traffic. At present the Convention does not address such issues.

Some social scientists may interprete the existing evidence and suggest that at present, in numbers, the extent of benzodiazepine abuse may not constitute a significant public health and social problem. It must be reiterated that abuse of benzodiazepines is a fact. The debate relates directly to the extent of abuse. From a preventative point of view it may be argued that since there is an acknowledged abuse problem effective international control could curb the worsening of the problem.

Another area to be addressed by the Commission is to whether international control would assist parties to the 1971 Convention. Concerns expressed regarding the 1971 Convention itself should be evaluated. Consideration should also be given to those already overburdened countries which currently have difficulties in fulfilling the Convention (e.g. prescription control), whether scheduling of these substances will truly enable these countries to achieve better control and thus contribute not only to their national but also to global reduction of benzodiazepine abuse.

The Commission must examine all these issues and reach an appropriate conclusion.

CONCLUSION

The *objectives* of the IMPACT study were to develop and apply data gathering methodology to obtain and assess relevant information on benzodiazepines which the Commission might usefully consider in fulfilling to its functions as envisaged by the 1971 Convention. The researchers are of the opinion that these objectives have been achieved. It is *recommended* that the developed procedure could be applied to all future psychoactive substances being considered for scheduling.

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ANNEX

Table 3(i): Consumption of Benzodiazepine Anxiolytics (in DDD/1000 inhabitants/day) adapted from Blaha and Brukmann

	1966	1967	1968	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978
Czechoslovakia	0.1	0.3	2.3	3.4	6.2	8.3	10.3	10.2	11.5	12.1	12.6	13.9	13.0
Finland		12.5	16.9	19.8	24.6	18.3	15.5	14.4	14.6	14.9	15.2	14.4	
Iceland					49.0	45.0	46.4	47.0	48.0	51.7	55.3		
Northern Ireland	9.2	12.5	15.2	19.0	21.0	23.0	25.2	27.3	29.7	32.8	34.2	32.4	
Norway		14.8	19.0	25.3	27.4	25.2	24.0	25.4	23.8	23.4	24.2		
Sweden						19.2	19.2	17.7	17.7	18.0	18.7	19.0	

Table 3(ii): Consumption Figures from Various (in kg. unless stated)

Country / Drug Type	AUSTRALIA					CYPRUS					HONG KONG				
	1976/77	1977/78	1978/79	1979/80	1980/81	1977	1978	1979	1980	1981	1977	1978	1979	1980	1981
Chlordiazepoxide	–	–	–	–	–				1,050,380 tab.		–	222.6	–	–	–
Clonazepam	–	–	–	–	–				37,410 tab. 10 bottles		–	0.178	0.261	0.330	NM
Clorazepate	–	–	–	–	–				330,000 tab.		–	0.440	1.670	2.470	–
Diazepam	473	412	382	319	295				4,161,585 tab. 1,833,bottles		–	178.87	8.65	221.37	–
Flurazepam	–	–	–	–	–				–		–	9.190	9.350	16.820	–
Lorazepam									1,452,000 tab.		–	5.770	4.360	8.140	–
Medazepam	–	–	–	–	–	N/I	N/I	N/I	177,290 tab.	NI	–	2.436	2.133	2.695	–
Nitrazepam	304.5	313.5	313.5	277	269				547,920 tab.		–	3.480	1.460	1.200	–
Oxazepam	1926	2556	3294	3684	4332				45,725 tab.		–	4.208	7.990	6.230	–
Oxazolam	–	–	–	–	–				–		–	2.500	4.640	7.860	–
Prazepam	–	–	–	–	–				–		–	3.876	12.690	3.590	–
Tenazepam	–	–	–	–	–				63,000 tab.		–	10.160	6.890	3.590	–
Bromazepam	–	–	–	–	–				–		NM	NM	NM	NM	NM
Flunitrazepam	–	–	–	–	–				–		NM	NM	NM	NM	NM

Country / Drug Type	INDONESIA					JAPAN					MALAYSIA				
	1977	1978	1979	1980	1981	1977	1978	1979	1980	1981	1977	1978	1979	1980	1981
Chlordiazepoxide	–	0.347	0.528	0.509	–		–	–			–	24.963	29.122	3.920	1.488
Clonazepam	NM	NM	NM	NM	NM		–	–			–	0.395	0.603	0.726	0.469
Clorazepate	NM	NM	NM	NM	NM		–	–			–	–	0.75	–	–
Diazepam	–	0.129	0.128	0.116	–		1750	1959			–	50.512	39.898	4.579	17.617
Flurazepam	NM	NM	NM	NM	NM		–	–			–	2.012	2.163	2.232	1.425
Lorazepam	–	0.003	0.004	–	–		–	–			–	–	–	1.276	–
Medazepam	–	0.019	0.015	0.013	–	N/I	–	–	N/I	N/I	–	2.017	1.885	1.739	0.845
Nitrazepam	–	0.008	0.013	0.016	–		992	1174			–	3.614	3.383	2.168	1.160
Oxazepam	NM	NM	NM	NM	NM		–	–			NM	NM	NM	NM	NM
Oxazolam	NM	NM	NM	NM	NM		–	–			NM	NM	NM	NM	NM
Prazepam	–	0.004	0.003	0.002	–		–	–			–	–	–	–	–
Tenazepam	–	0.004	0.004	0.004	–		–	–			–	–	–	2.345	–
Bromazepam	–	0.007	0.010	0.013	–		–	–			–	1.509	1.098	0.975	0.529
Flunitrazepam	–	0.006	0.833	0.964	–		–	–			–	3.430	4.232	5.501	2.53

Country / Drug Type	PHILIPPINES					SINGAPORE					THAILAND				
	1977	1978	1979	1980	1981	1977	1978	1979	1980	1981	1977	1978	1979	1980	1981
Chlordiazepoxide	10.298	22.731	31.375	–	–	–	2.308	1.952	2.290	1.026	–	–	–	4.020	–
Clonazepam	–	0.091	0.566	–	–	–	0.071	0.071	0.069	0.048	NM	NM	NM	NM	NM
Clorazepate	0.476	1.310	0.754	–	–	–	–	–	–	–	NM	NM	NM	NM	NM
Diazepam	–	26.373	29.237	32.032	–	–	4.383	3.578	3.528	1.943	–	–	–	6.762	–
Flurazepam	24.018	32.070	29.104	–	–	–	6.364	7.980	9.002	4.970	–	–	–	1.328	–
Lorazepam	2.905	2.796	3.012	–	–	–	–	–	–	–	–	–	–	0.162	–
Medazepam	2.177	2.351	0.966	–	–	–	1.747	1.363	1.198	0.549	–	–	–	0.943	–
Nitrazepam	4.055	0.925	1.102	–	–	–	2.504	2.593	2.719	1.410	–	–	–	1.118	–
Oxazepam	4.995	5.105	5.511	–	–	–	–	–	–	–	–	–	–	–	–
Oxazolam	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	–	–	–	–	0.175
Prazepam	NM	NM	NM	NM	NM	–	–	–	–	–	–	–	–	0.385	–
Temazepam	NM	NM	NM	NM	NM	–	–	–	–	–	–	–	–	0.125	–
Bromazepam	NM	NM	NM	NM	NM	–	1.129	–	1.228	0.622	NM	NM	NM	NM	NM
Flunitrazepam	NM	NM	NM	NM	NM	–	0.596	0.081	0.086	0.038	NM	NM	NM	NM	NM

Nm : Not marked
– : Data not available

Table 4(i) Illicit Traffic - 1979-1981

Drug Type \ Country	Argentina	Austria	Australia	Chile	Cyprus	Denmark	Finland	F.R. of Germany	Greece	Hong Kong	Ireland	Israel	Japan	Kuwait
Bromazepam	+		+							+		+	+	
Clobazam	+							+		+		+		
Cloxazolam													+	
Chlordiazepoxide			+	+	+			+		+				+
Clorezepate					+									+
Clonazam										+				
Diazepam		+	+	+	+	+		+	+	+	+			+
Flurazepam			+	+		+				+	+			
Flunitrazepam	+		+				+			+		+		
Estazolam													+	
Lorazepam										+	+			
Nitrazepam			+			+				+	+			
Nimetazepam													+	
Medazepam			+		+			+		+				
Oxazepam			+		+					+	+			
Prazepam										+				
Triazolam										+				
Temaprazepam														

Source: Report compiled by the UNITED NATIONS DIVISION OF NARCOTIC DRUGS

Drug Type \ Country	Malaysia	Malta	Norway	Philippines	Portugal	Italy	Spain	Sweden	Switzerland	Singapore	Tunisia	Uruguay	United Kingdom
Bromazepam													
Clobazam													+
Cloxazolam													
Chlordiazepoxide	+		+		+			+	+				+
Clorazepate					+								
Clonazam	+		+					+					+
Diazepam	+	+	+	+		+		+	+				+
Flurazepam	+	+	+	+	+				+		+		+
Flunitrazepam	+	+	+		+		+	+		+		+	+
Estazolam													
Lorazepam	+				+	+			+				
Nitrazepam	+		+	+				+	+				+
Nimetazepam										+			
Medazepam	+		+		+								+
Oxazepam	+		+		+			+	+				+
Prazepam	+					+							+
Triazolam										+			+
Temaprazepam													+
Ketazolam													+

Drug Type \ Country	U.S.A.	Guatemala	New Zealand	Sri Lanka	South Africa
Brozemapam					
Clobazam					
Cloxazolom					
Chlordiazepoxide	+		+		+
Clorazepate	+		+		
Clonazam	+				
Diazepam	+	+	+	+	+
Flurazepam	+				+
Flunitrazepam					
Estazolam					
Lorazepam	+		+		+
Nitrazepam	+	+	+		+
Nimetazepam					
Medazepam	+				
Oxazepam	+		+		+
Prazepam	+				+
Triazolam					
Temaprazepam					
Ketazolam					

Table 4(ii): Illicit Trafic - Amount of Seizures for 1979, 1980 and 1981

Country / Drug Type	CYPRUS			DENMARK			HONG KONG			AUSTRIA			SINGAPORE		
	1979	1980	1981	1979	1980	1981	1979	1980	1981	1979	1980	1981	1979	1980	1981
Diazepam	813mg.			841 tab.	347 tab.		1186 tab.	83622 tab. 9.5g. powder		165 tab. 7 amp.	4 amp.				
Flurazepam	–						503 tab.	57 tab.							
Nitrazepam	–			16 tab.	13 tab.		1336 tab.	392 tab.							
Chlordiazepoxide	131mg.						8903 tab.	4472 tab.							
Medazepam	Traces.						300 tab.	–							
Oxazepam	Traces.						646 tab.	60 tab.							
Clorazepam	160mg.														
Lorazepam	–						276 tab.	–							
Clonazepam	–						30 tab.	21 tab.							
Prazepam	–						300 tab.	–							
Tempazepam	–						–	9 tab.							
Flunitrazepam	–						–	5 tab.	130 tab.					15006 tab.	36001 tab.
Nitetazepam	–														2 tab.
Triazolam	–						–	3 tab.	13 tab.					15 tab.	60 tab.
Bromazepam	–						–	22 tab.	99 tab.						
Clobazam	–						–	28 tab.	161 tab.						

Source 1: Report compiled by the UNITED NATIONS DIVISION OF NARCOTIC DRUGS
Source 2: IMPACT STUDY

Country / Drug Type	PHILIPPINES			AUSTRALIA			GERMANY			PORTUGAL			MALAYSIA		
	1979	1980	1981	1979	1980	1981	1979	1980	1981	1979	1980	1981	1979	1980	1981
Diazepam	239,256 D.U.	2,326 D.U.		14 amp. 592 tab. 5.1 g.	31 1mp. 165 tab.		20mg. 9 amp. 567 tab.	648 tab.					9445 tab.	13620 tab.	
Flurazepan	338 D.U.	46 D.U.		36 cap.	–		–	–		150 cap.	257 cap.		10 tab.	37tab.	
Nitrazepam	65,432 D.U.	67,066 D.U.		179 tab.	40 tab.		–	–		–	–		585 tab.	313 tab.	
Chlordiazepoxide				18 cap. 191 tab.	–		–	15 cap. 5 tab.		650 cap.	–		17,712 tab	12,388 tab.	
Medazepam				55 tab.	–		–	–		25 cap.	189 cap.		160 tab.	–	
Oxazepam				362 tab.	148 tab.		–	100 tab.		45 tab.	10 tab.		56 tab.	–	
Clorazepate										10 cap. 663 tab. 5 amp.	31 cap.		–	–	
Lorazepam										96 tab.	398 tab.		948 tab.	86 tab.	
Clonazepam													2 tab.	2 tab.	
Prazepam													133 tab.	–	
Flunitrazepam						25 tab. 8 mg.					340 tab.	1767 tab.	–	–	
Bromazepam						1 tab.									
Clobazam									50 tab.						

Illicit Traffic - Amount of Seizures for 1979, 1980 and 1981

Illicit Traffic - Amount of Seizures in D.U. unless stated

Country/ Years / Drug Type	NEW ZEALAND			PHILIPPINES			SRI LANKA		
	1978	1979	1980	1978	1979	1980	1979	1980	1981
Chlordiazepoxide	33	31	46	500	–	–	–	–	–
Clorazepate	–	1	–	207	–	–	–	–	–
Diazepam	1109	714	2621	122,637	239,256	2,326	210 tabs.	190 tabs.	66 tabs.
Lorazepam	39	112	60	–	–	–	–	–	–
Flurazepam	–	–	–	20	338	46	–	–	–
Nitrazepam	579	245	261	64,500	65,432	67,066	–	–	–
Oxazepam	81	71	143	–	–	–	–	–	–

Country / Drug Type	FINLAND			JAPAN			NORWAY		
	1979	1980	1981	1979	1980	1981	1979	1980	1981
Diazepam									
Flurazepam									
Nitrazepam									
Chlordiazepoxide									
Medazepam									
Oxazepam									
Clorazepam									
Lorazepam									
Cloxazolam						292 g.			
Estazolam					12 g,				
Flunitrazepam			115 tab.					15 tab.	143 tab.
Bromazepam					15 g.				
Ninetazepam					7 g.				

Country / Drug Type	IRELAND			MALTA		
	1979	1980	1981	1979	1980	1981
Diazepam		954 tab.		200 tab.	–	
Flurazeapam		1,129 tab.		–	2 tab.	
Nitrazepam		2 tab.				
Chlordiazepoxide						
Medazepam						
Oxazepam						
Clorazepam						
Lorazepam		1 tab.				
Clonazepam						
Prazepam		1 tab.				
Flunitrazepam		Bromazepam				
Bromazepam						
Clobazam						

Illicit Drug Traffic in the United States of America

Drug Type / Seizures	July '75 - April '82					Oct. '77 - Apr. '82	Jan. '74 - Apr. '82		July '75 - Apr. '82	Dec. '76 - Apr. '82
	Chlordiazepoxide	Clonazepam	Clorazepate	Diazepam	Flurazepam	Lorazepam	Medazepam	Nitrazepam	Oxazepam	Prazepam
Amount seized in dosage units (unless stated)	153,000	160	640	6.7 million	21,600	10,000	9,313	104,114 tablets	2,009	18,898
Number of cases involved	217	2	36	1,519	109	14	3	20	39	8

Table 4(iii)

Country	Are Benzodiazepines Available in Your Market	Does a Benzodiazepine Abuse Problem Endangering Public Health Exist	Has Illicit Traffic been Reported
Australia	+	+	+
Austria	+	–	+
Belgium	+	+	N/I
Brazil	+	–	N/I
Burma	+	+	–
Canada	+	–	+
Central African Republic	+	N/I	N/I
Cuba	+	–	N/I
Cyprus	+	+	N/I
Czechoslovakia	+	N/I	–
Denmark	+	+	N/I
Egypt	+	–	N/I
France	+	+	N/I
German Democratic Republic	+	–	N/I
German Federal Republic	+	N/I	+
Greece	N/I	–	+
Guatemala	N/I	N/I	+
Haiti	–	–	–
Honduras	+	–	N/I
Hong Kong	+	+	+
Hungary	+	–	N/I
Iceland	+	N/I	N/I
Iraq	+	N/I	–
Ireland	+	N/I	N/I
India	+	–	–
Indonesia	+	+	N/I
Japan	+	–	N/I
Kuwait	+	N/I	–
Liechtenstein	N/I	N/I	–

Source: Report compiled by the UNITED NATIONS DIVISION OF NARCOTICS DRUGS 1981/1982

Country	Are Benzodiazepines Available in Your Market	Does a Benzodiazepine Abuse Problem Endangering Public Health Exist	Has Illicit Traffic been Reported
Madagascar	+	+	–
Malaysia	+	–	+
New Zealand	+	–	–
Norway	+	N/I	N/I
Pakistan	+	–	N/I
Papua New Guinea	+	–	–
Philippines	+	+	+
Poland	+	–	–
Qatar	+	N/I	–
Senegal	+	–	N/I
Seychelles	+	–	–
Singapore	+	N/I	–
South Africa	+	N/I	–
Spain	+	+	+
Sri Lanka	+	N/I	+
Sweden	+	+	+
Switzerland	+	–	N/I
Thailand	+	+	–
Tonga	+	–	–
Trinidad and Tobago	+	–	–
Turkey	+	+	N/I
Tunisia	+	–	–
Tuvalu	–	–	–
United Arab Emirates	+	N/I	N/I
United Kingdom	+	N/I	+
United States of America	+	+	+
Yugoslavia	+	N/I	N/I
Zambia	+	–	–

N/I - No Information available

Table 4(iv): ABUSE - DATA

Drug Type \ Country	Australia	Austria	Belgium	Burma	Cyprus	Chile	Denmark	France	German Democratic Republic	Honduras	Hong Kong	Iran	Kuwait	Madagascar
Alprazolam							+							
Bromazepam	+	+	+				+	+						
Camazepam			+											
Clobazam			+					+		+				+
Chlordiazepoxide												+		
Diazepam				+	+							+		
Estazolam							+							
Flunitrazepam		+	+				+	+		+				
Flurazepam												+		
Kelazolam			+											
Lorazepam												+		
Clorazepate														
Nitrazepam				+								+		
Nordazepam			+											
Oxazepam												+		
Triazolam			+				+							
Cloxazolam							+							
Clonazepam														
Prazepam														

Source: Report compiled by the UNITED NATIONS DIVISION OF NARCOTIC DRUGS 1981/1982

Drug Type \ Country	Philippines	Singapore	Sweden	Switzerland	Turkey	Malaysia	U.S.A.
Alprazolam				+			
Bromazepam	+						
Camazepam							
Clobazam				+			
Chlordiazepoxide					+		+
Diazepam	+						+
Estazolam							
Flunitrazepam		+				+	
Flurazepam	+		+				+
Kelazolam				+			
Lorazepam	+		+				+
Clorazepate							
Nitrazepam	+						+
Nordazepam							
Oxazepam	+						+
Triazolam							
Cloxazolam							
Clonazepam							+
Prazepam							+

Table 4(v): ABUSE - DATA

No. of cases of abuse / Drug Type	SINGAPORE			PHILIPPINES			CHILE			KUWAIT			SWITZERLAND			HONG KONG		
	1979	1980	1981	1979	1980	1981	1979	1980	1981	1979	1980	1981	1979	1980	1981	1979	1980	1981
Diazepam						375		1		14	15			2		40	40	
Nitrazepam						140								1				
Oxazepam													3	1				
Flunitrazepam			175															
Lorazepam						71												
Clonazepam						35										1	1	
Flurazepam						145							4	1				
Chlordiazepoxide								1		1	7			1		20	21	
Clorazepate											1							

ABUSE - DATA

No. of cases / Drug Type	Cyprus	Australia
	1980	1978 - 1979
Chlordiazepoxide	5	–
Clorazepate	1	–
Diazepam	13	112
Medazepam	1	–
Oxazepam	1	138
Nitrazepam	–	50

Table 4(vi): Table Showing General Drug Abuse, Opiate Abuse and Benzodiazepine Abuse in 1980 / 1981

Country	Population (in millions)	Number of Persons Arrested for General Drug Abuse 1980 1981	Number of Persons Arrested for Opiate Abuse 1980 1981	Number of Cases of Benzodiazepines Abuse 1980 1981
Algeria	18.59	461 - 539	– –	N/I
Argentina	27.06	2,023 - 2,790	60 - 1714	N/I
Australia	14.62	23,764 - 19,484	2032 - 2170	300
Austria	7.56	4,900 - 2102	1422	
Bahamas Bangladesh	87.66	290 - 296	33 - 26	
Barbados	0.25	226 - 261	–	
Belgium	9.86	1,630 - 189	45 - 35	
Brazil	123.03	2,498 - 3040	–	N/I
Bulgaria	8.86	N/I - 25	N/I - 41	
Burma	35.3	2,748 - 2918	2345 - 2,492	
Burundi	4.51	N/I - N/I	N/I	
Cameroon	–	84 - 106	–	
Canada	23.94	38,498 - 56,224	436 - 1010	200
Chile	11.10	1,889 - 1,740	– - 58	2

Country	Population (in millions)	Number of Persons Arrested for General Drug Abuse 1980 1981	Number of Persons Arrested for Opiate Abuse 1981	Number of Cases of Benzodiazepines Abuse
Colombia	27.09	1,492 – 892	– –	N/I
Costa Rica	2.24	– – 107	–	N/I
Cyprus	0.63	43 . 46	2	21
Czechoslovakia	15.32	6 – 55	–	
Denmark	5.12	3,126 3126	N/I	
Djibouti	N/I	3 26	N/I	
Egypt	41.99	8,658 7107	N/I	
Finland	4.78	N/I 364	N/I	
France	53.71	10,958 13850	3610 – 5330.	N/I
French Polynesia	0.16	126 165		
German Democratic Republic	16.74	63 38	25 – 17	
German Federal Republic	61.56	55,447 56388	N/I – 18100	
Greece	9.6	536 – 732	54 – 224	
Grenada	0.10	112 –	–	

Country	Population (in millions)	Number of Persons Arrested for General Drug Abuse	Number of Persons Arrested for Opiate Abuse	Number of Cases of Benzodiazepines Abuse
Guyana	0.10	112 120	–	
Honduras	3.69	264 – 463	–	
Hong kong	5.07	– – 7649	– 7553	
Hungary	10.71	N/I – 4	N/I – (2)	
Iceland	0.23	451 –	N/I	
India	66.36	1,058 – 1205	737 – [illegible]	
Indonesia	151.89	523 – 525	63 – [illegible]	N/I
Iran	37.45	2,623 4342	N/I	
Iraq	12.08	4 – 13	N/I	
Italy	57.04	7,783 – 9469	3526 — 4471	
Ivory Coast	7.97	N/I –	N/I	
Jamaica	2.19	465 960	–	
Japan	116.78	21,793 23,720	56 48	
Jordan	3.19	21	–	

Country	Population (in millions)	Number of Persons Arrested for General Drug Abuse	Number of Persons Arrested for Opiate Abuse	Number of Cases of Benzodiazepines Abuse
Kenya	16.4	6,448 –	N/I	N/I
Korea	17.91	655 725	35 – 31	N/I
Kuwait	1.37	189 223	37 – 57	23
Lebanon	3.16	263 251	115 – 109	
Lesotho	1.34	339 – 462	N/I	
Liechtenstein	0.03	28 –	5 – 11	
Luxembourg	0.36	66 387	47	
Madagascar	8.74	614 561	–	
Malaysia	13.44	5,660 5660	4962 – 7,444	N/I
Malta	0.36	73 –	– – 5	
Mauritius	0.96	356 426	91 – 132	
Mexico	71.91	2,883 4063	443 – 387	
Monaco	0.03	35 35	9	
Morocco	20.24	3,996 7789	N/I – 1	
Netherlands	14.14	7,153 8409	2917 – 3764	

Country	Population (in millions)	Number of Persons Arrested for General Drug Abuse	Number of Persons Arrested for Opiate Abuse	Number of Cases of Benzodiazepines Abuse
Netherlands Antilles	0.27	481 - 804	N/I - 23	
New Caledonia	0.15	19 -	1	
New Zealand	3.10	6,257 8017	N/I	
Nigeria	77.08	1,259 - 1352	N/I	
Norway	4.09	4,048 - 4757	N/I	
Pakistan	82.44	13,991 - 17,192	2048 - 4351	
Panama	1.84	- 1,251	-	
Philippines	48.40	- 3,100	- - 2	N/I
Poland	35.58	169 437	N/I - 15	
Romania	22.27	- -	-	
St. Vincent and the Grenadines	0.12	99 96	-	
Singapore	2.39	3,288 4,528	2849 - 4079	
Somalia South Africa	29.29	32,170 33,092	-	
Sri Lanka	14.74	N/I -	N/I	
Spain		10,580		

Country	Population (in millions)	Number of Persons Arrested for General Drug Abuse	Number of Persons Arrested for Opiate Abuse	Number of Cases of Benzodiazepines Abuse
Sweden	8.31	5,219 – 3419	N/I	
Switzerland	6.37	8,224 – 9699	N/I	
Thailand	47.17	– 35,102	– – 11411	
Togo	2.7	84 – 65	81	
Tunisia	6.37	156 – 59	–	
Turkey	44.92	3,418 – 3920	297 – 556	
Turks and Caicos Island	–	63 – 26	–	N/I
United Kingdom	05.95	18,366 – 19000	1519 – 1476	
United States of America	227.66	12,158 – 12216	2080 – 2521	
Union of Soviet Socialist Republic	265.54	27 – 25	2 – 2	
Venezuela	13.91	993 – 576	2	
Yemen	5.93	N/I –	N/I	
Yugoslavia	22.34	178 139	87 – 89	
Zambia	23.94	9 –	–	

Opiates: Heroin, Morphine, and other opiates.

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