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Geneva, 23–26 June 1998

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1. Introduction

The WHO Expert Committee on Drug Dependence met in Geneva from 23 to 26 June 1998. The meeting was opened by Dr V.K. Lepakhin, Assistant Director-General, who emphasized the significant role the Committee has played in the international drug control system. Since WHO was founded in 1948, it has been the task of the Committee, which was established specifically to undertake this work, to carry out a medical and scientific evaluation of the abuse liability of dependence-producing drugs, and to make recommendations to the United Nations Commission on Narcotic Drugs concerning the level of international control to be applied to them. The first meeting of the (then) Expert Committee on Habit-Forming Drugs was held in 1949 to review several new narcotic drugs. The name of the Committee has since changed a few times, and the present name, the Expert Committee on Drug Dependence, was established at the sixteenth meeting of the Committee in 1968. Since the entry into force of the Convention on Psychotropic Substances in 1976, the Committee has evaluated not only narcotic drugs but psychotropic substances as well. The resulting recommendations concerning the control status of the reviewed substances are often referred to as "scheduling recommendations", because lists of controlled substances are called "schedules" in the Conventions. Almost all the scheduling recommendations of WHO have been accepted by the United Nations Commission on Narcotic Drugs, with minor modifications made in a few exceptional cases. Through this procedure, WHO and the United Nations have scheduled 115 narcotic drugs and 111 psychotropic substances. Thus, the Committee has played an important role in keeping up to date the international drug control system. Dr Lepakhin stressed the high level of impartiality and objectivity required in reviewing substances because of the significant commercial and other implications scheduling recommendations could have.

Dr J. Idänpään-Heikkilä, Director, Division of Drug Management and Policies, WHO, outlined the normative functions of the division in the area of pharmaceuticals and explained the close linkage between the task of the Committee and these activities.

2. Critical review of psychoactive substances

2.1 Scheduling criteria

In making scheduling recommendations, the Committee is guided by both the relevant drug control conventions as well as the guidelines

adopted by the Executive Board of WHO (*1*). The Committee decided to maintain the same scheduling criteria as used in the past, in order to ensure the necessary consistency in applying the drug control Conventions. The main points of the criteria are presented below.

2.1.1 *Narcotic drugs*

The Executive Board guidelines indicate that, for substances falling within the terms of the 1961 Single Convention on Narcotic Drugs, the Committee should first decide whether the substance under review has morphine-like, cocaine-like, or cannabis-like effects, or is convertible into a scheduled substance having such effects. If either of these conditions is fulfilled, the Committee should then determine if the substance:

- is liable to similar abuse and produces similar ill effects to the substances in Schedule I or Schedule II, respectively; or
- is convertible into a substance already in Schedule I or Schedule II.

This determination is necessary because the 1961 Single Convention on Narcotic Drugs indicates that similarity in both "abuse liability" and "ill effects" to drugs already in Schedule I or Schedule II is the criterion to be used for scheduling recommendations. Substances are scheduled as follows:

Schedule I or II — if a substance is liable to similar abuse and produces similar ill effects to the drugs in Schedule I or Schedule II, or is convertible into a drug already in Schedule I or Schedule II.

A drug in Schedule I can also be placed in Schedule IV if it is found that it:

Schedule IV — "is particularly liable to abuse and to produce ill effects . . . , and that such liability is not offset by substantial therapeutic advantages not possessed by substances other than drugs in Schedule IV" (*2*).

Schedule III contains only exempt preparations of specified compositions containing drugs in Schedule I or II.

Examples of narcotic drugs in the three principal schedules of the 1961 Convention are:

Schedule I	cannabis, cocaine, heroin, morphine, pethidine
Schedule II	codeine, dihydrocodeine, pholcodine
Schedule IV	cannabis, heroin

2.1.2 *Psychotropic substances*

The 1971 Convention on Psychotropic Substances defines WHO's role in the scheduling process with respect to substances falling within the terms of this convention as follows:

> "If the World Health Organization 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 hallucinations 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 Organization shall communicate to the Commission [on Narcotic Drugs] 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" (*3*).

With regard to the selection of a particular Schedule, the Expert Committee has been using the following additional criteria, first developed at its seventeenth meeting in 1969, when it discussed the then-new international drug control system for psychotropic substances:

"*Schedule I* Substances whose liability to abuse constitutes an especially serious risk to public health and which have very limited, if any, therapeutic usefulness.

Schedule II Substances whose liability to abuse constitutes a substantial risk to public health and which have little to moderate therapeutic usefulness.

Schedule III Substances whose liability to abuse constitutes a substantial risk to public health and which have moderate to great therapeutic usefulness.

Schedule IV Substances whose liability to abuse constitutes a smaller but still significant risk to public health and which have a therapeutic usefulness from little to great" (*4*).

The Committee confirmed these criteria at its twenty-ninth meeting in 1994 and worked out the following supplementary guidelines:

> "In cases where the 1969 criteria apply only in part, the scheduling recommendation should be made with a higher regard to the risk to public health than to therapeutic usefulness.
>
> Notwithstanding the above, recommendations for inclusion in Schedule I should be made only when the 1969 criteria are fully met, with respect to both therapeutic usefulness and the risk to public health" (*5*).

Thus, when the abuse liability of a psychotropic substance constitutes a "significant" risk to public health, it would be placed in Schedule IV, regardless of its therapeutic usefulness. If the degree of risk to public health is "substantial", the substance would be placed in either Schedule II or III, depending on its therapeutic usefulness. In principle, the placement of a therapeutically useful substance in Schedule I is ruled out. Moreover, lack of therapeutic usefulness should not be used to justify a recommendation for inclusion of a substance in Schedule I if its abuse liability does not constitute "an especially serious risk" to public health and society.

Examples of psychotropic substances in the four schedules of the 1971 Convention are:

Schedule I	(+)-lysergide (LSD), mescaline
Schedule II	amphetamines,[1] methylphenidate, secobarbital
Schedule III	amobarbital, pentobarbital, flunitrazepam
Schedule IV	most benzodiazepines, phenobarbital, pemoline

2.2 Dihydro*etorphine*[2]

Substance identification

Dihydro*etorphine* (CAS 14357-76-7), chemically 7,8-dihydro-7-α-[1-(*R*)-hydroxy-1-methylbutyl]-6,14-endo-ethanotetrahydrooripavine.

Previous review

In 1996, at its thirtieth meeting, the Committee recommended critical review of dihydro*etorphine*.

Similarity to known substances and effects on the central nervous system

Dihydro*etorphine* is chemically similar to etorphine, which is included in Schedule I of the 1961 Convention. Pharmacologically, animal

[1] The term "amphetamines" refers to amphetamine, methamphetamine and their stereoisomers. These terms are used throughout this report in preference to the INNs as being of wider currency in the drug control community.

[2] In composite drug names containing both a chemical prefix and an INN, the INN is distinguished by being italicized.

studies indicate that dihydro*etorphine* is a highly potent analgesic, 6000 and 11000 times as potent as morphine in mice and rabbits, respectively. In mice and rabbits, the peak analgesic effect was attained 15 minutes after subcutaneous injection of dihydro*etorphine*, and the duration of analgesic effect lasted 60–90 minutes, which was shorter than that of morphine (120–150 minutes). Radioligand binding assay indicates that dihydro*etorphine* is a selective μ-opioid-receptor agonist.

Dependence potential

Animal studies indicate that dihydro*etorphine* possesses a strong psychological dependence potential, 5000–10000 times more potent than morphine in self-administration tests in rats, 500 and 100 times more potent than morphine and heroin in self-administration studies in monkeys, and 8000 and 1000 times more potent than morphine and heroin in drug discrimination studies in rats. However, animal studies show that the physical-dependence-producing properties of dihydro*etorphine* are relatively low. The withdrawal syndromes caused by dihydro*etorphine* in mice used in jumping (analgesic effect) tests were weaker than those caused by morphine. In monkey withdrawal precipitation tests and abrupt withdrawal tests, the withdrawal syndromes of dihydro*etorphine* were significantly less severe than those of morphine.

Actual abuse and/or evidence of likelihood of abuse

Abuse of dihydro*etorphine* began soon after it was marketed in China in 1992. Although indicated for use as an analgesic, it was also used for suppressing opiate withdrawal syndrome. Abuse of dihydro*etorphine* spread very quickly in the country. Epidemiological studies have shown two kinds of reasons for starting to abuse dihydro*etorphine*: iatrogenic and social. One group of individuals began to use the drug for medical purposes but increased the doses because tolerance developed quickly, and the potent dependence-producing properties of dihydro*etorphine* played a dominant role in compelling them to start abusing the drug. Opiate abusers were another group of people who took the drug as a substitute for heroin because of its stronger psychological-dependence-producing properties, cheaper price, and less strict control.

Therapeutic usefulness

Dihydro*etorphine* was registered in China in December 1992 for the relief of acute severe pain. However, it is not useful for substitution treatment of opioid withdrawal because of its short duration of action.

Recommendation

Dihydro*etorphine* is a potent μ-opioid-receptor agonist. On the basis of its pharmacological properties and dependence potential as demonstrated in animal studies, as well as the pattern of abuse observed in China, it was assessed that dihydro*etorphine* is liable to similar abuse and produces similar ill effects to drugs in Schedule I of the 1961 Convention. It was therefore recommended that dihydro*etorphine* be placed in Schedule I of the 1961 Single Convention on Narcotic Drugs.

2.3 Ephedrine

Substance identification

Ephedrine (2-methylamino-1-phenylpropan-1-ol) exists in four stereoisomeric forms and two corresponding racemic mixtures. The four stereoisomers were designated traditionally as *l*-ephedrine, *d*-ephedrine, *l*-pseudoephedrine and *d*-pseudoephedrine but are now described, respectively, as (–)-ephedrine, (+)-ephedrine, (–)-pseudoephedrine and (+)-pseudoephedrine. (–)-Ephedrine is chemically (1*R*,2*S*)-2-methylamino-1-phenylpropan-1-ol. Racemic ephedrine, or (±)-ephedrine, is chemically (1*RS*,2*SR*)-2-methylamino-1-phenylpropan-1-ol.

Previous review

In 1996, at its thirtieth meeting, the Committee recommended critical review of ephedrine.

Similarity to known substances and effects on the central nervous system

Ephedrine is chemically and pharmacologically similar to amphetamines. It is also similar to cathine, which is (+)-norpseudoephedrine. Ephedrine is both an α- and a β-adrenergic agonist and enhances the release of norepinephrine from sympathetic neurons. In general, ephedrine is viewed as being a less potent central nervous system stimulating agent but a more effective bronchodilator than amphetamines. Ephedrine increases motor activity and mental alertness and diminishes the sense of fatigue. Ephedrine decreases appetite and promotes weight loss.

Dependence potential

In humans with a history of substance abuse, (–)-ephedrine, (+)-amphetamine (INN = dexamfetamine), (+)-methamphetamine (INN = metamfetamine), phenmetrazine, and methylphenidate injected subcutaneously produced similar increases in respiratory rate and blood pressure and similar types of subjective changes, including euphoria. The agents differed only in their relative potencies. Subsequently, oral administration of ephedrine was studied. Again, (–)-

amphetamine (INN = levamfetamine) and other amphetamine-like stimulants differed from ephedrine only in their relative potencies. (–)-Ephedrine was five times less potent than amphetamine in producing amphetamine-like subjective and physiological effects in substance abusers, but was more potent than amfepramone (diethylpropion).

In rhesus monkeys trained to self-administer cocaine, (–)-ephedrine maintained responding rates greater than saline in substitution tests. In rats trained to discriminate cocaine from placebo, (–)-ephedrine generalized to cocaine, though at a slightly lower rate than (+)-amphetamine. Ephedrine generalized to cocaine and (+)-amphetamine in other drug discrimination studies in rats. In monkeys trained to self-administer amphetamine, an oral dose of 10 mg racemic ephedrine was discriminated as amphetamine. In monkeys trained to self-administer cocaine, (–)- and racemic ephedrine had definite reinforcing effects. (+)-Ephedrine was both less efficacious and less potent than the (–)-isomer in its capacity to generalize to amphetamine.

Actual abuse and/or evidence of likelihood of abuse

Of the 50 countries returning questionnaires to WHO, ephedrine was available for medical use in 46. Of these 46 countries, the following 12 countries have indicated present or past ephedrine abuse or illicit traffic in ephedrine presumably associated with its abuse: Belgium, Burkina Faso, China, Costa Rica, Germany, Finland, France, Ireland, Slovakia, Sudan, Thailand and the USA. Although quantitative information is difficult to obtain, the extent of ephedrine abuse was significant enough for some governments to implement various regulatory controls. Current abuse problems seem to be particularly serious in certain African countries. Where abuse exists, it seems to involve single-entity ephedrine products. In addition, in the USA, combination products consisting of ephedrine in herbal preparations have been abused.

The Committee was informed of the problem of ephedrine diversion. In particular, in the material provided by the International Narcotics Control Board, it is evident that a few countries serve as the major suppliers of ephedrine to other countries. In such countries, there is a large gap between the amount required for licit use and the amount imported into the countries, the difference presumably reflecting diversion to abuse. Ephedrine is also used as a precursor for synthesis of methamphetamine, for which purpose it is exported and imported in dosage forms.

Therapeutic usefulness

Ephedrine is widely used as a bronchodilator in the symptomatic treatment of reversible bronchospasm, which may occur in associa-

tion with asthma, bronchitis, emphysema, and other obstructive pulmonary diseases. Hypotension and shock have been treated with parenteral ephedrine because of its cardiac stimulation and vasoconstriction effects. Less common indications for use include obesity, motion sickness and enuresis.

The widespread use of ephedrine as a medicine is demonstrated by the fact that 92% of countries responding to the WHO questionnaire (46/50) indicated therapeutic use of ephedrine. Certain countries have indicated the presence of a large number of pharmaceutical products containing ephedrine on the market, often in combination with other substances.

Recommendation

On the basis of the available information concerning the pharmacological profile, dependence potential and likelihood of abuse of ephedrine, the public health and social problems associated with the abuse of ephedrine were assessed to be significant. The current problem appeared to be particularly serious in certain African countries. The Committee therefore recommended that (–)-ephedrine and its racemate be placed in Schedule IV of the 1971 Convention. The (+)-isomer is significantly less potent than the (–)-isomer. The Committee noted, in making this recommendation, that according to the 1971 Convention, ephedrine combination products would be eligible for exemption.

The Committee also noted that there are questions of overlapping jurisdiction concerning the 1971 and 1988[1] Conventions that may make fully effective international regulation difficult. The interrelationship and interpretation of these conventions needs clarification by appropriate international bodies including the International Narcotics Control Board and WHO. In addition, the Committee recommended that WHO and the International Narcotics Control Board develop ways to alert Member States exporting pharmaceutical formulations of ephedrine that these preparations have the potential for abuse and for use as a precursor of illicit stimulants.

2.4 Remifentanil (INN)

Substance identification

Remifentanil (CAS-132875-61-7), chemically 1-(2-methoxycarbonylethyl)-4-(phenylpropionylamino)-piperidine-4-carboxylic acid methyl ester, is also known as GI87084X. Remifentanil hydrochloride (CAS-132539-07-2) is also known as GI87084B. There are no chiral

[1] United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, 1988.

carbon atoms in the molecule; no stereoisomers or racemates are possible.

Previous review

In 1996, at its thirtieth meeting, the Committee recommended critical review of remifentanil.

Similarity to known substances and effects on the central nervous system

Remifentanil has been classified as a relatively selective μ-opioid-receptor agonist with a profile similar to fentanyl, alfentanil and sufentanil, but with an ultra-short duration of action. Comparison of potency in *in vitro* binding assays specific for the μ-opioid receptor has demonstrated similar potencies for remifentanil and fentanyl. Analgesic potency of remifentanil was found to be similar to fentanyl, alfentanil and sufentanil in rats, mice and dogs.

In clinical pharmacology studies, remifentanil exhibited properties (including adverse effects) similar to other fentanyl analogues. The most serious adverse effects were attributable to its properties as a μ-opioid-receptor agonist and included hypotension, bradycardia, muscle rigidity and respiratory depression.

Dependence potential

Withdrawal signs have developed in rats following cessation of remifentanil administration. Remifentanil substitutes for morphine in morphine-dependent withdrawn monkeys. Remifentanil is reinforcing in self-administration studies in monkeys. In opiate-experienced non-dependent human subjects, the very rapid subjective peak effects of remifentanil were not significantly different from those of fentanyl. In another study involving human subjects with no history of exposure to opiates, euphoria occurred with about the same incidence for remifentanil as for fentanyl and alfentanil.

Actual abuse and/or evidence of likelihood of abuse

One case of remifentanil abuse and overdose by intranasal administration occurred during clinical study of the drug. Remifentanil had been administered over a period of several weeks, which led to an overdose resulting in loss of consciousness, tachycardia, depressed respiration and seizures. Following emergency room treatment, the patient recovered.

Therapeutic usefulness

Remifentanil is used as an analgesic during induction and maintenance of general anaesthesia, in postoperative anaesthesia, and in

monitored anaesthesia care. Remifentanil has been approved for marketing in 17 countries.

Recommendation

Remifentanil is a short-acting μ-opioid-receptor agonist. On the basis of its pharmacological properties and dependence potential, it was assessed that remifentanil is liable to similar abuse and produces similar ill effects to the drugs in Schedule I of the 1961 Convention. The Committee therefore recommended that remifentanil be placed in Schedule I of the 1961 Convention.

2.5 Proposal of the Government of Spain

2.5.1 *Outline of the proposal*

In 1997, the Spanish Government submitted a proposal to the Secretary-General of the United Nations to amend the 1971 Convention by adding to Schedules I and II the isomers, esters and ethers of psychotropic substances already in these schedules, as well as any modified chemical compounds producing effects similar to those produced by the original substances (referred to here as "analogues"). The proposal was forwarded to the Expert Committee for its recommendations. An English translation of the proposal is attached as an annex to this report. The Spanish proposal also recommends the scheduling of the salts of these substances. The Committee did not discuss the question of the scheduling of salts, since the salts of scheduled substances are already subjected to international control. An in-depth analysis of potential advantages and disadvantages of the proposal of the Spanish government has led to the following conclusions.

2.5.2 *Conclusions and recommendations*

With regard to the scheduling of analogues or "any modified chemical compounds producing effects similar to those produced by the original substances", the Committee was of the opinion that extending control collectively to groups of substances that are related to, but potentially pharmacologically different from, the substances in Schedules I and II may be in conflict with the scheduling procedure stipulated in Article 2 of the 1971 Convention, which requires WHO to evaluate individual substances. Furthermore, the lack of specificity in such group designations may lead to problems, such as disagreements among parties concerning the precise scope of substances under control. With regard to the scheduling of esters and ethers, the same question may arise with regard to conformity with Article 2 of the 1971 Convention. In addition, advantages in terms of the extended scope of control would be rather limited. Though difficult to evaluate, controlling analogues, esters and ethers is likely to have a

negative impact on legitimate industrial and research activities involving these substances.

For these reasons, the Committee did not recommend amending Schedule I and II of the 1971 Convention to extend international control collectively to esters, ethers and analogues of controlled substances. It was noted, however, that control can be applied to criminal activities involving analogues of scheduled substances at the national level, without extending unnecessary administrative and regulatory control to such substances when used for legitimate industrial and research purposes. In one country, this was achieved by applying criminal controls only to certain specified acts involving analogues. Governments that recognize the existence of problems with analogues in their countries should consider the desirability of adopting similar selective control measures, an option not available under the 1971 Convention once analogues have been scheduled.

In some countries, introducing national-level control for new analogues synthesized by clandestine laboratories is very difficult. Ideally, a combination of national and international control measures should be developed concurrently. WHO should therefore expedite the critical review of substances brought to its attention by governments.

With regard to the scheduling of isomers, the Committee recognized a need for clarification, and agreed that this could be achieved by modifying a qualifying phrase in the proposal of the Spanish Government regarding the substances to be included in Schedule I. The phrase would read as follows (modification underlined):

> "The stereoisomers, except where expressly excluded, of psychotropic substances in this Schedule whenever the existence of such stereoisomers is possible within the specific chemical nomenclature in this Schedule."

This modification renders the proposal chemically precise and consistent with the current interpretation of the Schedules. Thus modified, the proposal would provide explicit clarification of the scope of controlled isomers, including racemates.

With regard to stereoisomers in Schedules II, III and IV, confusion arising from inconsistencies in the present nomenclature should be clarified by means of interpretive guidelines developed by an appropriate international body, such as the International Narcotics Control Board, in collaboration with WHO.

3. Pre-review of psychoactive substances

Pre-review is undertaken by the Committee in order to determine whether a psychoactive substance should be subjected to critical

review in the context of its international control under either the 1961 or the 1971 Convention. The criterion for judging whether critical review is necessary is whether WHO has information that may justify the scheduling of the substance.

3.1 Benzodiazepines

Until 1994, most benzodiazepines were placed in Schedule IV of the 1971 Convention. At its twenty-ninth meeting in 1994, the Committee recommended rescheduling flunitrazepam to Schedule III, and recommended pre-review of alprazolam and diazepam. However, the Committee was of the opinion, as expressed at its thirtieth meeting in 1996, that it would be preferable to consider benzodiazepines as a class. On this basis, it recommended that a pre-review of several representative benzodiazepines (e.g. alprazolam, bromazepam, chlordiazepoxide, diazepam, temazepam), as well as any other benzodiazepines identified by the Secretariat in accordance with certain criteria (i.e. increase in abuse, illicit trafficking or criminal activity involving the benzodiazepine) be conducted at the meeting to be held in 1998.

Recommendation

A review of the literature provides sufficient data to suggest that a few individual benzodiazepines may have a greater abuse liability than other members of the same class. A strong case could be made that flunitrazepam, diazepam and injectable dosage forms of temazepam have greater abuse liabilities than other benzodiazepines. In human studies of subjects with histories of drug abuse, diazepam has been shown to have an abuse liability comparable to that of pentobarbital, which is in Schedule III of the 1971 Convention.

Of the three above-mentioned benzodiazepines, flunitrazepam has already been rescheduled to Schedule III. With respect to temazepam, high abuse liability applies only to its injectable preparation, the availability and abuse of which are geographically limited at present. For this reason, only diazepam meets the criterion for recommending critical review, namely the availability of information that may justify its rescheduling to Schedule III of the 1971 Convention.

In the process of review, the Committee requested that Member States specifically be asked to comment on the impact of the scheduling of benzodiazepines on their use and abuse.

Certain benzodiazepines, such as alprazolam and triazolam, may have greater potential to produce adverse effects than other benzodiazepines. However, information available at present is not sufficient to recommend their critical review.

3.2 Tobacco

3.2.1 *Previous review*

When the Committee pre-reviewed nicotine at its thirtieth meeting in 1996, it did not recommend critical review because, when existing nicotine preparations were used, it was found that blood levels of nicotine did not reach a high enough level to produce the psychotropic effect the 1971 Convention is concerned with, and there was no evidence of significant abuse of such preparations. However, the Committee recommended tobacco for pre-review because of the potential for a higher blood concentration of nicotine when tobacco is smoked, resulting in a greater liability for abuse and associated public health problems.

3.2.2 *International framework convention for tobacco control*

Even though existing Conventions were not appropriate for regulating tobacco, WHO initiated a procedure to develop a framework convention that includes a strategy for Member States to adopt a comprehensive tobacco control policy and to deal with aspects of tobacco control that transcend national boundaries (WHA49.17). This convention is expected to be developed in the near future.

3.2.3 *Summary and recommendation*

Smoking tobacco is dependence-producing, causes serious public health problems and has no therapeutic use. However, judging from the control measures provided for, the scheduling criteria specified and the substances already under control, existing international drug control measures for narcotic drugs and psychotropic substances appear to be unsuitable for controlling tobacco, a dependence-producing natural substance widely used for non-medical purposes at the time of adoption of the relevant conventions. Even though new information indicates health risks greater than those previously known, tobacco would not meet the criteria for scheduling under the existing international drug control treaties. Furthermore, once scheduled, total prohibition would be the only control measure applicable to tobacco, since the regulated supply of controlled substances is not allowed for non-medical and non-scientific purposes.

The international framework convention for tobacco control would appear to achieve the result anticipated by the Committee in 1996 in requesting the pre-review of tobacco. Therefore, a critical review of tobacco was not recommended.

Since the nicotine present in tobacco is a dependence-producing substance, and WHO has considerable experience concerning the

application of the 1961 and 1971 Conventions, the Committee recommended that experts knowledgeable in these areas be invited to participate in the development of the framework convention for tobacco control.

Finally, the Committee requested that a progress report on the framework convention be provided at each of its subsequent meetings until the convention is adopted. In requesting this, the Committee wished to identify its strong interest in this subject and the urgency of controlling dependence-producing substances that affect public health internationally.

3.3 Gamma-hydroxybutyric acid (GHB)

Gamma-hydroxybutyric acid (GHB), the sodium salt of which is known as sodium oxybate, is a metabolite of gamma-aminobutyric acid (GABA) and is naturally found in the human brain. GHB has affinity for at least two binding sites in the brain, a GHB-specific binding site and the $GABA_B$ receptor. There is approximately a thousand-fold greater affinity for GHB at its specific binding site than at the $GABA_B$ receptor. GHB can affect several neurotransmitter systems. It can increase acetylcholine and serotonin levels and decrease norepinephrine concentrations in specific brain areas. GHB can produce opioid-like effects, and although some of its effects are antagonized by naloxone, naloxone does not bind to the GHB-selective binding site nor does GHB bind to the μ-, δ-, or κ-opioid receptors. GHB's effects on the dopaminergic system is complex. Inhibition of dopamine release can occur, resulting in an increase in dopamine concentration in the nerve terminals.

GHB is abused by bodybuilders for its alleged effect as a growth hormone releasing agent, and by young poly-drug abusers ("clubbers" and "ravers") in Europe and the USA, often in combination with amphetamine-type stimulants, for its ability to produce euphoric and hallucinatory states. The extent of GHB abuse in Europe is not well documented but several countries (e.g. France, Sweden, United Kingdom) have reported its abuse. In the USA, approximately 500 incidents involving GHB have been documented through information gathered from law enforcement authorities, poison control centres and hospitals. There have been many cases of overdose attributed to GHB abuse. In addition, 19 cases in which GHB was found in the biological fluids of deceased individuals have been reported.

Recommendation

GHB is used therapeutically for anaesthesia in several countries in Europe and has potential usefulness for the treatment of narcolepsy

and drug abuse disorders. Although GHB enjoyed early favour with health enthusiasts and was sold in health food stores as a safe and "natural" food supplement in the USA, the medical community soon became aware of overdoses and other problems caused by its abuse. GHB produces drowsiness, dizziness, nausea, visual disturbances, unconsciousness, hypotension, bradycardia, seizures, severe respiratory depression and coma, and a withdrawal syndrome has been described following discontinuation of its long-term use. Severe cases of overdose have required emergency medical treatment, including intensive care. GHB is manufactured using a relatively simple synthesis and inexpensive starting materials. Although results from preclinical studies of GHB do not uniformly predict it to have a high abuse liability, abuse of GHB has increased in the USA and has been reported in several European countries as well. A chemical derivative, gamma-butyrolactone (GBL) is also being abused. GHB and GBL have evident abuse liability, which may justify their being scheduled if more information about their abuse can be gathered from other countries. On this basis, the Committee recommended GHB and GBL for critical review.

3.4 4-Bromo-2,5-dimethoxyphenethylamine (2C-B)

4-Bromo-2,5-dimethoxyphenethylamine, also known as 2C-B, is a phenethylamine derivative structurally similar to 4-bromo-2,5-dimethoxy-α-amphetamine (DOB) and 4-methyl-2,5-dimethoxyamphetamine (DOM) and displays a high affinity and selectivity for central serotonin receptors. Radioligand binding assays suggest that 2C-B is a 5-HT_2 receptor agonist with a high affinity but less selectivity than DOB for 5-HT_2 receptors.

Abuse of 2C-B was first reported in the USA in Louisiana in 1978. Over the next several years, incidents involving 2C-B were sporadically reported by law enforcement personnel in Arizona, California, Iowa, Oregon, Pennsylvania and Texas. Clandestine laboratories involved in the manufacture of 2C-B were seized in California (1986 and 1994) and in Arizona (1992). In 1993, the pattern and extent of abuse of 2C-B in the USA changed drastically. Under the name of "Nexus", 2C-B started being supplied in kilogram quantities from a South African source. A sophisticated promotional and distribution campaign was initiated in Florida. Records seized from members of the distribution network indicate that several thousand dosage units (5- and 10-mg tablets and capsules) were distributed to individuals in 23 different states and 67 cities in the USA. Promotional materials provided with the tablets and capsules claimed that the substance was "all natural" and could alleviate impotence, frigidity and diminished libido.

Other countries where incidents involving 2C-B have been reported include Australia, Canada, Germany, Japan, the Republic of Korea and the United Kingdom.

Recommendation

4-Bromo-2,5-dimethoxyphenethylamine (2C-B) is a centrally active hallucinogenic substance. It is structurally and pharmacologically similar to other phenethylamine hallucinogens and has been encountered in several countries. Its ease of clandestine synthesis and its popularity as a purported sexual "enhancer" are likely to encourage the production and abuse of 2C-B. On this basis, critical review of 4-bromo-2,5-dimethoxyphenethylamine (2C-B) was recommended.

3.5 *N*-Methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB)

N-Methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine, also known as MBDB, is a positional isomer of *N*-ethyl-*tenamfetamine*. The psychoactive effects of MBDB have been described as different from those of classic hallucinogens like LSD and as generally similar to the effects of *N*,α-dimethyl-3,4-(methylenedioxy) phenethylamine (MDMA). Preclinical studies using discriminative stimulus techniques suggest that MBDB does not produce LSD-like effects in rats but that both MDMA and tenamfetamine fully substitute for MBDB.

An oral dose of 210mg of MBDB produces intense euphoria and considerable intoxication in humans. Effects develop rapidly, peak about 30 minutes after ingestion and last for 4 to 6 hours. MDMA-like visual effects and stimulant-like activity were judged to be significantly less pronounced than but very similar to those of MDMA.

As a positional isomer of *N*-ethyl-*tenamfetamine*, MBDB is included in Schedule I in the USA. Incidents involving MBDB have also been reported in Austria, Belgium, Denmark, Finland, Germany, Ireland, Italy, Spain, Thailand and the United Kingdom. However, there is no information indicating significant abuse of the substance.

Recommendation

Although there was no information indicating significant abuse of MBDB at present, it is structurally and pharmacologically similar to MDMA and *N*-ethyl-*tenamfetamine*. Incidents involving MBDB have been reported in more than 10 countries in Asia, Europe and the USA. In view of this, there is a likelihood of MBDB being abused so as to produce similar public health problems to those

produced by MDMA. Critical review of MBDB was therefore recommended.

3.6 Zolpidem (INN)

Zolpidem, chemically *N*,*N*,6-trimethyl-2-*p*-tolylimidazo[1,2-α]pyridin-3-acetamide, was pre-reviewed in 1994 at the twenty-ninth meeting of the Committee, at which continued surveillance, but not critical review, was recommended.

Zolpidem is a short-acting hypnotic first licensed for marketing in France in 1988. Zolpidem possesses an imidazopyridine structure and differs from the classic benzodiazepines in terms of its binding profile with respect to benzodiazepine receptors. Like diazepam, zolpidem enhances the function of GABAergic synapses, with an efficacy, however, qualitatively and quantitatively different from that of diazepam, suggesting that zolpidem is a partial agonist at the benzodiazepine recognition site. Zolpidem has greater affinity with ω_1 than ω_2 benzodiazepine receptor sites. The sedative action of zolpidem can be seen at a much lower occupancy rate of benzodiazepine recognition sites than that needed for myorelaxant or anticonvulsant effects. However, a review of the literature comparing zolpidem with triazolam concluded that zolpidem offers no distinct therapeutic advantage over triazolam for the treatment of insomnia.

Early studies in rodents did not demonstrate development of tolerance and withdrawal syndromes upon discontinuation of zolpidem. However, both tolerance and withdrawal syndromes were demonstrated in baboons, as were high levels of self-injection. Like the baboon studies, abuse liability studies in humans did not show a difference between zolpidem and triazolam under experimental conditions. However, several authors wrote that zolpidem, as a selective ω_1 benzodiazepine receptor agonist, posed a smaller risk of tolerance and dependence than benzodiazepines.

Despite such a perception, cases of zolpidem dependence recently began to be reported in the literature. Formerly, withdrawal syndromes, dependence and abuse had not been reported, and zolpidem was thought to be less dependence-producing than benzodiazepines. With increasing clinical use, cases of adverse effects diagnosed as withdrawal syndromes and dependence began to be reported under the national post-marketing surveillance programme in a few countries. By December 1997, Germany had reported 19 cases of dependence and 11 cases of withdrawal syndrome. In response to a questionnaire sent by WHO, Sweden reported nine cases of dependence and Armenia one. Switzerland informed WHO that some cases

of dependence had been reported but not confirmed. A total of 16 other countries reported marketing of zolpidem with no known dependence or abuse.

Recommendation

Although data obtained in studies in rodents suggest that zolpidem would have a lower abuse potential than benzodiazepines, baboon and human studies do not support the existence of a difference in abuse potential between zolpidem and benzodiazepine hypnotics. In general, when findings in animal and human studies are contradictory, greater weight should be given to data obtained in human studies. There have been no reports of illicit activities involving zolpidem. Spontaneous reports obtained through the drug safety monitoring system indicate that a few countries in Europe have experienced cases of adverse effects of zolpidem in clinical use. Although the cases of zolpidem discontinuation syndrome that have been reported to date do not appear to be serious enough to justify its international control, such reports were very few at the time of the last meeting of the Committee in 1996, and have increased in number along with the increasing medical use of zolpidem. The significance of the increases is unknown. It is likely that data addressing this will be available by the time of the 2000 Expert Committee meeting. Critical review of zolpidem was therefore recommended.[1]

3.7 Substances for future review

The Committee recommended that the following substances be subjected to pre-review: amfepramone (diethylpropion), carisoprodol, dronabinol and tramadol. A suggestion was made to consider pre-review of serotonin uptake inhibitors. After a brief discussion, the Committee did not recommend pre-review. At the request of the International Narcotics Control Board, the Committee recommended pre-review of poppy straw.

4. Other issues

4.1 Guideline revision

In an effort to provide timely advice and decisions, the Committee recommended that the guidelines formulated in 1990 be reviewed and

[1] One member, Professor U. Rydberg, expressed reservations about the usefulness of critical review of zolpidem. In his view, the drug is very effective as a hypnotic and few, if any, severe adverse effects have been reported. Additionally, illicit activity is unknown, and disadvantages of conducting the review may outweigh advantages.

modified so as to provide the Expert Committee greater latitude for proceeding expeditiously and efficiently from substance identification to critical review and scheduling recommendations. This recommendation is made particularly with reference to clandestinely manufactured substances and substances of especially serious risk to public health and society and of no recognized therapeutic utility. Psychiatric and clinical data, wherever relevant, must be collected with the same care as chemical and pharmacological data.

4.2 Substance nomenclature

The Committee has from time to time identified inconsistencies in substance nomenclature as reflected in the Schedules of the 1971 Convention. A question of possible confusion between acronyms used to designate substances in Schedule I of the 1971 Convention was raised in the discussion of the nomenclature of substances under control. It was noted that this latter issue had been raised by the International Conference on Drug Abuse and Illicit Trafficking held in 1987 (*6*). The lack of clarity arising from these two matters has led to conflicting interpretations of the Schedules and to varying degrees of precision in designating psychotropic substances for scheduling. To rectify this situation, the Committee recommended review of the nomenclature of all substances in the 1971 Convention by the appropriate international bodies. Such a review should take into account similar inconsistencies in the 1961 and 1988 Conventions.

Acknowledgements

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The Committee also wished to thank Dr G. Feussner, United States Drug Enforcement Administration, Arlington, VA, USA, for her contribution to the preparation of the working documents for the meeting.

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Annex

Letter addressed to the United Nations Secretary-General communicating the proposal of the Government of Spain[1]

Sir,

Recent years have witnessed an alarming phenomenon in the field of production, trafficking and illicit use of drugs, namely the sudden spread of synthetic drugs.

This phenomenon, which affects a large number of countries and has international ramifications, is developing extensively, so much so that prevention mechanisms need to be urgently created within the framework of international law in order to forestall its further spread.

Synthetic drugs are easy to produce. It is sufficient to modify the chemical structure of an amphetamine-type stimulant in order to obtain the new final product, which is then introduced into the illicit drug market, predominantly among young people. It is chemically possible to obtain a large number of modified structures in which the basic composition of the amphetamine is maintained unchanged.

Although some derivatives are subject to control under the United Nations Convention on Psychotropic Substances of 1971 (for example, MDMA, MDA, MDE and DOB), others are still not subject to such control (for example, MBDB).[2]

It is the view of Spain that, as a matter of urgency, the 1971 Convention should generate mechanisms to prevent the appearance of new psychotropic substances.

It has been noted that the individual inclusion of substances in the Schedules is a slow process which does not prevent new substances being created on the basis of similar chemical compounds.

The Government of Spain considers that it would be advisable to open up discussion on the control of synthetic drugs through the Convention's Schedules with the aim of achieving tighter control over the production and traffic of this type of substance.

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[1] The text reproduced here is a translation of the proposal of the Government of Spain.

[2] MDMA = *N*,α-dimethyl-3,4-(methylenedioxy)phenethylamine.
MDA = tenanfetamine.
MDE = *N*-ethyl-α-methyl-3,4-(methylenedioxy)phenethylamine.
DOB = 4-bromo-2,5-dimethoxy-α-methylphenethylamine.
MBDB = *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine.

Consequently, convinced of the need to open up the system of Schedules to all psychotropic substances liable to engender a serious problem of addiction, the Government of Spain seeks, by means of the text given below, the addition to Schedules I and II of the 1971 Convention of the chemical compositions of the isomers, salts, esters and ethers of the psychotropic substances, as well as any modified chemical compounds producing effects similar to those produced by the original substance:

> "The isomers, except where expressly excluded, of psychotropic substances listed in this Schedule whenever the existence of such isomers is possible within the specific chemical nomenclature in this Schedule;
>
> The esters and ethers of psychotropic substances listed in this Schedule, except where included in a different Schedule, whenever the existence of such esters or ethers is possible;
>
> The salts of psychotropic substances listed in this Schedule, including the salts of esters, ethers and isomers under the conditions stated above, whenever the formation of such salts is possible;
>
> Any other modified chemical compound which produces effects on the organism similar to those produced by the original controlled substance".

In addition to the arguments put forward above, I should like to make a number of further points in support of this proposal:

1. It would mean the acquisition of a legal instrument which would reinforce action against drug organizations and traffickers by preventing them from evading the controls on existing substances by creating altered forms of those substances with similar effects.

2. Courts of justice would be furnished with the scientific and legal foundations they require to make an effective judicial response to the new amphetamine-type stimulants being introduced into the market.

3. The use would be averted of conflicting criteria for action by Governments in their campaigns directed at prevention, treatment and law enforcement in relation to the new synthetic drugs.

4. The health systems of the United Nations Member States would be provided with a legal response enabling them to formulate specific treatment strategies with respect to the use of synthetic drugs appearing in future.

5. This proposed text would forestall the possibility of illicit substances being processed by illicit drug trafficking organizations in such a way that the chemical substance obtained produces the same effects as those sought but through a slight chemical alteration of the molecular structure or through the use of optical, positional or other isomers.

By means of this text, as provided for in article 2 of the United Nations Convention on Psychotropic Substances of 1971, the Government of Spain seeks to set in motion the process of amending Schedules I and II through the inclusion of this proposal.

I look forward to receiving your reply and remain,

Yours sincerely,
(Signed) Gonzalo Robles Orozco

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