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Contents

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Geneva, 26–29 September 1994

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1. Introduction

The WHO Expert Committee on Drug Dependence met in Geneva from 26 to 29 September 1994. The meeting was opened on behalf of the Director-General by Mr H. Emblad, Director, Programme on Substance Abuse, who emphasized the significant role the Committee has played in the international drug control system since its first meeting in 1949. The Committee is the WHO body responsible for assessing psychoactive substances and for making recommendations for their international control status. The Director-General then can, on behalf of WHO, convey these scheduling recommendations to the Secretary-General of the United Nations for action by the United Nations Commission on Narcotic Drugs. Mr Emblad noted that both the Single Convention on Narcotic Drugs, 1961, and the Convention on Psychotropic Substances, 1971, acknowledged and utilized WHO's technical expertise.

Mr Emblad further explained that, according to the mandate of the United Nations Commission on Narcotic Drugs, WHO's assessment of psychotropic substances ought to be considered determinative regarding medical and scientific matters, although the Commission can reject or, under the 1971 Convention, alter WHO's scheduling recommendations on the basis of other considerations. Since most of the Committee's recommendations have been accepted by the United Nations Commission on Narcotic Drugs, the Committee plays an important role. Mr Emblad finally stressed the need for the Committee to recognize its authority and responsibility in reviewing each substance on the agenda.

2. Review of psychoactive substances

2.1 Scheduling criteria

In making scheduling recommendations, the Committee is guided by the relevant drug control conventions as well as the guidelines adopted by the Executive Board of WHO in January 1990 (*1*). In the past, there has been some difficulty in applying the scheduling criteria presented in the guidelines, particularly those for psychotropic substances.

According to the 1971 Convention on Psychotropic Substances, the Committee should determine whether the substance has the capacity to produce "a state of dependence, and central nervous system stimulation or depression, resulting in hallucinations or disturbances in motor function or thinking or behaviour or perception or mood"; or the substance has the capacity to produce "similar abuse and similar ill effects as a substance in Schedule I, II, III or IV" of the Convention. It is then necessary to determine whether "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".

In addition, the guidelines present specific criteria for selecting a particular schedule:

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.

The above criteria were first developed at the seventeenth meeting (*2*) of the Expert Committee on Drug Dependence in 1969 in classifying psychotropic substances that were proposed for inclusion in the original schedules of the Convention on Psychotropic Substances, 1971. The United Nations *Commentary on the Convention on Psychotropic Substances* (*3*) also refers to these criteria.

The 1969 criteria, however, do not specifically cover the following possible cases:

- substances whose liability to abuse constitutes an especially serious risk to public health and which have little to moderate therapeutic usefulness;
- substances whose liability to abuse constitutes an especially serious risk to public health and which have moderate to great therapeutic usefulness;
- substances whose liability to abuse constitutes a substantial risk to public health and which have very limited, if any, therapeutic usefulness; and
- substances whose liability to abuse constitutes a smaller but still significant risk to public health and which have very limited, if any, therapeutic usefulness.

In order to fill these gaps, the Committee at its present meeting agreed on the following supplementary working 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.

Furthermore, the Committee noted that the 1969 criteria do not specifically address the dimension of social problems, although the 1971 Convention does. The Committee therefore agreed that the "risk to public health" in the above criteria should be interpreted to mean both social and public health problems.

2.2 Aminorex (INN)

Substance identification

Aminorex (CAS 2207-50-3), chemically 2-amino-5-phenyl-2-oxazoline, is also known as aminoxaphen and aminoxafen; aminorex fumarate was formerly marketed as Apiquel and Menocil. Aminorex has an asymmetric carbon atom, so two stereoisomeric forms and one racemate are possible.

Previous review

In 1969, the 17th meeting (2) of the Committee recommended aminorex for international control in a group which is equivalent to Schedule IV of the Convention on Psychotropic Substances, 1971. However, aminorex was not included in the original list of controlled substances when the 1971 Convention was adopted. In 1992, the 28th meeting of the Committee recommended critical review of aminorex.

Similarity to known substances and effects on the central nervous system

Aminorex is chemically similar to 4-methyl*aminorex,*[1] which has been classified in Schedule I of the Convention on Psychotropic Substances, 1971. Aminorex produces the characteristic effects of central nervous system stimulants like amfetamine, and has been used clinically for its anorectic effects. Its adverse effects are also similar to those produced by central nervous system stimulants. When used as an anoretic, however, aminorex is considered to have been responsible for a significant incidence of pulmonary hypertension. This led to its withdrawal from the market in 1968.

Dependence potential

In drug discrimination studies, aminorex generalizes to amfetamine and cocaine. Animal self-administration studies indicate that aminorex has some reinforcing effects and suggest that it has a moderate dependence potential.

Actual abuse and/or evidence of likelihood of abuse

Police and forensic reports indicate that aminorex is illicitly distributed in the USA as well as in Germany to a limited degree. Such reports

[1] In composite drug names containing both chemical prefixes and INNs, the INN is distinguished by being italicized.

document its distribution as amfetamine or metamfetamine, which suggests that the population using aminorex is primarily composed of stimulant abusers. In spite of the limited level of actual abuse, aminorex is assessed to have a moderate abuse liability in view of the simplicity of its manufacture in clandestine laboratories.

Therapeutic usefulness

Because of its serious adverse effects, aminorex is assessed to have very little, if any, therapeutic usefulness.

Recommendation

On the basis of the available data concerning its pharmacological and toxicological profile, dependence potential and likelihood of abuse, the public health and social problems associated with the abuse of aminorex are assessed to be significant. On the basis of this and the assessment of its therapeutic usefulness, it is recommended that aminorex be placed in Schedule IV of the Convention on Psychotropic Substances, 1971.

2.3 Brotizolam (INN)

Substance identification

Brotizolam (CAS 57801-81-7), chemically 2-bromo-4-(*o*-chlorophenyl)-9-methyl-6*H*-thieno[3,2-*f*]-*s*-triazolo[4,3-*a*][1,4]diazepine, is also known as Ladormin, Lendorm, Lendormin, Lindormin, Noctilan, Dormex and Sintonal.

Previous review

Brotizolam was reviewed by the 26th (*4*) and 27th (*5*) meetings of the Committee in 1989 and 1990, respectively. It was not recommended for international control because of the absence of evidence concerning its abuse at those times. In 1992, the 28th meeting (*6*) of the Committee recommended brotizolam for critical review.

Similarity to known substances and effects on the central nervous system

Brotizolam produces the typical pharmacological effects of benzodiazepines and binds with high affinity to benzodiazepine receptors. A number of studies have demonstrated that brotizolam is a short-acting hypnotic with a mean elimination half-life of 4–5 hours.

Dependence potential

Animal studies show that brotizolam has barbiturate-type effects. It produces mild-to-severe withdrawal symptoms similar to those of alcohol or barbiturates and has some reinforcing effects. The few clinical studies available demonstrate the occurrence of rebound insomnia upon withdrawal of the drug. These findings indicate that brotizolam has a moderate dependence potential similar to other benzodiazepine hypnotics.

Actual abuse and/or evidence of likelihood of abuse

In spite of its pharmacological similarity to other benzodiazepine hypnotics, and its marketing in 18 countries, abuse of brotizolam has been reported only in Germany and Hong Kong. Although there has been some abuse and illicit activity involving brotizolam in Germany, these were not considered serious enough by the German authorities to subject the drug to the additional restrictions which are applicable to controlled substances.

Following its introduction to Hong Kong in 1988, the abuse of brotizolam increased rapidly among young people there, leading to the application of stricter control measures in 1990. The company marketing brotizolam withdrew it from Hong Kong in 1992.

On the basis of the experiences of Germany and Hong Kong, it is assessed that brotizolam has an appreciable abuse liability. The problem may be more acute in situations where prescription requirements are not effectively implemented or are not applicable.

Therapeutic usefulness

Brotizolam is marketed as a hypnotic in 18 countries and is assessed to have a moderate to great therapeutic usefulness.

Recommendation

On the basis of the available data concerning its pharmacological and toxicological profile, dependence potential and likelihood of abuse, the public health and social problems associated with the abuse of brotizolam are assessed to be significant in cases where prescription requirements are not effectively implemented or are not applicable, a situation which exists in many developing countries. On the basis of this and the assessment of its therapeutic usefulness, it is recommended that brotizolam be placed in Schedule IV of the Convention on Psychotropic Substances, 1971.

2.4 Etryptamine (INN)

Substance identification

Etryptamine (CAS 2235-90-7), chemically 3-(2-aminobutyl)indole, is also known as α-ethyltryptamine and Monase. Etryptamine has a single chiral centre, so two stereoisomeric forms and one racemate are possible.

Previous review

In 1992, the 28th meeting (*6*) of the Committee recommended that etryptamine be critically reviewed.

Similarity to known substances and effects on the central nervous system

Chemically, etryptamine is similar to the hallucinogenic tryptamines, some of which are already listed in Schedule I of the 1971 Convention. Animal studies indicate that etryptamine produces effects similar to those

produced by 3,4-methylenedioxy*metamfetamine* (MDMA), but its hallucinogenic effects are more pronounced than its stimulant effects. Like amfetamine, etryptamine increases locomotor activity in rodents. In a study using the method of behavioural pattern monitoring, etryptamine significantly decreased investigatory behaviour, which is typical of hallucinogens and MDMA-like substances. The stimulant effects of etryptamine are slower in onset and more prolonged than those of amfetamine.

In the early 1960s, etryptamine acetate was placed on the United States market as an antidepressant. Soon after its release, it was reported that etryptamine was associated with a high incidence of agranulocytosis, a potentially fatal condition. More recently, there are isolated reports of etryptamine being associated with the deaths of drug abusers in Germany, Spain and the United States.

Dependence potential

Drug discrimination studies in animals indicate that etryptamine produces effects resembling MDMA. Self-administration studies indicate that etryptamine has a moderate dependence potential lower than that of cocaine.

Actual abuse and/or evidence of likelihood of abuse

Information from various sources indicates that there has been abuse of etryptamine in Germany, Spain and the United States. Etryptamine is assessed to have a high abuse liability.

Therapeutic usefulness

In view of its association with serious adverse reactions such as agranulocytosis, the therapeutic usefulness of etryptamine is assessed to be very limited, if any.

Recommendation

On the basis of the available data concerning its pharmacological and toxicological profile, dependence potential and likelihood of abuse, the public health and social problems associated with the abuse of etryptamine are assessed to be especially serious. On the basis of this and the assessment of its therapeutic usefulness, it is recommended that etryptamine be placed in Schedule I of the Convention on Psychotropic Substances, 1971.

2.5 Flunitrazepam (INN)

Substance identification

Flunitrazepam (CAS 1622-62-4), chemically 5-(*o*-fluorophenyl)-1,3-dihydro-1-methyl-7-nitro-2*H*-1,4-benzodiazepin-2-one, is also known as Absint, Darkene, Fluninoc, Flunipam, Flunita, Flunitrazepam-ratiopharm, Hypnodorm, Hypnosedon, Inervon, Narcozep, Parnox, Primum, Rohipnol, Rohypnol, Roipnol and Valsera.

Previous review

In 1984, flunitrazepam was included in Schedule IV of the Convention on Psychotropic Substances, 1971, together with a number of other benzodiazepines. In 1990, the 27th meeting (*5*) of the Committee compared 37 benzodiazepines and recommended that this drug should be kept under surveillance to determine whether it merited being placed under critical review for possible rescheduling. In 1992, the 28th meeting (*6*) of the Committee noted that the number of reports of illicit activities associated with flunitrazepam was higher than for any other benzodiazepine and recommended flunitrazepam for critical review.

Similarity to known substances and effects on the central nervous system

Flunitrazepam has typical benzodiazepine effects, with a greater sedative-hypnotic potency than diazepam or chlordiazepoxide. Flunitrazepam binds with high affinity to central benzodiazepine receptors and is rapidly absorbed after oral administration. The elimination half-life of flunitrazepam following a single oral dose ranges between 9 and 25 hours in humans. Accumulation occurs with chronic administration.

Dependence potential

Drug discrimination, drug withdrawal and self-administration studies indicate that flunitrazepam has a dependence potential similar to other benzodiazepines. Rebound insomnia, considered a form of withdrawal from sedative-hypnotics, may contribute to a tendency to continue the medication. These data do not suggest any substantive difference between flunitrazepam and other benzodiazepine hypnotics. Drug preference studies in opioid users, however, have shown that flunitrazepam and diazepam stand out from other benzodiazepines by producing a strong positive reinforcing effect in these subjects. Therefore, flunitrazepam is estimated to have a moderate abuse potential which may be higher than that of other benzodiazepines. The rapid onset and longer duration of action, coupled with the stronger sedative-hypnotic effects, may contribute to its higher abuse potential.

Actual abuse and/or evidence of likelihood of abuse

Available information indicates that the non-medical use or abuse of flunitrazepam is widespread among drug abusers, particularly opioid and cocaine abusers. Flunitrazepam is reported to be the most widely abused benzodiazepine by opioid abusers in many large cities in Europe, Asia and Oceania. Flunitrazepam abuse is reported even in the United States, where the drug is not marketed for therapeutic use.

Reported reasons for the abuse of flunitrazepam include potentiation of opioid effects, substitution for the opioid when it is difficult to obtain and self-medication for opioid withdrawal. Oral intake is the most common route of administration of flunitrazepam, but some abusers take the drug by intravenous injection or by "snorting". Health problems associated with the abuse of flunitrazepam include deaths directly or indirectly

related to its use, drug dependence, withdrawal syndrome, paranoia, amnesia and other psychiatric disorders.

Information on the extent of the association of 37 benzodiazepines with illicit activities during the period 1984-1989, available to the 27th meeting of the Committee in 1990, indicated a higher incidence of association with illicit activities for both diazepam and flunitrazepam than for other benzodiazepines. At that time, however, the data were not evaluated in relation to drug availability. After an adjustment for the amounts manufactured and for potency, although diazepam is no longer outstanding, flunitrazepam further stands out with respect to both seizures of the drug and the number of cases involving it.

Information on drug involvement in illicit activities after 1990, received from governments in response to the WHO questionnaire in 1994, is limited and does not allow comparison between a large number of benzodiazepines. None the less, a recent report from Interpol and an increasing use-trend in the United States, despite a lack of licit supplies in that country, together with several recent reports showing flunitrazepam as the main non-opioid drug abused by opioid abusers in major European cities, further substantiate the high abuse liability of flunitrazepam.

Therapeutic usefulness

Flunitrazepam is useful for the treatment of insomnia. It is also indicated as a pre-anaesthetic medication to assist in the induction and maintenance of anaesthesia. Flunitrazepam has a therapeutic usefulness similar to other benzodiazepine hypnotics, i.e. from moderate to great.

Recommendation

Flunitrazepam has a greater likelihood of abuse than other benzodiazepines. Although part of the reason for the abuse of flunitrazepam is self-medication for opioid withdrawal, the abuse of flunitrazepam by opioid abusers complicates its abuse profile, as it implies multiple drug dependence. Its abuse is also prevalent among youths and cocaine abusers. In addition to oral and intravenous use, abuse by "snorting" has recently been reported and as yet, no other benzodiazepine has been reported as being abused by three different routes of administration. Flunitrazepam abuse has been associated with various behavioural problems. Illicit activities involving flunitrazepam are increasing even in the United States, where it is available despite the lack of legal distribution channels.

On the basis of the available data concerning its pharmacological and toxicological profile, dependence potential and likelihood of abuse, and particularly in view of the above characteristics, the public health and social problems associated with the abuse of flunitrazepam are assessed to have become substantial. On the basis of this and the assessment of its therapeutic usefulness, it is recommended that flunitrazepam be moved

from Schedule IV to Schedule III of the Convention on Psychotropic Substances, 1971.

2.6 Mesocarb (INN)

Substance identification

Mesocarb (CAS 34262-84-5), chemically 3-(α-methylphenethyl)-*N*-(phenylcarbamoyl)sydnone imine, is also known as Pharmanocarb, Sidnocarb and Sydnocarb. Mesocarb has one asymmetric carbon atom, so two stereoisomeric forms and one racemate are possible.

Previous review

In 1992, the 28th meeting (*6*) of the Committee recommended a critical review of mesocarb if positive results were obtained from dependence studies which had been arranged. These test results were made available, and the Committee decided to conduct a critical review.

Similarity to known substances and effects on the central nervous system

Chemically, mesocarb is a sydnone imine having an amfetamine-like moiety in its molecule. Of the two stereoisomers of mesocarb, only the laevorotatory isomer exerts a stimulant effect on the central nervous system, which is significantly weaker than that of dexamfetamine. Mesocarb produces locomotor stimulation, anorectic activity, enhancement of conditioned reflexes, and shortening of the period of action of hypnotic agents. Mesocarb has been reported to increase work capacity and improve cardiovascular function without requiring above-normal oxygen consumption. Its adverse reactions are similar to those of other central nervous system stimulants. Several studies in humans have shown that mesocarb increases resistance to environmental stresses, such as cold temperature, low gravity and low oxygen levels. In addition, there are several pharmacological studies in animals of mesocarb used in combination with other substances, such as a mesocarb–acetylsalicylic acid combination.

Dependence potential

Drug discrimination studies in animals indicate that mesocarb generalizes to central nervous system stimulants such as dexamfetamine and cocaine. It also has some reinforcing effects in monkeys, suggesting a low to moderate dependence potential.

Actual abuse and/or evidence of likelihood of abuse

There is some evidence to indicate that mesocarb is abused in sports, and its use has been banned by the International Olympic Committee.

Information from the International Narcotics Control Board (INCB) indicates that large quantities of a pharmaceutical preparation containing mesocarb and acetylsalicylic acid have been illegally exported to West Africa, though this has been reportedly discontinued. Although

epidemiological data are not available, it is believed that most if not all of the exported combination product was abused. On the basis of available information, mesocarb is assessed to have an appreciable abuse liability.

Therapeutic usefulness

Mesocarb is used in several countries, mainly in eastern Europe, as a stimulant to counteract acute intoxication by depressants, for the treatment of hyperactivity and nocturnal enuresis in children and as an "energizer" to enhance resistance to environmental stress. The therapeutic usefulness of mesocarb is estimated to be between little and moderate.

Recommendation

Although no epidemiological data are available on health problems associated with the abuse of mesocarb, there is evidence that mesocarb is abused in sports, and illicit activities involving mesocarb have been reported. On the basis of this and the available data concerning its pharmacological and toxicological profile, dependence potential and likelihood of abuse, the public health and social problems associated with the abuse of mesocarb are assessed to be significant. On the basis of this and the assessment of its therapeutic usefulness, it is recommended that mesocarb be placed in Schedule IV of the Convention on Psychotropic Substances, 1971.

2.7 Meth*cathinone*

Substance identification

Meth*cathinone* (CAS 5650-44-2), chemically 2-(methylamino)-1-phenyl-propan-1-one, is also known as ephedrone and methyl*cathinone*. It has one chiral centre, so two stereoisomeric forms and one racemate are possible.

Previous review

In 1992, the 28th meeting (*6*) of the Committee, after a review of preliminary data, did not recommend meth*cathinone* for critical review. In 1994, however, the Secretary-General of the United Nations forwarded to the Director-General of WHO the notification of the Government of the United States proposing that meth*cathinone* be placed under international control.

Similarity to known substances and effects on the central nervous system

Meth*cathinone* is the *N*-methyl derivative of cathinone, and is closely related to metamfetamine. Animal studies have shown that meth-*cathinone* produces central nervous system stimulant effects similar to those produced by amfetamine, metamfetamine, cathinone and cocaine. Of the two stereoisomers, the laevorotatory form is more biologically active.

Dependence potential

Drug discrimination and self-administration studies in animals indicate that meth*cathinone* has a dependence potential similar to central nervous system stimulants like amfetamine and cocaine. Case reports and a study conducted in the United States on meth*cathinone* abusers also suggest that meth*cathinone* has a high dependence potential similar to that of metamfetamine.

Actual abuse and/or evidence of likelihood of abuse

Significant abuse of meth*cathinone* has been reported in Estonia, Latvia, the Russian Federation and some other countries of the Commonwealth of Independent States as well as in the United States. Meth*cathinone* is readily manufactured from ephedrine by oxidation and is assessed to have a high abuse liability.

Therapeutic usefulness

Meth*cathinone* has not been marketed for therapeutic purposes. Its therapeutic usefulness is assessed to be very limited, if any.

Recommendation

Studies from the Russian Federation and the United States have confirmed that meth*cathinone* abuse results in adverse health effects similar to those associated with the abuse of metamfetamine, including fatal cases of acute intoxication. Illicit activities involving meth*cathinone*, including clandestine manufacturing, are also reported widely.

On the basis of the available data concerning its pharmacological and toxicological profile, dependence potential and likelihood of abuse, and particularly in view of the above characteristics, the public health and social problems associated with the abuse of meth*cathinone* are assessed to be especially serious. On the basis of this and the assessment of its therapeutic usefulness, it is recommended that meth*cathinone* be placed in Schedule I of the Convention on Psychotropic Substances, 1971.

2.8 Zipeprol (INN)

Substance identification

Zipeprol (CAS 34758-83-3), chemically α-(α-methoxybenzyl)-4-(β-methoxyphenethyl)-1-piperazineethanol, is also known as Antituxil-Z, Cerm-3024, Chilvax, Delaviral, Dovavixin, Jactus, Eritos, Mirsol, Ogyline, Respilene, Respirase, Respirex, Sanotus, Santus, Silentos, Sousibim, Talasa, Tusigen, Tussiflex and Zitoxil. Zipeprol has three asymmetric carbon atoms, so eight stereoisomeric forms are possible.

Previous review

Zipeprol was pre-reviewed by the 28th meeting (*6*) of the Committee in 1992, which recommended it for critical review.

Similarity to known substances and effects on the central nervous system
In laboratory animals, zipeprol has been shown to have an antitussive activity weaker than codeine and comparable to dextromethorphan. Its pharmacological properties are different from those of opioid antitussives, such as codeine, in that zipeprol has anticholinergic activities. It also does not produce respiratory depression, bile duct constriction or constipation, which are often associated with narcotic antitussives. Unlike opioids, zipeprol is essentially devoid of analgesic activity, but at high doses, zipeprol acts as a weak opioid agonist. Also, unlike opioids zipeprol shows a bi-phasic effect in competing for binding sites in rat brain homogenates.

Dependence potential
In rats, low doses of zipeprol amplify some opioid withdrawal manifestations whereas high doses suppress some symptoms. Zipeprol is assessed to have a moderate dependence potential.

Actual abuse and/or evidence of likelihood of abuse
There have been a number of reports on the abuse of zipeprol from Brazil, Chile, France, Italy, Mexico, the Republic of Korea, Switzerland and the former Yugoslavia. These reports suggest that its sedative, hallucinatory and euphorigenic effects, and its ability to suppress some signs of opioid withdrawal at high doses, may be the reasons for its abuse. Over-the-counter distribution of zipeprol preparations may have contributed to its widespread abuse in some places. In view of this, zipeprol is assessed to have a moderate abuse liability.

Adverse health consequences of zipeprol abuse include seizures, hallucinations, confusion and amnesia. Dose escalation is not uncommon, and fatal cases from acute intoxication have been reported from several countries. The tablet form of zipeprol has been used for intravenous administration.

Therapeutic usefulness
A number of clinical studies have demonstrated the therapeutic efficacy of zipeprol for the treatment of cough. The therapeutic usefulness of zipeprol is assessed to be between little and moderate.

Recommendation
Although zipeprol is a weak opioid agonist at high doses, its toxicity, hallucinogenic and other psychotropic effects constitute a significant element in its abuse. It is therefore appropriate to consider its control under the Convention on Psychotropic Substances, 1971. On the basis of the available data concerning its pharmacological and toxicological profile, dependence potential and likelihood of abuse, the public health and social problems associated with the abuse of zipeprol are assessed to be substantial. On the basis of this and the assessment of its therapeutic usefulness, it is recommended that zipeprol be placed in Schedule II of the Convention on Psychotropic Substances, 1971.

2.9 Triazolam (INN)

In 1984, triazolam was included in Schedule IV of the Convention on Psychotropic Substances, 1971, together with a number of other benzodiazepines. The 27th meeting (*5*) of the Committee reviewed 37 benzodiazepines in 1990 and found that triazolam was appropriately controlled in Schedule IV. However, the 28th (*6*) meeting of the Committee recommended in 1992 that a critical review should be undertaken if there was any indication that triazolam had a lower therapeutic usefulness than previously considered.

The Expert Committee decided to conduct such a critical review of triazolam in view of the fact that a downward assessment of triazolam's therapeutic usefulness at higher doses has resulted in the lowering of the recommended dose for triazolam in many countries.

The information currently available supports the previous assessment that triazolam has an intermediate abuse liability relative to other benzodiazepine agonists. This limited information does not suggest that the risk to public health and society due to the abuse of triazolam is greater than that assessed in 1990.

No rescheduling recommendation is therefore required since, according to the scheduling criteria, a change in the assessment of therapeutic usefulness alone does not provide a basis for rescheduling a substance in Schedule IV of the Convention on Psychotropic Substances, 1971. However, the Committee considers it useful to continue the monitoring of abuse-related adverse drug reactions and behavioural problems associated with triazolam. Continued vigilance is also recommended with regard to illicit activities involving the drug. The Expert Committee recommends that WHO bring to the attention of appropriate international agencies the association of triazolam with criminal activities.

3. Pre-review of psychoactive substances

Pre-review is performed by the Committee in order to determine whether a psychoactive substance should be subjected to critical review in the context of its international control.

3.1 Trihexyphenidyl (INN)

Chemical name: α-cyclohexyl-α-phenyl-1-piperidinepropanol.

Previous review
Trihexyphenidyl has not been reviewed by the Expert Committee.

Conclusion
Trihexyphenidyl is an anticholinergic agent used in the treatment of parkinsonism and the extrapyramidal side-effects of neuroleptics. In

animal tests, it is not reinforcing. In humans, it has hallucinogenic effects. Although there are a number of reports of abuse of trihexyphenidyl, the tendency for the abuser to repeat its use is limited because of its unpleasant anticholinergic effects. The Committee does not recommend trihexyphenidyl for critical review at this time.

3.2 Zolpidem (INN)

Chemical name: *N,N*,6-trimethyl-2-*p*-tolylimidazo[1,2-*a*]pyridine-3-acetamide.

Previous review

Zolpidem has not been reviewed by the Expert Committee.

Conclusion

Zolpidem is chemically a non-benzodiazepine hypnotic. However, it is a ligand that binds specifically to the ω_1 benzodiazepine receptor. Zolpidem is reported to be a short-acting hypnotic which does not significantly alter natural sleep characteristics. It has been reported that, at equipotent hypnotic doses, zolpidem has fewer disturbing effects on memory than triazolam. Zolpidem has been on the market for only a relatively short period of time, and its liability for abuse appears to be minimal on the basis of available reports. The Committee does not recommend zolpidem for critical review at this time but suggests that surveillance should be continued.

3.3 Zopiclone (INN)

Chemical name: 4-methyl-1-piperazinecarboxylic acid ester with 6-(5-chloro-2-pyridyl)-6,7-dihydro-7-hydroxy-5*H*-pyrrolo[3,4-*b*]pyrazin-5-one.

Previous review

Zopiclone was pre-reviewed in 1988 but was not recommended for critical review.

Conclusion

Zopiclone is a hypnotic that is chemically different from, but pharmacologically similar to, benzodiazepines. It binds to central but not to peripheral benzodiazepine receptors. Zopiclone is currently marketed in 40 countries. Since its introduction in 1987, 1.6 billion dosage units have reportedly been manufactured. The dependence potential of zopiclone may be comparable to benzodiazepines. It is, however, not possible to consider its liability for abuse as significant, since there are very few reports of actual abuse of the drug at present. The Committee does not recommend zopiclone for critical review at this time but suggests that surveillance of it should be continued.

3.4 Substances for pre-review

The Committee recommends that alprazolam, diazepam and ephedrine be considered for pre-review at a future meeting.

Since nicotine's various medicinal formulations (chewing gum, patches, nasal sprays) are being used internationally in smoking cessation programmes, the Committee felt that these preparations should also be considered for pre-review.

4. International drug control system

In response to resolution 48/12 of the General Assembly (*7*), the United Nations has initiated measures to review the international control system for narcotic drugs and psychotropic substances. It was therefore considered opportune for the Committee to address some related issues.

4.1 Distribution control and reporting obligations

The drug conventions exist, in part, to ensure the availability of drugs for medical and scientific purposes. However, it is observed that in emergency situations, the operation of these conventions causes delays in making drugs available for medical care. It has therefore become necessary to evolve rational measures to alleviate the difficulties encountered in procuring and making available controlled drugs in emergency or disaster situations. The Expert Committee believes WHO should bring this matter to the attention of the United Nations Commission on Narcotic Drugs. It is the judgement of the Expert Committee that the benefits of the implementation of a simplified procedure in such instances would more than outweigh the limited harm that could be caused.

The Committee recognizes that accurate reporting by national authorities would enhance the work of INCB. However, many national authorities are presently unable to respond accurately to the INCB questionnaires for a variety of reasons. The Committee therefore suggests that consideration should be given to a different periodicity of reporting and to the simplification of procedures, paperwork and the kinds of information to be supplied by national authorities to INCB. Such measures may encourage fuller compliance by national authorities with the conventions.

4.2 Treatment and rehabilitation

Strategies for combating drug abuse and illicit drug traffic would ideally involve developing treatment and rehabilitation programmes as a major component of a comprehensive demand reduction strategy. The Committee believes they would also involve the collaboration and cooperation of national governments and the joint efforts of the international and intergovernmental organizations with relevant expertise

in this field. Further, the mandate of WHO on matters of international health confers upon it a leadership role in assisting national governments that lack experience and expertise in the treatment and rehabilitation of drug-dependent persons. Therefore, the Committee believes it will be desirable for WHO to initiate the development of guidelines for the treatment and rehabilitation of drug-dependent persons, as a form of assistance to national health authorities.

4.3 Principles of demand reduction

The Committee also recognizes that unless there is a balanced emphasis on both supply and demand reduction by national governments and relevant international organizations, success in combating drug abuse and illicit drug traffic will be elusive. The international drug conventions exist to help national governments and international organizations in their efforts to minimize the risk of drug abuse and illicit traffic. Although these conventions appear to address adequately the diversion of licit drugs to illicit supply and trafficking, they give less attention to demand reduction, and the imbalance in these conventions ought to be addressed. It may therefore be desirable for WHO to emphasize this understanding to the United Nations Commission on Narcotic Drugs, as there seems to be a need to strengthen and expand the provisions of the conventions dealing with drug demand reduction. Such enhanced provisions may also foster greater long-term commitment by national governments to the reduction of both supply and demand for illicit drugs.

The Committee therefore recommends that the World Health Organization:

1. Initiate the development of guidelines for the treatment and rehabilitation of drug-dependent persons.
2. Bring to the attention of the United Nations:
   (a) the imbalance in the drug conventions, which do not pay significant attention to drug demand reduction;
   (b) the desirability of developing a simplified procedure for making controlled drugs available in emergency or disaster situations; and
   (c) the fuller compliance by national authorities that a simplification of the reporting requirements to the INCB might achieve.
3. In the context of its responsibility for international health matters, bring to the attention of Member States resolution 48/12 of the United Nations General Assembly.

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