



WHO Technical Report Series

915

WHO EXPERT COMMITTEE ON DRUG DEPENDENCE

Thirty-third Report



World Health Organization

Geneva



This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization

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Geneva, 17–20 September 2002

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1. Introduction

The WHO Expert Committee on Drug Dependence met in Geneva from 17 to 20 September 2002. The meeting was opened by Dr L. Rågo, Coordinator, Quality Assurance and Safety: Medicines, who emphasized the significant role this Committee has played in the implementation of the international drug control system based on the existing drug control conventions. As a specialized agency of the United Nations system, WHO is responsible for conducting the medical and scientific evaluation of dependence-producing drugs and makes recommendations to the Commission on Narcotic Drugs of the United Nations concerning the level of international control to be applied to them. As WHO has the sole responsibility for this function, no drug can be controlled internationally without first being evaluated by WHO. The WHO Expert Committee on Drug Dependence has been entrusted with the task of evaluating such drugs since WHO was founded in 1948. Dr Rågo stressed the importance of balancing the need for preventing diversion of therapeutic substances with abuse potential by means of appropriate controls against the need for ensuring access to these drugs for therapeutic use.

2. Scheduling criteria

In order to ensure consistency in the review process, WHO has developed a formal procedure for its review of dependence-producing psychoactive substances. This procedure has been updated as the need has arisen. The current review procedure follows the guidelines (hereinafter referred to as “the Guidelines”) that were adopted by the Executive Board of WHO in 2000 (1).

The scheduling criteria described in the Guidelines are based on the relevant provisions of the international drug control conventions and additional guiding principles worked out by this Committee at previous meetings. In essence, similarity in terms of abuse and ill effects to drugs already controlled is the criterion applied to narcotic drugs. In accordance with the 1961 Single Convention on Narcotic Drugs (hereinafter referred to as “the 1961 Convention” (2)), the Expert Committee, when deciding whether to recommend international control, first determines 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 so, the Committee then determines if the substance is liable to similar abuse and produces similar ill effects to the substances in Schedule I or Schedule II, or



confirms that it is convertible into a substance already in one of these Schedules.

However, no specific guidance is given in the Guidelines as to how similar to the original drug a substance must be for it to be considered as morphine-like, cocaine-like or cannabis-like. The lack of specific guidance on this matter poses considerable difficulty for the Committee when the drug under review has some similarity for example to both a narcotic drug and a psychotropic substance, because the scheduling criteria in the 1971 Convention on Psychotropic Substances (3) (hereinafter referred to as “the 1971 Convention”) also includes a similarity rule. The decision as to whether to control analgesic and stimulant drugs under the 1961 or 1971 Convention is a major problem. Most potent analgesics are controlled under the 1961 Convention, but a few are controlled as psychotropic substances under the 1971 Convention. Of the stimulants of the central nervous system, cocaine is under the 1961 Convention, whereas amphetamines are under the 1971 Convention. Thus, the criteria for choosing between the two Conventions are ambiguous for these classes of drug.

There are two levels of scheduling criteria for psychotropic substances. At the first level, in addition to similarity to scheduled substances, dependence liability, together with psychotropic effects is an optional criterion. In applying this criterion, it is necessary to confirm that the substance in question has dependence liability and can produce “central nervous system stimulation or depression, resulting in hallucinations or disturbances in motor function, thinking, behaviour, perception or mood”. This criterion has enabled the scheduling of new types of dependence-producing psychotropic substances that are not similar to substances already scheduled. However, the scheduling criteria for psychotropic substances, unlike those for narcotic drugs, have an additional requirement for “evidence that the substance is being or is likely to be abused so as to constitute a significant public health and social problem warranting the placing of the substance under international control”. This provision has deterred this Committee from proposing “preventive” controls for psychotropic substances.

Further details of the scheduling criteria in the 1961 Convention concern the scheduling of:

- preparations of narcotic drugs that can be exempted from certain control measures, such as prescription requirements, (Schedule III); and
- narcotic drugs that are particularly liable to abuse and are replaceable for medical use (Schedule IV).





Examples of narcotic drugs under the 1961 Convention in these Schedules are:

- Schedule I* morphine, hydromorphone
- Schedule II* codeine, dextropropoxyphene
- Schedule III* codeine tablets containing not more than 100mg/tablet or a cough syrup containing not more than 2.5% codeine
- Schedule IV* heroin, cannabis

The Guidelines also provide guidance for selecting an appropriate schedule for psychotropic substances under the 1971 Convention, as follows:

- 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.

In cases where the above 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 above criteria are fully met, with respect to both therapeutic usefulness and the risk to public health.

Examples of psychotropic substances in these Schedules under the 1971 Convention are:

- Schedule I* lysergide (LSD), *N*, α -dimethyl-3,4-(methylenedioxy)phenethylamine (MDMA)
- Schedule II* amphetamines, methaqualone
- Schedule III* amobarbital, flunitrazepam, buprenorphine, pentazocine
- Schedule IV* diazepam, amfepramone

It should be noted that the ordering of the Schedules in the two Conventions is not comparable. In the 1961 Convention, Schedule IV



is the most restrictive whereas it is the least restrictive in the 1971 Convention. Further confusion may be created by national regulatory systems that use their own scheduling systems.

3. **Critical review of psychoactive substances**

3.1 **Critical review**

A critical review is conducted by the Expert Committee in any of the following cases: (1) there has been notification from a Party to the 1961 or the 1971 Convention concerning the scheduling of a substance; (2) there has been an explicit request from the UN Commission on Narcotic Drugs to review a substance; (3) pre-review of a substance has resulted in a recommendation for critical review; (4) information is brought to the attention of WHO that a substance of especially serious risk to public health and society, and of no recognized therapeutic use by any Member State is clandestinely manufactured. If therapeutic use of the substance is confirmed subsequently by any Member State in respect of case (4), the substance shall be subject to a pre-review.

All the five substances under critical review at the present meeting were pre-reviewed at the previous meeting of the Committee (4) and recommended for critical review.

3.2 **Amfepramone (INN)**

Substance identification

Amfepramone is chemically 2-(diethylamino)propiofenone (CAS No. 90-84-6 for base, 134-80-5 for hydrochloride). It is also known as diethylpropion. Amfepramone is marketed under many trade names.

Previous review

Amfepramone was included in Schedule IV of the 1971 Convention at the time of its adoption. It was reviewed by a WHO Review Group in 1980 (5), which concluded that there was no evidence to recommend a change in the level of its international control. Amfepramone was pre-reviewed at the previous meeting of the Committee (4) when a critical review was recommended based on information from the International Narcotics Control Board (INCB) that abuse and illicit trafficking of amfepramone had been reported from nearly all regions of the world, and had become particularly widespread in Asia and the Russian Federation.



Similarity to known substances and effects on the central nervous system

Amfepramone is an anorectic amphetamine analogue used for treating obesity. It has a spectrum of pharmacological effects similar to that of scheduled amphetamines, including the release of dopamine.

Dependence potential

Dependence on amfepramone can occur but there are few data available on its incidence. In some patients, tolerance to the anorectic effects of the drug may occur within 6 to 12 weeks. Amfepramone has been shown to produce euphoria and other mood changes characteristic of drugs of abuse.

Actual abuse and/or evidence of likelihood of abuse

Information from INCB indicates that illicit traffic in amfepramone has been reported from many countries and regions. In several countries in South America, overuse of anorectic stimulants has led to additional educational and regulatory actions being undertaken by the authorities. However, the small number of adverse drug reaction reports related to abuse received by the international drug monitoring programme does not suggest a high liability of amfepramone to abuse. The response of governments to the WHO questionnaire also indicated that diversion and abuse of the drug were limited.

Therapeutic usefulness

Amfepramone has been used as an oral anorectic in the treatment of obesity, although stimulants are not generally recommended for this indication. The drug is indicated only as an adjunct to other forms of therapy (such as caloric restriction, exercise and behaviour modification techniques). Some medicinal regulatory authorities in the European Union have already withdrawn amfepramone from the market because of concerns about its safety. The global consumption of amfepramone has been decreasing since 1997, in line with the decline in the total consumption of stimulants in Schedule IV of the 1971 Convention.

Recommendation

The Committee judged that according to the scheduling criteria set out in the Guidelines, a psychotropic substance in Schedule IV of the 1971 Convention, such as amfepramone, should have a liability to abuse that poses a “significant” risk to public health. The Committee did not recommend a change in the scheduling status of amfepramone since the information available to it was insufficient to justify placing



this drug in Schedule II or III which require that a substance constitutes a “substantial” risk to public health. Law enforcement data on the extent of illicit activities involving stimulants in other schedules of the 1971 Convention may enable the risk of abuse of amfepramone to be compared with abuse of other stimulants in the future. In the meantime, in view of the existing concern about its safety in medical use, the Committee recommended that informational and educational activities to curb its overuse be intensified.

3.3 **Amineptine (INN)**

Substance identification

Amineptine (7-[(10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)amino]heptanoic acid) is available as either the free base (CAS 57574-09-1) or as the hydrochloride salt (CAS 30272-08-3). There are no chiral carbon atoms, therefore, no stereoisomers or racemates are possible.

Previous review

Amineptine was pre-reviewed at the thirty-second meeting of the Committee (4) and critical review was recommended.

Similarity to known substances and effects on the central nervous system

Amineptine is a synthetic, atypical tricyclic antidepressant with stimulating effects on the central nervous system. It is an indirect dopamine agonist, which selectively inhibits dopamine uptake and induces dopamine release, with additional stimulation of the adrenergic system. Its antidepressant effects are similar to those of other tricyclic antidepressant drugs but amineptine has a more rapid action, is better tolerated and has few cardiovascular, analgesic or anorectic effects. It produces a similar spectrum of pharmacological effects to the psychomotor stimulants in Schedule II of the 1971 Convention.

Dependence potential

There have been few animal studies on the potential for dependence or abuse of amineptine. However, some clinical studies have indicated that amineptine has the potential both for dependence and abuse, particularly in patients with a previous history of substance abuse. Members of the Committee reported on their observations of significant abuse and dependence in patients treated with amineptine in France. The dependence potential of the drug appeared to be associated with its psychomotor stimulant effect. The clinical manifes-



tations of withdrawal include anxiety, insomnia, psychomotor agitation and bulimia. Instances of dependence have been reported in Asia and Europe.

Actual abuse and/or evidence of likelihood of abuse

Amineptine abuse has been reported mainly in Asia and Europe. The drug has been withdrawn from the market in France, where it was developed a few decades ago, because of its considerable hepatotoxicity and abuse. However, its medical use in developing countries, as well as its abuse continue. The reports of adverse drug reactions collected by the international drug monitoring programme indicated a larger number of case reports of abuse and dependence for amineptine than for other anorectic stimulants currently placed in Schedule IV of the 1971 Convention, such as amfepramone. The responses of governments to the WHO questionnaire also indicated limited diversion and abuse of the drug although some reported hospital admissions have been linked to the use or abuse of amineptine.

Therapeutic usefulness

The therapeutic usefulness of amineptine is limited because of its hepatotoxicity, secondary features such as acne eruption and anxiety, and the availability of safer antidepressants. Of the 103 countries that responded to the WHO questionnaire, only 17 indicated amineptine use.

Recommendation

The Committee considered that the degree of risk to public health and society associated with the abuse liability of amineptine is substantial and noted that its use is associated with significant hepatotoxicity. Its therapeutic usefulness has been assessed to be from little to moderate, at best. Although it has already been withdrawn from the market in several countries, amineptine continues to be available in a number of others. The Committee therefore considered that the likelihood of its abuse warranted its placement under international control. The Committee recommended that amineptine be placed in Schedule II of the 1971 Convention.

3.4 Buprenorphine (INN)

Substance identification

Buprenorphine is chemically 21-cyclopropyl-7- α -[(S)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-endo-ethano-6,7,8,14-tetrahydrooripavine





(CAS 53152-21-9 for hydrochloride; 52485-79-7 for free base). It is marketed under at least 26 trade names.

Previous review

In 1983, a WHO Review Group did not recommend international control of buprenorphine, although it recommended the inclusion of pentazocine (a pharmacologically related substance) in Schedule III of the 1971 Convention (6). A critical review of buprenorphine was again undertaken at the twenty-fifth meeting of the Committee (7), which recommended its placement in Schedule III of the 1971 Convention. However, other than the difference between the partial μ -opioid agonist buprenorphine and such prototypic μ -opioid agonists as heroin, morphine and methadone, the Committee did not provide any additional explanation for the choice of the 1971 Convention over the 1961 Convention. In its report for 1995, INCB requested a revision of the control system of buprenorphine by WHO. In consideration of these issues and evidence of significant abuse and illicit trafficking despite international control in Schedule III of the 1971 Convention, the Committee recommended critical review of buprenorphine at its thirty-second meeting (4).

Similarity to known substances and effects on the central nervous system

Buprenorphine is a partial μ -opioid agonist and κ -opioid receptor antagonist. It has been widely marketed as an analgesic and more recently has been used in the treatment of opioid dependence. As a partial μ -opioid agonist it produces pharmacological effects similar to those of low-to-moderate doses of morphine and other full μ -opioid agonists, but has a significantly lower maximal effect. Because of its low intrinsic activity, high affinity for, and slow dissociation from, the μ -opioid receptor it precipitates withdrawal syndrome in morphine-dependent animals and humans. Furthermore, pretreatment with buprenorphine attenuates the effects of morphine and other full μ -opioid agonists. For these reasons buprenorphine is both an opioid agonist and an antagonist.

Dependence potential

Buprenorphine has reinforcing effects in animal studies, produces euphoria and other positive mood changes in opioid abusers and produces mild physical dependence. No studies published after the twenty-fifth meeting of the Committee (7) have suggested the need for revising their earlier conclusion that buprenorphine does have significant dependence potential.



Actual abuse and/or evidence of likelihood of abuse

Although buprenorphine is widely marketed, France and the United Kingdom consume far more of the drug on a per capita basis than the other countries. In France, where buprenorphine is the main maintenance treatment for patients with opioid dependence that general practitioners are allowed to prescribe, there have been reports of diversion and abuse by polydrug abusers. Information from other countries and INCB on diversion and abuse indicates that buprenorphine is liable to be abused so as to constitute a substantial risk to public health and society. Despite the diversion and abuse of buprenorphine in France the number of deaths from opioid overdose has decreased significantly following the introduction of buprenorphine substitution therapy. Overall, the risk–benefit ratio for the use of buprenorphine in the treatment of opioid dependence was judged by the Committee to be favourable.

Therapeutic usefulness

Buprenorphine is currently used in about 60 countries as an analgesic and in about 30 countries for substitution treatment of opioid dependence. However, its use as a treatment for opioid dependence is rapidly increasing.

Application of the Guidelines

The majority of the Members of the Committee considered that, on the basis of the similarity criterion, buprenorphine should be reclassified under the 1961 Convention. The Committee considered that buprenorphine has greater similarity to morphine than to lefetamine, the only analgesic drug controlled as a psychotropic substance at the time the 1971 Convention was adopted. Although lefetamine is an analgesic that binds to brain opioid receptors it was abused during the 1950s in Japan for its stimulant effects on the central nervous system.

The Committee also noted that the scheduling criterion for psychotropic substances would apply to almost all drugs controlled under the 1961 Convention. Morphine and cocaine are clearly psychoactive substances capable of producing stimulation or depression of the central nervous system, “resulting in hallucinations or disturbances in motor function, thinking, behaviour, perception or mood”. They are also dependence-producing. Therefore, morphine and cocaine meet the first-level requirement for being scheduled as psychotropic substances. There is no authoritative guidance, in either the 1971 Convention or in the Guidelines, as to which of the two optional criteria the Committee should apply. The Committee was also informed that



the Guidelines require stronger justification for recommending a change in the control status of a substance from one convention to another.

Recommendation

For the reasons stated above, the Committee considered that the final decision on buprenorphine should be taken at a future meeting of the Committee. The Committee also recommended that WHO, in consultation with the United Nations, develop guiding principles for making the choice between the two optional scheduling criteria for psychotropic substances and elaborate the Guidelines with regard to the choice of the more appropriate convention when a substance under review has some similarity to both a psychotropic substance and a narcotic drug. This issue is of particular relevance to the consideration of changing the control of a substance from one convention to the other.

3.5 **Delta-9-tetrahydrocannabinol**

Substance identification

Delta-9-tetrahydrocannabinol is chemically 6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol. Dronabinol (CAS 1972-08-3) is the INN for one of the stereochemical variants of *delta-9-tetrahydrocannabinol*, namely (–)-*trans-delta-9-tetrahydrocannabinol*.

Previous review

Delta-9-tetrahydrocannabinol was included in Schedule I of the 1971 Convention at the time of its adoption. At its twenty-sixth meeting, the Committee recommended that dronabinol be moved to Schedule II, while keeping the other isomers and their stereochemical variants in Schedule I. This proposal was rejected by the Commission on Narcotic Drugs, and the Committee reviewed the question again at its twenty-seventh meeting when it recommended that all the stereochemical variants of *delta-9-tetrahydrocannabinol* be rescheduled to Schedule II (8). This recommendation was adopted by the United Nations. At its thirty-second meeting, the Committee pre-reviewed dronabinol and recommended its critical review for consideration of the rescheduling on the grounds that the rate of abuse of dronabinol was extremely low (4).



Similarity to known substances and effects on the central nervous system

Delta-9-tetrahydrocannabinol is the main active principle of cannabis which is a well known psychotropic substance and exhibits the perception-altering effects possessed by cannabis.

Dependence potential

Although cannabis abuse is widespread, there is no evidence that dronabinol shares the high abuse liability of cannabis.

Actual abuse and/or evidence of likelihood of abuse

In terms of abuse potential, there may not be any significant difference between *delta-9*-tetrahydrocannabinol and cannabis, in which this psychoactive substance occurs naturally. In terms of likelihood of abuse, however, there is a very significant difference between the two. Cannabis abuse is widespread throughout the world whereas the abuse of *delta-9*-tetrahydrocannabinol or of its preparations is rare. Of the 103 countries that responded to the WHO Questionnaire, only two indicated some abuse of this substance: Denmark reported some abuse of “cannabinol”, clarifying that it meant the detection of *delta-9*-tetrahydrocannabinol in the exhibit, and the questionnaire from the USA mentioned three cases of abuse reported by the American Association of Poison Control Centers during the period from 1992 to 1994.

Therapeutic usefulness

Dronabinol is indicated for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments and for the treatment of anorexia associated with weight loss in patients with acquired immunodeficiency syndrome (AIDS). Of the 103 countries that responded to the WHO Questionnaire, only six reported the regular availability of pharmaceutical products containing dronabinol.

Recommendation

The abuse liability of dronabinol is expected to remain very low so long as cannabis continues to be readily available. The Committee considered that the abuse liability of dronabinol does not constitute a substantial risk to public health and society. In accordance with the established scheduling criteria, the Committee considered that dronabinol should be rescheduled to schedule IV of the 1971 Convention on Psychotropic Substances. To avoid placing different



stereochemical variants of the same substance under different control systems, the Committee recommended that all stereochemical variants of *delta-9-tetrahydrocannabinol* be moved to Schedule IV of the 1971 Convention.

3.6 Tramadol (INN)

Substance identification

Tramadol, chemically (+/-)*trans*-2-dimethylaminomethyl-1-(3-methoxyphenyl) cyclohexanol, is available as either the free base (CAS 27203-92-5) or as the hydrochloride salt (CAS 36282-47-0). It is marketed under over 100 trade names.

Previous review

Tramadol was pre-reviewed at the twenty-eighth meeting of the Committee at which time critical review was not recommended (9); however following pre-review at the thirty-second meeting, critical review was recommended (4).

Similarity to known substances and effects on the central nervous system

Tramadol has been found to be an opioid agonist with selectivity for the μ -opioid receptor but with some weak affinity for the κ - and δ -opioid receptors. The affinity for the μ -opioid receptor is approximately 10-fold less than that of codeine and 6000-fold less than that of morphine. The *O*-desmethyl metabolite (ODT or M1) of tramadol has a 200-fold greater affinity than the parent compound for the μ -opioid receptor. In addition to its actions on brain opioid receptors tramadol is an inhibitor of serotonin reuptake (+ isomer) and of noradrenaline reuptake (- isomer). Tramadol induces analgesia, but is associated with less respiratory depression than other opioids and has no significant cardiac effects. It has been found to reduce the seizure and sweating thresholds but reduces postoperative shivering. Tramadol has been noted to have some effects on the central nervous system, notably dizziness; sedation; headache and, to a lesser extent, euphoria; central nervous system stimulation (e.g. tremor, agitation, anxiety and hallucinations); dysphoria and seizures. In the 1% of patients who suffered seizures, they were found to be linked to a predisposing factor such as epilepsy, alcohol or drug withdrawal or antidepressant therapy. Toxic effects can be produced directly by the drug and these effects may be exacerbated by the presence of monoamine antidepressant drugs or central nervous system depressant drugs. Overdose has been reported to result in bradycardia, convulsions, respiratory depression and coma.



Dependence potential

Animal studies have indicated that tramadol produces little tolerance, has mild withdrawal symptoms and a lower abuse potential than codeine and pentazocine. Nevertheless, together with the rapid increase in the medical use of tramadol worldwide, there have been reports of dependence and abuse, particularly in opioid-dependent individuals. The actions of the drug on brain monoamine systems must also be considered in relation to its abuse potential.

Actual abuse and/or evidence of likelihood of abuse

Of the 103 countries that responded to the WHO Questionnaire, 88 indicated the medical use of tramadol. Of these, 21 reported some abuse and illicit traffic. The reported cases of abuse originated primarily from Europe and the United States. Deaths from overdose were reported from France and the United States. In a few of these countries, abuse of tramadol has led to regulatory actions such as temporary suspension of marketing registration or the use of special prescription forms. However, the assessment of its abuse liability is made difficult by the scarcity of quantitative data and considerable differences in the experiences of individual countries. In Germany where the drug was developed and has been on the market for 25 years without additional controls other than prescription requirements, the data from the drug abuse warning system suggest that tramadol has lower abuse liability than buprenorphine and pentazocine. The data from the drug abuse warning network of the USA, on the other hand, suggest that its abuse potential may be roughly comparable to that of codeine or dextropropoxyphene in the USA. The regulatory authorities in the USA required that the sponsor of tramadol set up an independent group of scientists to conduct post-marketing studies of abuse of and dependence on tramadol. These studies found that the rate of abuse in the year following the introduction of tramadol to the market was 2–3 cases per 100 000 patients. Subsequently, this rate declined to one case per 100 000. The adverse drug reaction reports related to abuse of tramadol collected by the international drug monitoring programme indicate larger numbers of case reports of abuse, dependence and withdrawal syndrome for tramadol than for any other analgesic, except butorphanol, which ranks first in the list of drugs for which “drug dependence” has been reported. Many of these reports originated from the USA, where the consumption of tramadol has been increasing rapidly since it was first marketed in 1995, a situation conducive to higher rates of reporting adverse events.





Therapeutic usefulness

Tramadol is used as an analgesic agent for the treatment of moderate to severe pain. It became available in Germany in the 1970s and was subsequently marketed in Africa, the Americas and Asia, and is currently used in 104 countries. It is however difficult to judge whether the rapid increase in its medical use reflects the recognition of its therapeutic usefulness. The absence of international control may be a contributing factor.

Recommendation

Pharmacologically, tramadol is more complex than prototypic μ -opioid receptor agonists, but one of its metabolites is a potent μ -opioid receptor agonist. This is consistent with its pattern of abuse which is similar to that of opioids by opioid abusers, as well as its opioid-like analgesic effects. The likelihood of abuse of tramadol appears to vary between countries, depending on the prevalence of opioid dependence, types of marketing strategy and other factors. The information available is not sufficient for the Committee to recommend international control of tramadol, but is adequate to recommend that WHO keep the drug under surveillance.

4. Pre-review of psychoactive substances

The review of psychoactive substances by WHO is carried out in two steps. The first step is referred to as pre-review; this is a preliminary review carried out by the Committee to determine whether or not a fully documented review (critical review) of the substance is required. The criterion for judgement of whether critical review is necessary is whether or not WHO has information that may justify the scheduling of the substance. In the case of psychotropic substances, this requires information on actual abuse of the drug causing significant public health and social problems in more than one country.

In addition to the Secretariat, any member of the Expert Committee or any representative of the other organizations invited to participate in the Expert Committee meeting can submit a proposal to pre-review a substance together with supporting information. At the present meeting, ketamine, zalepron and zopiclone were proposed by the Secretariat while butorphanol and khat were proposed by a Member of the Committee. The representative of the International Narcotics Control Board proposed oripavine.



4.1 Ketamine (INN)

Ketamine, chemical name (\pm) -2-(2-chlorophenyl)-2-(methylamino)cyclohexanone, has not previously been reviewed by WHO. Ketamine is indicated to provide anaesthesia for short diagnostic and surgical procedures that do not require skeletal muscle relaxation. Its use in veterinary medicine must also be considered in relation to its control. Ketamine hydrochloride has been abused as a hallucinogen for almost 30 years. The drug produces effects similar to those of phencyclidine, but with a much shorter duration. Limited abuse by medical personnel has been reported in a number of countries. In recent years, the abuse of ketamine mixed with or presented as *N*, α -dimethyl-3,4-(methylenedioxy) phenethylamine (MDMA) has raised a serious concern in Europe. Ketamine abuse is reported from a number of countries in Asia, Europe and North America and it has already been placed under national control in several countries.

Recommendation

On the basis of the information presented above, the Committee recommended critical review of ketamine at a future meeting.

4.2 Zaleplon (INN)

Zaleplon, chemical name 3'-(3-cyanopyrazolo[1,5-*a*]pyrimidin-7-yl)-*N*-ethylacetanilide, has not previously been reviewed by WHO. Zaleplon selectively binds to the brain alpha subunit of the GABA_A omega-1 receptor. Its pharmacological properties are similar to those of zolpidem, and it is indicated for the short-term (2 to 4 weeks) management of insomnia. It produces a benzodiazepine-type withdrawal syndrome upon discontinuation of long-term use and studies on subjective effects show its similarity to triazolam. Zaleplon has been on the market for only a short time and the number of reports of abuse-related adverse drug reactions received by the international drug monitoring programme are as yet very few.

Recommendation

Although the abuse potential of this substance is considered to be similar to that of zolpidem and triazolam, critical review was not recommended at this stage as the information on actual abuse available to the Committee was insufficient to confirm the existence of significant public health and social problems in more than one country. However, the Committee recommended that WHO continue the surveillance of zaleplon¹.

¹ One Member of the Committee (Professor M.S. Bourin) expressed his concern regarding the potential for abuse of and dependence on zaleplon and felt that a critical review was warranted.



4.3 Zopiclone (INN)

Zopiclone, 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, was pre-reviewed at the twenty-ninth meeting of the Committee in 1994 (10), which recommended continued surveillance, but not a critical review.

The pharmacological profile of zopiclone is similar to that of chlor-diazepoxide. The pharmacological activity of zopiclone is believed to be related to its binding to the benzodiazepine receptor complex. Studies of abuse liability in animals and humans have indicated that zopiclone has some abuse potential together with the capacity to produce withdrawal syndrome upon its discontinuation. In terms of the number of adverse drug reaction reports related to abuse received by the international drug monitoring programme, zopiclone ranks higher than nitrazepam and temazepam. Furthermore, the Committee was informed that the government of Switzerland had submitted a formal notification to the United Nations concerning the scheduling of zopiclone.

Recommendation

In accordance with the Guidelines, the Committee recommended the critical review of zopiclone.

4.4 Butorphanol (INN)

Butorphanol, chemical name (-)-17-(cyclobutylmethyl)morphinan-3,14-diol, was reviewed by a WHO Review Group in 1981 (11) and 1983 (6), and at the twenty-fifth meeting of the Committee (7), which did not recommend international control.

Butorphanol is a synthetically derived opioid compound with mixed agonist-antagonist properties at the μ -opioid receptor. It exerts its analgesic effect by acting as an agonist at the κ -opioid receptors. Butorphanol has a profile of actions similar to those produced by pentazocine. Two to three milligrams of parenterally administered butorphanol produce analgesia and respiratory depression approximately equal to that caused by 10 mg of morphine. There have been a significant number of reports of abuse, withdrawal syndrome and dependence related to butorphanol and this drug ranks first in the list of all drugs for which drug dependence has been reported as an adverse drug reaction to the WHO International Drug Monitoring Programme. Most of these reports originated from Canada, Italy, the United Kingdom and the USA. In Canada, drug-seeking behaviour has been reported in association with the use and abuse of



butorphanol nasal spray. At least four countries have taken regulatory actions to control butorphanol, indicating that its abuse is considered as a significant problem in more than one country.

Recommendation

On the basis of the above data the Committee recommended the critical review of butorphanol.

4.5 Oripavine

Oripavine, *O*³-demethylthebaine, is a phenanthrene alkaloid contained in species of the *Papaver* plant. It is a major metabolite of thebaine.

Oripavine has not previously been reviewed by WHO in the context of international control. However, in a WHO review of the dependence potential of thebaine held in 1980 (12), oripavine was suggested to be a metabolite of thebaine in animals possibly involved in the dependence potential.

In recent years, large quantities of concentrate of poppy straw (defined as “all parts (except the seeds) of the opium poppy after mowing”) containing oripavine as the main alkaloid has been produced, traded and used for the production of opium alkaloids. It is an easy industrial process to convert oripavine into thebaine through methylation. Thebaine is in Schedule I of the 1961 Convention because it is a precursor of codeine and morphine. For this reason, the convertibility of oripavine may meet the scheduling criteria for placing it in the same Schedule as thebaine. However, the Commentary on the 1961 Convention indicates that the purpose of controlling drugs which are convertible to scheduled narcotic drugs, is to prevent the abuse of the narcotic drugs manufactured by the conversion process. Although animal tests have shown that thebaine has some abuse potential, no actual abuse of thebaine has been reported. It is therefore questionable whether the convertibility criterion could be applied for the scheduling of a substance when the drug produced by its conversion is used only as a starting material for the manufacture of other narcotic drugs. An additional problem is that there is no authoritative guidance on how to distinguish between the criteria of the 1961 Convention concerning convertibility and the criteria introduced by the 1988 Convention (13) concerning the control of precursors. Since the Guidelines do not provide any guidance on this question, the Committee was unable to recommend critical review of oripavine at this stage.



Recommendation

The Committee urged WHO to develop additional scheduling guidelines in consultation with appropriate bodies of the United Nations for clarifying issues related to the conversion of precursors into scheduled substances.

4.6 Khat

Khat or qat refers to the leaves and the young shoots of the plant *Catha edulis* Forsk. It has not previously been reviewed by WHO in the context of international control.

In many countries in Africa and the Arabian peninsula khat is traditionally consumed by chewing the tender leaves and stems. The principal psychoactive substances contained in the khat leaves are cathinone and cathine. Cathinone has been shown to have high abuse potential, and is in Schedule I. Reports of actual abuse of cathine have led to its being placed in Schedule III of the 1971 Convention. The migration of users of khat has resulted in the spreading of khat use to countries in other regions of the world. Khat is consumed at parties where friends gather and hold conversations while smoking cigarettes and drinking tea and soft drinks. The subjective effects of khat are rewarding; however, khat use produces significant toxic effects including increased blood pressure, tachycardia, insomnia, anorexia, constipation, a sense of general malaise, irritability, reactive depression, migraine and impaired sexual potency in men. Khat is believed to be dependence-producing. Cases of toxic psychosis and paranoia due to khat have been described by a number of authors. Other reported acute and chronic effects of khat include low birth weight in babies of khat chewing women, reduced sperm count and motility, increased risk of myocardial infarction and liver problems. In addition to the reported health problems, the regular consumption of khat is also associated with a variety of social and economic problems affecting the consumers and their families. A number of countries in Africa, Asia, Europe and North America have already placed khat under national control.

Recommendation

The Committee considered that there was sufficient information on khat to justify a critical review.



5. Terminology used in reporting abuse-related adverse drug reactions

The main function of the WHO Programme for International Drug Monitoring is to provide early warnings of drug-related problems, including drug abuse, dependence and withdrawal syndrome. Since the initiation of the Uppsala Monitoring Centre (UMC), nearly three million reports of adverse drug events have been received from health care professionals (reporters) from 69 different countries. Reports are originally sent as text, and then coded to provide medically useful terms. Unfortunately, the terms used by the reporters can be imprecise or contained within a large body of text. To enable the programme to provide early warnings, any terms that can possibly have a value as a pointer to dependence are coded as “dependence” to ensure that early signals are not missed.

There is a need for caution in the interpretation of the UMC data. At present, health care professionals do not use terminology related to drug abuse and dependence in a consistent manner. For example, the selective serotonin reuptake inhibitors (SSRIs) are important psychoactive substances where terminology possibly indicative of dependence poses a major problem (see Annex). The use of broad terms such as “drug discontinuation syndrome” instead of “withdrawal” also hampers data coding and interpretation.

The International Classification of Diseases (ICD) (14) is the most widespread tool used in health epidemiology. While it is correct to say that *withdrawal* and *tolerance* are neither required nor sufficient for a positive diagnosis of *dependence syndrome*, excessive emphasis on this aspect can lead to the misconception that *withdrawal* is unrelated to *dependence*.

Definitions should be consistent within WHO, but it must be recognized that terms may be used differently for different purposes. The terms used in reporting adverse drug reactions are intended to describe drug effects and to communicate them to patients and health care professionals. Avoiding terms that may be confusing for non-professionals as well as ensuring translatability into all languages are particularly important.

It was agreed that the Secretariat and the UMC should continue to work together to provide the best data to meetings of the Committee. The Committee discussed the definition of terms and emphasized the need for careful interpretation of the UMC data.





6. Other matters

The Committee noted the striking number of reports on paroxetine and “withdrawal syndrome” (see list of SSRIs in the Table in the Annex). The representative of Consumers International reported that a number of patients had experienced difficulty in withdrawing from SSRIs in general. It was agreed that withdrawal was indeed a problem in some patients, but there was a difference of opinion on the degree of dependence that was involved, given the possibility that the need for treatment of resistant or relapsing disease could make these drugs indispensable for patient care. The Committee expressed concern about the possibility of inappropriate prescribing resulting in the risk of problems of withdrawal outweighing the benefits of treatment with SSRIs.

The Committee agreed that there was a possible therapeutic problem with these drugs, but that there was no evidence of diversion of the drug for abuse because SSRIs are so widely available. The Committee recommended that SSRIs be placed on the agenda of the next Committee for consideration, not in the context of control, but to promote education and information on the appropriate use of psychoactive drugs.

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Annex

Terminology used in reporting abuse-related adverse drug reactions

The Expert Committee on Drug Dependence (ECDD) has been instrumental in developing appropriate terminology to aid understanding of the phenomena of drug dependence and abuse. At its thirteenth meeting (1), ECDD had already proposed using *drug dependence* to replace the terms *drug addiction* and *drug habituation*. This proposal was accepted globally during the 1970s.

However, the ICD-10 (2) employed certain technical terms that were slightly different from the conventional terms, such as *withdrawal*



state instead of *withdrawal syndrome* or *abstinence syndrome*. This led to the question of whether ICD-10 was entirely consistent with the definition of drug dependence worked out by the ECDD during the 1960s. At its twenty-eighth meeting (3) the Committee discussed this question and concluded that there was no inconsistency between the definition of drug dependence adopted by this Committee and the diagnostic guidelines for *dependence syndrome* developed by WHO in conjunction with ICD-10. This clarification has apparently reduced the conceptual confusion, at least among drug abuse researchers and treatment experts. However, in the area of postmarketing surveillance, which involves a much broader range of health professionals, conceptual confusion is still commonplace. Such confusion is particularly common with regard to the meaning of closely-related terms, as outlined below.

Drug addiction and drug dependence

Although the term drug addiction was eliminated from the technical terminology of WHO many years ago, it is still widely used as a general term. For example, the word *addictive* is commonly used to mean *dependence-producing*. Where drug addiction is used as a technical term it seems to refer to severe cases of *dependence*. However, as there is no internationally accepted definition of *addiction*, it is impossible to be certain in what way addiction differs from dependence.

Drug abuse and drug dependence

From the above-mentioned definition of *drug abuse*, it is clear that acceptable medical use of the drug, whether or not it results in drug dependence, is not *drug abuse*. There are situations in which treatment with a dependence-producing drug needs to be continued, even after the patient has become dependent on it. In this case, drug dependence may be reported as an adverse drug reaction, but not as drug abuse. In this connection, it is also useful to stress that *dependence liability* alone is not sufficient reason for proposing the international control of a psychoactive drug. It is the *abuse liability* (likelihood of abuse) of the drug that must be considered. It is necessary to make the distinction between the abuse of a psychoactive substance which tends to result in the deterioration of an individual's physical, psychological and social functioning, and its therapeutic use which is intended to improve any or all of these. It is also known that not all dependence-producing drugs are abused (e.g. caffeine is dependence-producing but it is seldom abused).



Drug abuse and drug maladministration

Drug abuse is defined as “persistent or sporadic excessive drug use inconsistent with or unrelated to acceptable medical practice”. Thus, the intentional use of excessive doses, or the intentional use of therapeutic doses for purposes other than the indication for which the drug was prescribed, is drug abuse. *Misuse* and *non-medical* use are synonyms of drug abuse. However, inappropriate prescribing (e.g. indiscriminate prescribing of antibiotics) or medication errors, if accidental or unintended, should not be classified as drug abuse. Such an inappropriate use of the drug should rather be considered as *drug maladministration*. Drug maladministration can cause many adverse reactions and it is a drug safety problem requiring an appropriate response, but it can rarely be a consequence of the normal therapeutic use of a drug. It is therefore difficult to imagine a situation in which drug maladministration needs to be reported to the adverse drug reaction database; it has to be addressed as a separate safety issue.

Physical (physiological) dependence and drug dependence

The ECDD (3) recommended against the use of the term *physical (physiological) dependence* for several reasons. Firstly, it noted that the distinction between *physical (physiological) dependence* and *psychic (psychological) dependence* was difficult to make in clinical situations. Such a distinction would also be inconsistent with the modern view that all drug effects are potentially understandable in biological terms. The term physical (physiological) dependence was also considered to be confusing because clinicians often interpreted the manifestation of withdrawal syndrome as evidence of both physical dependence and drug dependence. (This is not the case, as explained in more detail below.) Nonetheless, the term is still used to mean a state of adaptation evidenced by the manifestation of withdrawal syndrome upon discontinuation of the drug or the development of *tolerance* or both.

Drug dependence and withdrawal syndrome

The simplest explanation of drug dependence is “a state in which the individual has a need for repeated doses of the drug to feel good or to avoid feeling bad”. This is consistent both with general public understanding and with the more sophisticated definition of drug dependence used by the ECDD. The ICD-10 (2) emphasizes the loss of control over one’s drug-seeking behaviour as the core concept of drug



dependence and sets out diagnostic guidelines for dependence syndrome with six check-points. Two of them concern *withdrawal state* and *tolerance* while the remaining four could be considered as different manifestations of the state of *dependence* itself. For a positive diagnosis of *dependence syndrome*, at least three of the six criteria must be observed. Thus, even when both tolerance and withdrawal occur, this is not sufficient to meet the requirement for dependence syndrome unless one of the remaining four criteria is met. Conversely, even when both withdrawal and tolerance are absent, an individual can still have dependence syndrome if three of the remaining four requirements are met.

It is therefore correct to say that withdrawal and tolerance are neither required nor sufficient for a positive diagnosis of dependence syndrome. However, excessive emphasis on this can lead to the misconception that withdrawal syndrome is unrelated to dependence. A withdrawal state or syndrome is one of the six criteria of which at least three must be met for a positive diagnosis of dependence syndrome to be made. In other words, when withdrawal syndrome exists, one-third of the requirement for a positive diagnosis of dependence syndrome is met. Therefore, the notion that withdrawal is unrelated to dependence is inconsistent with the ICD-10 diagnostic guidelines.

SSRIs are an example of how a conceptual confusion over terminology can affect proper reporting, interpretation and communication of adverse drug reactions related to dependence. To avoid the association with dependence, an increasing number of researchers have used a different term, *discontinuation syndrome*, instead of withdrawal syndrome. The number of hits for discontinuation syndrome in searches of the international medical literature began to increase, relative to the occurrence of withdrawal syndrome, in 1997 after a symposium on antidepressant discontinuation syndrome held in 1996. In fact, dependence syndrome has been reported to the Uppsala Monitoring Centre for all SSRIs through the same postmarketing surveillance systems, although there are significantly fewer reports of dependence syndrome than of withdrawal syndrome. Also, the proportion of reports of drug dependence in relation to the number of reports of withdrawal syndrome varies considerably between individual SSRIs from 26% for fluoxetine to only 1% for venlafaxine (according to the global adverse drug reaction database of the Uppsala Monitoring Centre as of June 2002) (see Table below).



Drug name	Withdrawal syndrome reports (ws)	Drug dependence reports (dd)	Ratio (%) dd/ws
Fluoxetine	419	109	26.0
Sertraline	631	69	10.9
Mirtazapine	17	1	5.9
Fluvoxamine	69	4	5.8
Nefazodone	83	4	4.8
Paroxetine	2380	91	3.8
Citalopram	107	3	2.8
Venlafaxine	1185	13	1.1

Three SSRIs are among the 30 highest-ranking drugs in the list of drugs for which drug dependence has ever been reported to the Uppsala Monitoring Centre database; a total of 269 reports had been received as of June 2002 (109 reports for fluoxetine, 91 for paroxetine and 69 for sertraline).

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