

WHO Expert Committee on Drug Dependence

Thirty-fifth Report



World Health
Organization

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WHO Expert Committee on Drug Dependence

Hammamet, Tunisia, 4–8 June, 2012

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Abbreviations

1,4-BD	1,4-butanediol
AIDS	acquired immunodeficiency syndrome
BZP	N-benzylpiperazine
CND	Commission on Narcotic Drugs
ECDD	Expert Committee on Drug Dependence
ECOSOC	Economic and Social Council
EU	European Union
GABA	γ -aminobutyric acid
GBL	γ -butyrolactone
GHB	γ -hydroxybutyric acid
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	human immunodeficiency virus
ICD	International Classification of Diseases
INCB	International Narcotics Control Board
INN	International Nonproprietary Name
LAAM	levacetylmethadol
LSD	lysergic acid diethylamide
mCPP	1-(3-chlorophenyl)piperazine
MeOPP	1-(4-methoxyphenyl)piperazine
MDBP	1-(3,4-methylenedioxybenzyl)piperazine
MDBZP	1-(3,4-methylenedioxybenzyl)piperazine
MDMA	methylenedioxymethamphetamine
NMDA	N-methyl-D-aspartate
PCP	phencyclidine
pINN	proposed international nonproprietary name
TFMPP	1-(3-trifluoromethylphenyl)piperazine
UMC	Uppsala Monitoring Centre
UNODC	United Nations Office on Drugs and Crime
WHA	World Health Assembly
WHO	World Health Organization

Introduction

The thirty-fifth meeting of the World Health Organization (WHO) Expert Committee on Drug Dependence (ECDD) took place in Hammamet, Tunisia from 4 to 8 June 2012.

Dr Willem Scholten, Team Leader, Access to Controlled Medicines, WHO, opened the meeting on behalf of Dr Carissa F. Etienne, Assistant Director-General, Health Systems and Services. He welcomed all participants on behalf of the Director-General. He noted that the thirty-fifth meeting of the ECDD was in many respects special. It was the first ECDD meeting organized in line with the revised *Guidance on the WHO review of psychoactive substances for international control (1)* adopted by the WHO Executive Board in January 2010. Rules on the transparency of the process as a whole were introduced and, for the first time, all meeting documents were published on the WHO ECDD meeting website before the meeting. Further, all reviews on substances under evaluation were peer reviewed by experts, and the results of these reviews were also made available in the public domain prior to the meeting.

In general terms, the role of WHO is the assessment of medical properties and the liability for abuse of any substance, pure chemical or plant material, and to advise the United Nations Commission on Narcotic Drugs (CND) on which substances should be under international control. The purpose of this meeting of the ECDD was, therefore, to review a number of substances and to provide its advice to WHO on whether these substances should be recommended for scheduling under the international drug control conventions (in case of critical reviews) and recommend whether a critical review should be held at a subsequent meeting of the ECDD (in case of a pre-review). ECDD is mandated to draft recommendations to facilitate WHO's advisory role to the CND, attributed by the Single Convention on Narcotic Drugs, 1961 (2) and the Convention on Psychotropic Substances, 1971 (3). Although the primary mandate of the ECDD is the evaluation of psychoactive substances for international control, it also has to address other related scientific issues at its meeting.

Dr Scholten reminded the members of the ECDD that they serve as independent scientists and therefore they advise WHO in their individual capacity as experts and not as representatives of their government or organization. The experts were invited to deliberate on the issues, providing their best expertise and knowledge, to come to recommendations that will benefit the world as a whole.

The agenda as proposed by the Secretariat was accepted. The Expert Committee elected the Chair, Co-chair and Rapporteur. The Chair welcomed all participants. He reminded them that finding a proper balance between maintaining availability of psychoactive substances for medical purposes, while minimizing abuse of such

substances is important. He requested the Expert Committee to consider both aspects equally while making decisions. The Chair reminded the Expert Committee that all recommendations should be unanimously agreed upon if possible. In the event that a member has a divergent opinion, he or she can request the Rapporteur to include a special statement in the report. The Expert Committee appreciated the convening of the meeting after a six-year hiatus.

Before the discussions began, all Members of the Expert Committee and all temporary advisers attending the meeting were requested to declare any conflicts of interest. No declaration of conflicts of interest is required for observers. Mrs De Lima declared that as the Executive Director of the International Association for Hospice and Palliative Care (IAHPC), she has advocated the elimination of undue barriers to the rational medical use of controlled substances, in particular the use of opioids for pain relief. The IAHPC works with patients and health-care providers around the world and the outcomes of this meeting and its recommendations may have consequences for patients and care providers worldwide. Dr Pennings declared that he is a member of the Risk Assessment Committee on New Drugs of the Netherlands. Mr Dasgupta declared that he is a paid member of the Risk Safety Advisory Board of Covidien. In 2011, he also consulted for Pfizer during a one-day meeting on general non-product-specific epidemiological methods in pharmacovigilance. Dr Edwards declared that the research he presented at the meeting was funded under the European Union (EU) Monitoring Medicines Project FP7, Grant No 223566. The other Members and temporary advisers declared that they had no conflicts of interest.

The declared potential conflicts of interest were considered not to conflict with any agenda items discussed at the meeting or with the recommendations issued by the Committee.

Dr Galina Korchagina, observer for the International Narcotics Control Board (INCB), informed the Committee of the role of the Board. The Board was established in 1961 as an independent treaty body. It consists of 13 members elected by the Economic and Social Council (ECOSOC), three of whom are chosen from candidates nominated by WHO. Its mandate is to monitor and promote compliance with the three international drug control conventions. Its functions are to ensure availability of controlled substances for legal demands, and to prevent, if possible, illicit activities related to these substances. These functions should be seen in the light of the preambles of the Single Convention on Narcotic Drugs and the Convention on Psychotropic Substances, both of which state that the substances under control are indispensable for medical and scientific purposes. Dr Korchagina also gave an overview of the various reports and publications of the Board, including one of the most recent, the *Guide on Estimating Requirements for Substances under International Control (4)*, jointly developed by WHO and INCB.

1. Revision of guidelines

The Committee was informed that the Executive Board, at its 126th Session in January 2010, had adopted the revised document that contains specific guidance for substance evaluation and conduct of the ECDD, supplementary to the WHO regulations guiding Expert Advisory Panels and Committees, in general (5). The specific guidance was developed initially in 1986 and updated in 1990, 1994, 1999 and 2000. Subsequently, a proposal for supplementary guidelines, made at the request of the Expert Committee, was rejected by the WHO Executive Board in 2004 and 2005. The Board then invited the Secretariat and the Expert Committee to develop revised guidelines, which resulted in the *Guidance on the WHO review of psychoactive substances for international control*. The title of the document was changed, and the phrase “*dependence-producing*” was deleted, as that term suggests that it had already been established that the substances under review were dependence-producing.

The revision was drafted by a working group consisting of six representatives of Member States from four regions, and three experts from the Expert Advisory Panel on Drug Dependence (Dependence Liability Evaluation), in May 2007. Six invited observers also attended. The document was posted for public comment. Comments from individuals, nongovernmental organizations and other bodies were taken into consideration in the next draft, which was also posted on the Internet for public comment. These comments were also considered by the Secretariat in drafting the final proposal to the Executive Board.

The revised Guidelines are aimed to ensure that the WHO review process is based on scientific and public health-related principles. The current revision provides additional transparency and clarity to the process and procedures as a whole. In particular, it includes current best practices for assessing substances for their abuse liability, methodology for the Expert Committee to use to arrive at its decisions, and procedures for reporting and for publishing reports.

According to the Guidelines, information will be presented in a way that will facilitate evidence-based assessment; peer reviews will be made available to the Expert Committee in advance of the meeting. The new confidentiality provisions will help prevent pre-emptive or inaccurate disclosure of the Expert Committee’s recommendations. The revision clarifies that the same criteria apply for the assessment of substances not previously scheduled as for those being considered for rescheduling.

2. Work of international bodies concerned with controlled substances

The Committee was informed of the important events in the work of international bodies concerned with controlled substances since the thirty-fourth meeting of the ECDD (6).

WHO recommendations on oripavine and dronabinol were discussed at the fiftieth session of the CND in March 2007, where the recommendation to place oripavine in Schedule I of the Single Convention was accepted in decision 50/1 (7).

However, the WHO recommendation to move dronabinol and its stereoisomers from Schedule II to Schedule III of the 1971 Convention was rejected and WHO was requested to reconsider this issue in decision 50/2 (8). The Expert Committee noted that the Conventions allow the CND to decide differently from a WHO recommendation, based on considerations other than the medical and scientific ones considered by the ECDD. There was discussion on whether the ECDD should revisit the recommendation on dronabinol made at the thirty-fourth meeting, as requested by the CND at its fiftieth session, following its decision not to adopt the WHO recommendation to change the schedule from II to III. After discussion, the Expert Committee decided that the previous ECDD decision on dronabinol should stand. The Expert Committee was unaware of any new evidence that was likely to materially alter the scheduling recommendation made at its thirty-fourth meeting.

Resolutions related to ketamine were also discussed. The Expert Committee was informed that having already adopted resolution 49/6 in 2006 (9), CND adopted another resolution 50/3 in 2007 (10). The INCB made recommendations in its annual reports in 2007 (11), 2008 (12) and 2009 (13), that all countries consider scheduling ketamine at a national level.

In 2012, at the fifty-fifth session of the CND, Resolution 55/1 (14) on new psychoactive substances was adopted. This Resolution includes a paragraph calling on WHO to resume substance evaluation work and a paragraph inviting the countries to fund the activities mentioned in the Resolution. Making funding for continuing ECDD activities sustainable was also discussed in the plenary of the CND. Several countries showed interest in providing resources.

The ECDD acknowledged the additional resolutions since the last ECDD meeting, and noted that while they do not have direct impact on the scheduling decisions of the ECDD, they are part of the broader context of international drug policy.

The Expert Committee noted from the pertinent provisions in the international drug control conventions and the guidance on substance evaluation, that the involvement of WHO is indispensable in the process of scheduling of a substance

for international control, and that it will only recommend scheduling after scientific evaluation by the ECDD.

3. Critical review of psychoactive substances

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 Single Convention on Narcotic Drugs and the 1971 Convention on Psychotropic Substances concerning the scheduling of a substance.
2. There has been an explicit request from the United Nations CND 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 by any Party that a substance presenting an especially serious risk to public health and society, and of no recognized therapeutic use is clandestinely manufactured.

If therapeutic use of the substance is confirmed subsequently by any Party in respect of case 4, the substance shall be subject to a pre-review.

Two substances under critical review at the thirty-fifth meeting (γ -hydroxybutyric acid (GHB) and ketamine) had been examined at the thirty-fourth meeting and recommended for critical review (6).

3.1 Substance recommended for change in scheduling

γ -Hydroxybutyric acid (GHB)

This section provides information additional to the information presented in the report of the thirty-fourth meeting (6). The Expert Committee discussed GHB in the context of γ -butyrolactone (GBL) and 1,4-butanediol (1,4-BD), precursors of GHB, see sections 4.4 and 4.5.

Substance identification and pharmacodynamics

γ -Hydroxybutyric acid (GHB), also known as 4-hydroxybutanoic acid and sodium oxybate, is a naturally occurring substance found in low concentrations in mammalian tissues. It is considered to act by binding to GHB-specific receptors and γ -aminobutyric acid B (GABA_B) receptors. At pharmacological doses it acts as a central nervous system depressant.

Previous reviews

GHB was pre-reviewed during the thirty-first (15) and thirty-second (16) meetings, held in 1998 and 2000, respectively. In 2001, GHB was placed in Schedule IV of the 1971 Convention by a decision of the CND. It was again pre-reviewed at the thirty-fourth ECDD meeting in 2006 (6), at which time the Expert Committee recommended a new critical review to consider its possible rescheduling.

Evidence on dependence potential

The Expert Committee examined additional information from the updated critical review report and peer-review reports. The Expert Committee noted that there is compelling evidence that dependence on GHB exists in humans and noted withdrawal syndromes and withdrawal seizures.

Actual abuse

The Expert Committee noted that at present, GHB appears to be mainly used and abused in the United States of America, Europe and Australia. Most GHB used illicitly originates from clandestine manufacture.

In their discussions, the Expert Committee and advisers agreed on the narrow margin of safety of GHB. There have been numerous reports from Europe and

the United States of accidental fatal and non-fatal overdoses where GHB was implicated, both when used alone and with other substances.

The Expert Committee also noted there have been reports of GHB being used to facilitate sexual assault.

Therapeutic usefulness

GHB is used as a medicine in some countries on a small scale for various indications. GHB is not included in the WHO Model List of Essential Medicines (17).

Need for the substance for other purposes (e.g., industrial)

The Expert Committee acknowledged the use of GHB in the production of a wide variety of industrial polymers.

Measures taken by countries to curb abuse

The Expert Committee was made aware of measures taken by 30 out of the 51 countries that responded to the questionnaire circulated by WHO in 2008 in preparation for the meeting. For example, Norway is planning to implement legal limits for driving under the influence of non-alcohol drugs including GHB. In the United States, GHB (Xyrem[®]) is available for the treatment of narcolepsy in association with an extensive risk management programme. Postmarketing data from this programme show minimal abuse or diversion of this product. The Netherlands recently re-assessed the risk potential of GHB and found it to be moderate to high. On this basis GHB was upgraded to List 1 (hard drugs) of the Dutch Opium Act.

Recommendation

The Expert Committee considered the implications of rescheduling this substance. On the basis of available data on its toxicity and dependence potential, the Committee rated the abuse liability of GHB to be substantial, whereas the therapeutic usefulness is little to moderate. The Committee therefore came to the conclusion that GHB should be moved from Schedule IV to Schedule II of 1971 Convention.

3.2 Other substance critically reviewed

Ketamine (INN)

Substance identification

Ketamine (INN) is (\pm) -2-(*o*-chlorophenyl)-2-(methylamino)-cyclohexanone. It contains a chiral centre, resulting in two enantiomers: *S*-(+)-ketamine and *R*-(-)-ketamine. Usually, the racemate is marketed, but the more active *S*-(+)-enantiomer is increasingly present in commercially available preparations.

Previous reviews

During its thirty-third meeting in September 2002, the ECDD pre-reviewed ketamine (18). Based on the available information, a recommendation was made for a critical review of this substance. During its thirty-fourth meeting, the ECDD discussed the critical review report on ketamine and concluded that this information was not sufficient to warrant scheduling (6). The Committee therefore requested the Secretariat to produce an updated version of the critical review for the thirty-fifth meeting.

Evidence on dependence potential

Ketamine may produce dependence in animal models, but reports of dependence in humans are rare and largely limited to health-care professionals with access to ketamine. The short duration of action makes it difficult to maintain intoxication for sustained periods. Tolerance may occur, but there is insufficient evidence to show that ketamine causes a withdrawal syndrome in humans.

Actual abuse

Information on ketamine is not routinely collected in population surveys and morbidity and mortality data collection systems. Levels of use in the general population, however, appear to be very low with higher levels in groups with access to the substance (e.g., medical and veterinarian professionals) and party drug users. Ketamine is difficult to synthesize, so illicit production is rare in most countries. However, representatives of the INCB and United Nations Office on Drugs and Crime (UNODC) reported that illicit production of ketamine is of increasing concern in China and India. China reported an increase in the chronic use of ketamine among young adults, particularly in Macao and Hong Kong. The chronic use of ketamine was associated with urinary tract dysfunction. In the United States, a national survey of schoolchildren showed that ketamine use has remained very low and steady since 2007, and data from hospital emergency

departments suggest that ketamine-related visits constitute fewer than one out of every 2000 visits caused by illicit drug use per year.

Therapeutic usefulness

Ketamine is widely used as an anaesthetic in human and veterinary medicine, and is included in the WHO Model List of Essential Medicines (17) and WHO Model List of Essential Medicines for Children (19). Compelling evidence was presented about the prominent place of ketamine as an anaesthetic in developing countries, particularly in Africa. The ease of parenteral administration gives ketamine a major advantage when anaesthetic gases are impossible to use due to limited equipment and a lack of appropriately trained specialists. In many countries there are no suitable alternatives that are affordable.

Recommendation

Ketamine is a widely used anaesthetic, especially in developing countries, because it is easy to use and has a wide margin of safety when compared with other anaesthetic agents. While the Expert Committee acknowledged the concerns raised by some countries and UN organizations, ketamine abuse currently does not appear to pose a significant global public-health risk. Concerns were raised that if ketamine were placed under international control, this would adversely impact its availability and accessibility. This in turn would limit access to essential and emergency surgery, which would constitute a public-health crisis in countries where no affordable alternative anaesthetic is available. On this basis, the Expert Committee decided that bringing ketamine under international control is not appropriate. Furthermore, it noted that some countries have already placed this medicine under control. Countries with serious abuse problems may decide to maintain control measures, but should ensure ready access to ketamine for surgery and anaesthesia for human and veterinary care.

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 as to whether critical review is necessary is whether or not WHO has information that might justify the scheduling of the substance. In the case of psychotropic substances, this requires information on actual abuse of the drug, which causes significant public health and social problems.

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.

Prior to the thirty-fifth meeting of the ECDD, the Secretariat submitted each of the pre-review reports to an expert for peer review and made them available on the Internet.

4.1 Dextromethorphan (pINN)

Dextromethorphan is (+)-3-methoxy-17-methyl-(9 α ,13 α ,14 α)-morphinan. During the fourth meeting of the ECDD in 1953 (then: Expert Committee on Drugs Liable to Produce Addiction), the synthetic substances of the morphinan type, including dextromethorphan, were discussed (20). After reviewing the worldwide reports at that time, the Expert Committee concluded that dextromethorphan has no morphine-like actions, lacks the ability to sustain morphine dependence, and exhibited no signs of dependence liability. Therefore, the Expert Committee recommended against placing dextromethorphan under control of the Conventions. In order to update the scientific evidence on dextromethorphan, a member of the Expert Committee proposed that it be pre-reviewed.

Dextromethorphan is the *d*-isomer of the codeine analogue methorphan; however, unlike the *l*-isomer, it does not act through opioid receptors. Dextromethorphan binds with high affinity to sites associated with sigma ligands and low affinity to the phencyclidine (PCP) binding site of the *N*-methyl-D-aspartate (NMDA) receptor. The relationship of these receptor binding sites to the pharmacological mechanism of the antitussive effects of dextromethorphan is not known. Dextromethorphan produces PCP-like discriminative stimulus effects in rats and partial substitution for PCP in monkeys probably produced by the metabolite dextrorphan. Dextromethorphan can alter self-administration of several substances of abuse such as morphine, cocaine, and methamphetamine. Few data

exist on dextromethorphan dependence, with only a handful of cases described in scientific literature. Cases of abuse of dextromethorphan have been reported in several countries. However, these reports are still relatively infrequent. Dextromethorphan is produced commercially in many regions of the world, but synthesis is a complex and time-consuming process, making clandestine production impractical. Dextromethorphan is widely used as an antitussive in many over-the-counter and prescription-only preparations.

Recommendation

Following review of the documents presented at the thirty-fifth meeting, the Expert Committee concluded that the abuse potential of dextromethorphan is relatively low, intoxications are rare, and reports of dependence are infrequent. Dextromethorphan is widely used as an antitussive agent and placing it under international control could negatively impact its availability for medical use. On this basis, the Expert Committee concluded that a critical review is not warranted at this time.

4.2 Tapentadol (INN)

Tapentadol is 3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]-phenol hydrochloride. Tapentadol has two chiral centres and is manufactured as a single (*R,R*) stereoisomer. Tapentadol shares a 3-(3-hydroxyphenyl)propylamino structural fragment with morphine and its analogues. It is a novel analgesic agent with activity at the μ -opioid receptor and norepinephrine reuptake inhibition. Immediate release and extended release formulations of tapentadol are indicated for analgesia. Tapentadol demonstrates improved gastrointestinal tolerability (specifically in the incidence of nausea, vomiting, and constipation) compared with strong opioids at doses providing similar analgesia. Dependence has been demonstrated in animal models, but the level of dependence relative to morphine is not known. Mild withdrawal was observed in clinical trials submitted for the initial approval of tapentadol. Tapentadol has only been marketed since 2009 and therefore has not appeared in many substance use surveys or surveillance reports. Overall, toxicity for tapentadol does not appear to be greater than that for other μ -opioid receptor agonists. In the 3 years since tapentadol was launched in the United States, analyses of postmarketing surveillance data show lower abuse than oxycodone and slightly higher abuse than tramadol. The Expert Committee noted that tapentadol has been scheduled or recommended for scheduling in Australia, Germany, the Netherlands, New Zealand, Switzerland, the United States and the United Kingdom.

Recommendation

Given the action of tapentadol at the μ -opioid receptor, together with some evidence of abuse, the Expert Committee recommended that a critical review be conducted.

4.3 Piperazines

4.3.1 *N*-Benzylpiperazine (BZP)

N-Benzylpiperazine (BZP) is 1-benzylpiperazine. It is a piperazine derivative with stimulant properties (including euphoria). Animal studies have shown that BZP stimulates the release and inhibits the reuptake of dopamine, serotonin and noradrenaline, but dopaminergic and serotonergic effects predominate. In studies, BZP was found to be less potent than methylenedioxymethamphetamine (MDMA), methamphetamine or amphetamine. BZP has never been licensed as a medicine but was found to be an active metabolite of a proposed anti-depressant (piberaline, a product that was later not marketed). Abuse was first reported in the late 1990s in the USA and Scandinavia but has since been reported in other countries (particularly in Australia, Europe and New Zealand). The behavioural effects of BZP include amphetamine-like effects. Many suppliers of BZP market the substance as “legal ecstasy” or as a “legal high”. Such products typically contain other piperazine derivatives in variable quantities. Toxic effects have been reported (agitation, tachycardia and seizures) with associated hospital admissions, but cases involving BZP alone are rare. Although BZP has been found in substance-related deaths, in the vast majority of instances, other commonly abused substances were also present; therefore the role of BZP in these deaths is unclear.

Recommendation

Based on the reported psychostimulant effects, evidence of abuse, and adverse effects, the Expert Committee concluded that a critical review of *N*-benzylpiperazine is warranted.

4.3.2 *1*-(3-Trifluoromethylphenyl)piperazine (TFMPP)

1-(3-Trifluoromethylphenyl)piperazine (TFMPP) is a piperazine derivative with mild stimulant effects and hallucinogenic properties. TFMPP has never been licensed as a medicine but is a known metabolite of a previously used anti-inflammatory analgesic (antrafenine). Its use was first reported in the late 1990s in Scandinavia and the United States along with BZP, but has since been reported in various other countries (particularly Europe and New Zealand). Many suppliers of TFMPP market the substance as “legal ecstasy” or as a “legal high”. Such products typically contain other piperazine derivatives in variable quantities. Very few user reports involving the use of TFMPP alone have been documented. However, the toxic effects reported include: nausea, hallucinations and slight tremors. Hospital admissions have occurred, but all involved other substances (including piperazines). Although TFMPP has been found in drug-related deaths, in the vast majority of instances, other substances of abuse were also present; therefore the role of TFMPP in these deaths is unclear. Animal studies

have indicated that TFMPP is unlikely to possess abuse or dependence potential, but there are no human clinical studies to support this.

Recommendation

1-(3-Trifluoromethylphenyl)piperazine does not appear to have abuse and dependence potential. On this basis, the Expert Committee decided that a critical review is not warranted at this time.

4.3.3 1-(3-Chlorophenyl)piperazine (mCPP)

1-(3-Chlorophenyl)piperazine (mCPP) is a piperazine derivative with stimulant (including euphoric) and hallucinogenic properties. mCPP has never been licensed as a medicine but is a known metabolite of some antidepressants and is a tranquillizer. Its use was first reported in the mid-2000s across Europe but has since been reported in various other countries (e.g., the United States). mCPP is sometimes sold as “legal ecstasy” or as a “legal high” or as “ecstasy” itself. Such products can contain other piperazine derivatives as well as other psychoactive substances including MDMA. Very few user reports involving the use of mCPP alone have been documented. However, the toxic effects reported include: nausea, hallucinations, headache and most frequently, anxiety and panic attacks. There are no published reports of non-fatal or fatal hospital admissions. In Europe, a few cases reported to monitoring centres have mentioned hot flushes, some respiratory problems and coma, but all these cases also involved other unspecified substances. No specific studies have been performed to determine the abuse or dependence potential of mCPP but, in animal discrimination studies, it has been found to mimic TFMPP, ethanol and MDMA, but not lysergic acid diethylamide (LSD). Its abuse and dependence potential in humans is unclear.

Recommendation

The Expert Committee considered the information contained in the pre-review, and found that there is a paucity of data on 1-(3-chlorophenyl)piperazine. Furthermore its abuse and dependence potential in humans remains unclear. On this basis, the Expert Committee concluded that a critical review is not warranted at this time.

4.3.4 1-(4-Methoxyphenyl)piperazine (MeOPP)

1-(4-Methoxyphenyl)piperazine (MeOPP) is a piperazine derivative that appears to have mild stimulant effects (including euphoria) and some hallucinogenic properties. Very little information is available on this substance. MeOPP has never been licensed as a medicine. The first report of seized material containing MeOPP appeared in 2006 in the United Kingdom. Many suppliers market the substance as “legal ecstasy” or as a “legal high”. Such products typically contain other piperazine derivatives in variable quantities. There are no published reports of non-fatal or fatal hospital admissions. No specific studies have been performed to determine the abuse or dependence potential.

Recommendation

Given the limited information available, and the current lack of evidence of abuse, the Expert Committee recommended that a critical review for 1-(4-methoxyphenyl)piperazine not be conducted at this time.

4.3.5 1-(3,4-Methylenedioxybenzyl)piperazine (MDBP)

1-(3,4-Methylenedioxybenzyl)piperazine (MDBP or MDBZP) is a piperazine derivative but its effects are largely unknown. MDBP has never been licensed as a medicine but is a metabolite of a withdrawn nootropic medicine, fipexide. This medicine was withdrawn because it had adverse toxic effects (fever and hepatotoxicity). Use of MDBP has been noted by governmental organizations in the United States but there are no reports from other countries. There are no published reports of non-fatal or fatal hospital admissions. No specific studies have been performed to determine the abuse or dependence potential of MDBP.

Recommendation

Based on the lack of animal, human clinical, and epidemiological data on the abuse and dependence potential of MDBP, the Expert Committee did not recommend a critical review of 1-(3,4-methylene-dioxybenzyl) piperazine at this time.

4.4 γ -Butyrolactone (GBL)

γ -Butyrolactone (GBL) is oxolan-2-one. The pre-review of GBL was decided on the basis that GBL can be readily converted both chemically and in the body to GHB. GHB is a controlled substance under the 1971 Convention, and was subject to a critical review at the thirty-fifth meeting of the ECDD. The Expert Committee discussed GBL in the context of GHB and 1,4-butanediol (1,4-BD), another precursor of GHB, see sections 3.1 and 4.5. GBL is widely used as a solvent and reagent in the chemical industry. Since the end of the 1990s, reports of abuse of GBL have emerged, mainly from Australia, Europe and the United States. The epidemiology of the abuse of GBL is intrinsically linked to that of GHB since GBL is rapidly metabolized to GHB. A few deaths have been documented, but owing to the rapid metabolism it is difficult to establish whether GHB, GBL or 1,4-BD was consumed. Several cases of withdrawal from GBL, 1,4-BD and GHB have been documented. The new controls rapidly curtailed the previously open sale of GHB. This may also help to explain the emergent use of GBL, which does not currently fall under the controls of the international drug control convention. In view of concerns about the diversion of GBL and 1,4-BD for conversion to GHB, some Member States have chosen to control GBL, 1,4-BD, or both, under drug control or equivalent legislation and voluntary measures to prevent diversion.

Recommendation

Based on the evidence presented in the pre-review of GBL, its close association with GHB, and the recommendation made by the Expert Committee to reschedule GHB from Schedule IV to Schedule II of the 1971 Convention, the Committee recommended that a critical review of GBL be undertaken.

4.5 1,4-Butanediol (1,4-BD)

The pre-review of 1,4-BD was conducted on the basis that 1,4-BD can be readily converted both chemically and in the body to GHB. GHB is a controlled substance under the 1971 Convention, and was subject to a critical review at the thirty-fifth meeting of the ECDD. The Expert Committee discussed 1,4-BD in the context of GHB and GBL, another precursor of GHB, see sections 3.1 and 4.4. 1,4-BD is an industrial chemical and an important raw material widely used in the chemical, pharmaceutical, textile, paper making, and motor vehicle industries. Starting in the 1990s, it is believed that national controls on GHB prompted substitution of 1,4-BD and GBL for GHB as drugs of abuse. The epidemiology of the abuse of 1,4-BD is intrinsically linked to that of GHB since 1,4-BD is rapidly metabolized to GHB. A few deaths have been documented, but owing to the rapid metabolism it is difficult to establish whether GHB, GBL or 1,4-BD was consumed. It appears to be mainly used and abused in Australia, Europe, and the United States. The new controls rapidly curtailed the previously open sale of GHB. They may also help to explain the emergent use of 1,4-BD, which does not currently fall under the controls of the international drug control convention. In view of concerns about the diversion of GBL and 1,4-BD for conversion to GHB, some Member States have chosen to control GBL, 1,4-BD, or both, under drug control or equivalent legislation and voluntary measures to prevent diversion.

Recommendation

Based on the evidence presented in the pre-review of 1,4-BD, its close association with GHB, and the recommendation made by the Expert Committee to reschedule GHB from Schedule IV to Schedule II of the 1971 Convention, the Committee recommended that a critical review of 1,4-BD be undertaken.

5. Issues identified for consideration at future ECDD meetings

The Expert Committee was informed that the Secretariat was likely to propose several substances for inclusion on the agenda of a future ECDD meeting:

- The Commission on Narcotic Drugs, in its resolution 52/5 *Exploration of all aspects related to the use of cannabis seeds for illicit purposes* requested cannabis be reviewed (21).
- Noting the concerns of the CND expressed in Resolution 55/1, *Promoting international cooperation in responding to the challenges posed by new psychoactive substances* (14) and Resolution 53/11, *Promoting the sharing of information on the potential abuse of and trafficking in synthetic cannabinoid receptor agonists* (22), the Secretariat is planning to carry out reviews of mephedrone and of synthetic cannabinoids.
- Furthermore, the Secretariat was notified by the Secretary-General, United Nations, of the exemption by the Government of Germany of one cathine preparation and six flunitrazepam preparations from certain provisions under the 1971 Convention and this will be proposed for assessment according to Article 3 paragraph 4 of the Convention on Psychotropic Substances and paragraph 61 of the *Guidance on the WHO review of psychoactive substances for international control* (1).

One expert proposed the pre-review of zolpidem, which is currently in Schedule IV of the 1971 Convention. This will be included in the list of future pre-reviews.

There was a brief discussion as to whether ethanol (ethyl alcohol) should be considered for pre-review. The Secretariat informed the Expert Committee that WHO Secretariat and Member States are in the process of implementing the WHO Global Strategy to Reduce the Harmful Use of Alcohol, which was adopted by the World Health Assembly (WHA) in 2010 (Resolution WHA63.13) (23). Noting this, the Expert Committee referred the matter for consideration at a future Expert Committee meeting.

The Australian National Council on Drugs, a government-appointed expert panel, requested that the Secretariat consider reviewing levacetylmethadol (LAAM) at a future meeting. Their request was not based on its status under international control, but rather to determine if a recommendation should be made regarding access to this medicine for the management of opioid dependence. It is possible that the availability of LAAM may improve access to management of opioid dependence.

6. Other matters

6.1 Use of terms

The Expert Committee noted that revision of the International Classification of Diseases (ICD) is presently under way, and planned for submission for approval to the World Health Assembly in 2015. The current discussions by the pertinent groups of experts indicate that the relevant terms and their general definitions and meaning in the tenth revision (ICD-10) are likely to be retained in the eleventh revision (ICD-11). The Committee discussed the terms related to the work of the ECDD, their meanings, and development of terminologies for substance evaluation in the decades since the Single Convention on Narcotic Drugs and the Convention on Psychotropic Substances were adopted. The issues discussed are contained in the Annex (Developments in terminology: the drug treaties, scheduling criteria, and diagnostic terms). The Expert Committee agreed that several topics require further deliberation, and additional aspects may need to be considered.

The Expert Committee further recognizes that there is much stigma around drug use and drug use disorders, and that occasional changes in terminology may be needed to meet the goal of humane and respectful treatment for patients.

The Committee decided that redefining terminologies for substance evaluation requires thorough preparation and discussion of wording by multiple experts, followed by a proposal to the Committee which would be distributed well in advance. The Committee invited the Secretariat to organize the debate and to propose the issue of terminology for consideration again at its thirty-sixth meeting.

The Expert Committee recommended revisiting the definitions found in the 1994 *Lexicon of alcohol and drug terms* (24), as well as those in ICD-11, with the intention of providing further clarification on how this terminology relates to the terms used in the international drug control system. This should result in an updated version of the Lexicon.

6.2 Use of pharmacovigilance data for the assessment of abuse and dependence potential

During its thirty-fourth meeting, the ECDD discussed the use of pharmacovigilance data as a potential source to inform scheduling decisions. Accordingly, the Secretariat organized a discussion with experts on drug dependence assessment and pharmacovigilance in 2007, and the WHO Uppsala Monitoring Centre (UMC) undertook a study to identify indicators of drug abuse and dependence potential from its database, *VigiBase*TM. During the thirty-fifth meeting of the

ECDD, a representative of the UMC presented the results of analyses which the Expert Committee used to assess the utility of pharmacovigilance data in making scheduling decisions.

After examining the analyses conducted by the UMC, the Expert Committee considered that refinement of the methodology is warranted. However, it was noted that the pharmacovigilance systems being developed have the capacity for early identification of potential abuse and dependence. The Committee recommended that the Secretariat work together with the UMC to continue to use VigiBase to support scheduling decisions. The Expert Committee requested that the UMC adds, on a trial basis, to its quarterly analysis, those medicines with signals for “dependence” and “dependence relatedness” and any additional demographic and clinically descriptive data available on these medicines from VigiBase. This methodology could also be used to assist with analysing the medicines under review by the Committee. Further clarification was requested on the manner in which withdrawal syndromes are coded and analysed.

The Secretariat and UMC will further work on the best strategy for ongoing and periodic data mining for signals relevant to the work of the Expert Committee. The results from the analysis of VigiBase data will be included on a trial basis in the preparation of the pre-review and critical review reports for substances under review by the ECDD.

Finally, the Expert Committee suggested that the Secretariat explore the use of poison centre data for postmarketing surveillance of controlled substances.

6.3 Balancing medical availability and prevention of abuse of medicines manufactured from controlled substances

During its thirty-fourth meeting, the Committee discussed factors limiting the availability of controlled substances for medical use, including barriers inadvertently created by the application of laws and regulations, and requested the WHO Secretariat to suggest including on the proposed agenda of the thirty-fifth ECDD meeting, a discussion of the impact of scheduling on the balance between medical availability of controlled substances and the prevention of abuse (6).

The Committee was informed that WHO estimates that 5.5 billion people (83% of the world’s population) live in countries with low to non-existent access to controlled medicines and have inadequate access to treatment for moderate to severe pain. In these countries, each year tens of millions of patients are suffering without adequate pain management – for instance, 1 million patients with end-stage human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), 5.5 million patients with terminal cancer, 0.8 million patients with

injuries caused by accidents and violence, and women in labour (110 million births each year).

In addition, availability of pharmacological treatment for patients with opioid dependence can prevent many new HIV infections, and would also result in better health for patients with opioid dependence. Equally, maternal deaths could be prevented if emergency obstetric medicines were more readily available. Some of these obstetric medicines are controlled as precursors.

The Expert Committee took note of this information and considered that it is important that different stakeholders, including national governments, WHO, other international agencies and health-care workers, join forces to make these medicines accessible to all in need, while ensuring prevention of diversion and abuse.

The Expert Committee noted that it was important that any policy measures adopted by a country to counteract abuse and diversion of any substance used therapeutically should specifically target the actual mechanisms of diversion and abuse, as established by sound analysis of the situation, and should not negatively impact patients' access to adequate treatment. This requires rational prescribing according to guidelines.

The Expert Committee also noted the difficulty in establishing policies for issues of pain and palliative care, since these are cross-cutting topics that may involve many diseases, such as cancer, HIV/AIDS, extremely resistant tuberculosis and congenital disease.

Recommendations

The Expert Committee recommended that WHO continue to promote the implementation of its policy guidelines *Ensuring balance in national policies on controlled substances*, *Guidance for availability and accessibility of controlled medicines* (25), as well as the *WHO Guidelines on the pharmacological treatment of persisting pain in children with medical illnesses* (26) and the *WHO Guidelines on the psychosocially assisted pharmacological treatment of opioid dependence* (27). It further recommended that WHO continue to develop guidelines on the management of acute pain and of chronic pain in adults.

The Expert Committee recommended that WHO continue to promote the availability of all controlled medicines listed by the WHO in its Model List of Essential Medicines (17) and its Model List of Essential Medicines for Children (19). It should also promote the annual submission of adequate estimates for these medicines to the INCB using the *Guide on estimating requirements for substances under international control*, developed by the International Narcotics Control Board and the World Health Organization for use by the competent national authorities (4). If necessary, supplementary estimates should be submitted immediately to the INCB throughout the year.

6.4 Improving the process for substance evaluation

The Secretariat conducted a research project on the evaluation of substances since the first drug control conventions with the involvement of specialists who had served in the past as experts on the ECDD or as technical advisers (E. Danenberg *et al.*, unpublished data, 2012). The project also focused on the improvement of the process. The Expert Committee noted with approval a proposal to put in place a process to review each scheduled substance every 20 years. The Expert Committee welcomed the intention of the Secretariat to continually strengthen the review process by evaluating the evidence using systematic rating methodology, such as Grading of Recommendations Assessment, Development and Evaluation (GRADE) (28).

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Annex

Developments in terminology: the drug treaties, scheduling criteria, and diagnostic terms

A primary task of the Expert Committee on Drug Dependence is to provide technical determinations concerning particular substances under the provisions of the Single Convention on Narcotic Drugs, 1961 and the Convention on Psychotropic Substances, 1971. These technical determinations are made and documented using specific provisions and terms defined in the two Conventions. In the half-century since the Single Convention on Narcotic Drugs, 1961 was adopted, there has been considerable development in the terminology used to describe psychoactive substance use, problems and diagnoses. This annex reviews the terminology used in the Conventions, and discusses developments in the meaning and application of the terms, and how the Expert Committee currently applies the terms in its role under the Conventions.

The term “drug dependence”

Previous Expert Committee reports (1, 2) give the following definition of drug dependence: “A cluster of physiological, behavioural and cognitive phenomena of variable intensity, in which the use of a psychoactive drug (or drugs) takes on a high priority. The necessary descriptive characteristics are preoccupation with a desire to obtain and take the drug and persistent drug-seeking behaviour.” The physical phenomena of withdrawal and tolerance are thus included in dependence, but are not necessary to it. As the Expert Committee has used the term, it is applicable to all relevant psychoactive substances, whether licit or illicit, and whether used for medical or non-medical purposes.

Dependence was introduced with roughly this meaning at the thirteenth meeting of the Expert Committee, to replace the term “addiction” (3). However, addiction, as mentioned in the preamble to the Single Convention on Narcotic Drugs, 1961, has remained in common use in the English language, and there have been calls for its reinstatement as a technical term (4). Meanwhile, in English and some other languages (5), “addiction” has increasingly taken on a wider meaning and now includes behaviours such as addiction to gambling and Internet addiction.

A further reason for dropping “addiction” as a technical term has been the perception that its connotations are pejorative and stigmatizing. This reason also underlies moves away from other terms such as “abuse” as technical terms. The

stigma around drug use means that occasional changes in terminology may be needed to meet the goal of humane and respectful treatment of patients.

Terminology and concepts concerning drug use and problems also vary somewhat across languages and cultures, and attention to this issue is needed in the context of a system of drug control which is global in its reach.

The main WHO diagnostic terms for substance use disorders, “dependence” and “harmful use”, appear likely to remain in the forthcoming revision of the International Classification of Diseases.

The term “drug abuse”

“Abuse” is used in both the Single Convention on Narcotic Drugs, 1961 (Article 3, Section 3) and the Convention on Psychotropic Substances, 1971 (Article 2, Section 4b) as part of the criteria to be applied by the Expert Committee in deciding on the scheduling of substances for control, but the Convention does not define the term.

While the Conventions’ use of the term refers to patterns at a population level, the term is often also used to characterize behaviour at the individual level. In this context, a previous Expert Committee defined drug abuse as “persistent or sporadic excessive drug use inconsistent with or unrelated to acceptable medical practice” (6). It will be noted that the Expert Committee’s definition mentioned above is narrower than common usage of the term “abuse”, which usually refers to any nonmedical use.

“Drug abuse” was also used as a technical diagnostic term in earlier editions of the International Classification of Diseases, but WHO publications had already moved away from using the term in 1975 (7) due to its stigmatizing connotations, and it was dropped from the International Classification of Diseases in 1992. In interpreting the term as used in the Conventions, it is appropriate for the Expert Committee to use the broad characterization quoted from the Convention on Psychotropic Substances.

“Dependence potential” and “abuse potential”

Expert Committees have assessed the dependence potential of substances in accordance with the criterion of the Convention on Psychotropic Substances, 1971 that a drug “has the capacity to produce a state of dependence”. While attention is routinely paid to the phenomena of withdrawal and tolerance, the Expert Committee has generally given priority to the cognitive, behavioural and psychosocial dimensions of dependence, although the evidence available on

these aspects has often been relatively narrow, such as how pleasurable the drug is to an experienced drug user.

The Expert Committee has also generally considered “abuse liability” or “abuse potential” of the substance (considered as equivalent terms), although some Expert Committees have preferred longer formulations: “likelihood of abuse” (8) or “actual abuse and/or evidence of likelihood of abuse” (2). Although “the concept of abuse potential encompasses all the properties of a drug including, for example, chemical, pharmacological, and pharmacokinetic characteristics, as well as fads in usage and diversion history” (9), “abuse potential” as used in Expert Committee deliberations includes such matters as the severity and disabling nature of the intoxication a drug produces, as well as its dependence potential and public-health and social problems from its use.

Some previous Expert Committees have conceptualized dependence and abuse potential as separate concepts side by side, and there have also been complaints of the terms being used interchangeably (8), but it is more in accord with the frame of reference of the Convention on Psychotropic Substances, 1971 to follow the conclusions of the twenty-seventh (10) and thirty-third meetings of the Expert Committee (2) in conceptualizing abuse potential as an overarching concept, with dependence potential as a constituent part of it.

The range of public health and social problems to be considered

The Expert Committee presently seeks a wide range of information about potential dimensions of public-health and social problems arising from use of a particular substance as part of its responsibility for assessing abuse potential. These include the nature and sequelae of intoxication with the substance, and harm to the individual, for instance from overdose, adverse reactions to the drug, and other consequences of use for physical and mental health. They also include harm which may occur to others as well as to the user, such as drug-related traffic crashes, hospital emergency department admissions, and assaults. An effort is made to take into account whether the harm results directly from the drug use or arises from fears and other social responses to the drug use.

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This report presents the recommendations of a WHO Expert Committee responsible for reviewing information on psychoactive substances to assess the need for their international control.

The report contains a summary of the Committee's evaluations of γ -hydroxybutyric acid (GHB) and ketamine. GHB was recommended to be rescheduled from Schedule IV to Schedule II of the Convention on Psychotropic Substances. The report also discusses the nine substances that were pre-reviewed: dextromethorphan, tapentadol, N-benzylpiperazine (BZP), 1-(3-trifluoromethylphenyl)piperazine (TEMPP), 1-(3-chlorophenyl)piperazine (mCPP), 1-(4-methoxyphenyl)piperazine (MeOPP), 1-(3,4-methylenedioxybenzyl)piperazine (MDBP), γ -butyrolactone (GBL), and 1,4-butanediol (1,4-BD). Of these, tapentadol, BZP, GBL and 1,4-BD were recommended for critical review. Issues identified for consideration at future Expert Committee meetings are also listed.

Furthermore, the report discusses the use of terms, the use of pharmacovigilance data for the assessment of abuse and dependence potential, balancing medical availability and prevention of abuse of medicines manufactured from controlled substances, and improving the process for substance evaluation.

