

**WHO Expert Committee
on Drug Dependence**

Thirty-seventh report



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*This report contains the views of an international group of experts, and does not necessarily represent
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Geneva, Switzerland, 16–20 November 2015

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Abbreviations

α -PVP	α -pyrrolidinovalerophenone
AH-7921	3,4-dichloro- <i>N</i> -{[1-(dimethylamino)cyclohexyl]methyl}benzamide
AM-2201	[1-(5-fluoropentyl)-1 <i>H</i> -indol-3-yl](naphthalen-1-yl)methanone
AMT	alpha-methyltryptamine
AKB-48	APINACA
25B-NBOMe	2-(4-bromo-2,5-dimethoxyphenyl)- <i>N</i> -[(2-methoxyphenyl)methyl]ethanamine
25C-NBOMe	2-(4-chloro-2,5-dimethoxyphenyl)- <i>N</i> -[(2-methoxyphenyl)methyl]ethanamine
25I-NBOMe	2-(4-iodo-2,5-dimethoxyphenyl)- <i>N</i> -[(2-methoxyphenyl)methyl]ethanamine
1,4-BD	1,4-butanediol
BK-MDMA	methylone
BZP	<i>N</i> -benzylpiperazine
CND	Commission on Narcotic Drugs
4,4'-DMAR	para-methyl-4-methylaminorex
ECDD	Expert Committee on Drug Dependence
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EWA	Early Warning Advisory
4-FA	4-fluoroamphetamine
4-FMC	4-fluoromethcathinone
GBL	gamma-butyrolactone
INCB	International Narcotics Control Board
INN	International Nonproprietary Name
JWH-018	naphthalene-1-yl(1-pentyl-1 <i>H</i> -indol-3-yl)methanone
JWH-073	(1-butyl-1 <i>H</i> -indol-3-yl)(naphthalen-1-yl)methanone
JWH-250	2-(2-methoxyphenyl)-1-(1-pentylindol-3-yl)ethanone
LSD	lysergic acid diethylamide
MDMA	3,4-methylenedioxymethamphetamine
MDPV	3,4-methylenedioxypropylvalerone
4-MEC	4-methylethcathinone
MPA	methiopropamine
MT-45	(<i>R/S</i>)-1-cyclohexyl-4-(1,2-diphenylethyl)piperazine
MXE	methoxetamine
NPS	new psychoactive substances

PMMA	<i>para</i> -methoxymethylamphetamine
RCS-4	4-methoxyphenyl(1-pentyl-1 <i>H</i> -indol-3-yl)methanone
UNGASS	United Nations General Assembly Special Session
UNODC	United Nations Office on Drugs and Crime
UR-144	(1-pentyl-1 <i>H</i> -indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone
WHA	World Health Assembly
WHO	World Health Organization

Introduction

The thirty-seventh meeting of the WHO Expert Committee on Drug Dependence (ECDD) took place in Geneva, Switzerland from 16 to 20 November 2015.

Mr Cornelis de Joncheere, Director, WHO Department of Essential Medicines and Health Products (EMP), opened the meeting. He welcomed all participants on behalf of the Director-General. He then introduced Dr Marie-Paule Kieny, Assistant Director-General, Health Systems and Innovation, of WHO, who gave the welcoming remarks. She began by emphasizing the importance of the role of the ECDD in advocating for access to effective and safe essential medicines while preventing misuse and abuse of narcotic and psychoactive substances that harm health. She expressed hope that the perspectives on the topics provided during the open session had been useful to the Committee. These open session topics had included ketamine and cannabis, and updates on both of these drugs were to be provided during the ECDD Committee meeting. Dr Kieny argued that it was wrong to put ketamine in the same class as the non-therapeutic, often extremely harmful substances being marketed as recreational drugs. She enumerated the reasons for this view. First, ketamine was not new having first been synthesized more than 50 years ago. Secondly, she indicated that ketamine was possibly one of the most valuable anaesthetics we have: it is among the most widely used and it has been on the WHO Model List of Essential Medicines since 1985. Thirdly, she mentioned that ketamine was also the most widely used anaesthetic in veterinary medicine. Finally, she emphasized that ketamine has such wide use in human and veterinary medicine, in part, because of its high safety margin. She further commented that WHO had previously recommended to the Commission on Narcotic Drugs not to schedule ketamine, because doing so could have important implications for quality services for people's health, especially those in low-income countries and those in crisis situations. She also referred to the United Nations General Assembly Special Session (UNGASS) on the World Drug Problem which would take place in April 2016. Implementation of the conventions would be a focal point of the UNGASS, while shifting the emphasis from policing to health and medication needs. She described how the ECDD's main task during its meeting would be to evaluate new psychoactive substances (NPS) that presented a taxing issue for governments. Dr Kieny emphasized that the Committee should not yield to the temptation to simply schedule every substance that could be harmful, and that the problem needed to be tackled based on evidence.

The international drug control conventions describe the mandate and roles of WHO. A key WHO role within this framework is to assess medical properties and the liability for abuse of and dependence on any substance, pure chemical or plant material, and to advise the United Nations Commission on Narcotic Drugs (CND) on which substances should be placed under international control. The purpose of this meeting was for the ECDD to review a number of substances and to provide its advice on whether these substances should be recommended for scheduling under the international drug control conventions (following a critical review) and to recommend whether a critical review should take place at a subsequent meeting of the ECDD (following a pre-review). The ECDD is mandated to issue recommendations to facilitate WHO's advisory role to the CND, attributed by the Single Convention on Narcotic Drugs, 1961 (1) and the Convention on Psychotropic Substances, 1971 (2).

The WHO review procedure, grounded in considerations of public health, and taking an evidence-based approach, utilizes the best available relevant information. Consistent with the requirements of the 1961 and 1971 conventions, WHO develops scheduling recommendations guided by the provisions in the conventions regarding the changes in the scope of control of substances and also taking into account the preambles of the conventions, which highlight the need to reduce the risk to public health, including the risk of abuse and dependence, and to ensure availability of medicines. WHO also follows the relevant guidance of its governing bodies, in particular WHO's *Regulations on expert advisory panels and committees* (3) as well as the *Guidance on the WHO review of psychoactive substances for international control* (4). The conventions are legal instruments: WHO's review procedure is applied in a manner consistent with the letter and the spirit of the conventions.

The members of the ECDD were reminded by the WHO Secretariat 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 arrive at recommendations that would benefit the world as a whole.

Before the election of the Chair, Co-Chair and Rapporteur, and in accordance with WHO policy, all members of the Expert Committee and all temporary advisers attending the meeting were asked to disclose any circumstances that could represent a potential conflict of interest (i.e. any interest that may affect, or may reasonably be perceived to affect, an expert's objectivity and independence) in relation to the subject matter of the meeting. In the interest

of transparency, the following circumstances were disclosed by the Secretariat at the outset of the meeting.

Professor Buitrago has been a speaker for different pharmaceutical companies on the subjects of quality and regulatory issues for medicines in the past four years.

Professor Madras has been a consultant, reviewing grants and policy for agencies of the United States of America. She has been a scientific advisor to the Rivermend treatment centre and was a member of the prescription advisory committee for Prexa Pharmaceuticals, providing advice on the interpretation of preclinical research data. Dr Madras has also given speeches and talks for non-profit organizations, owns a number of patents related to dopamine transport inhibitors, was an expert witness for the United States of America Department of Justice in 2014–2015 and has been a writer for Rivermend treatment centre and of two books funded by Elsevier Press.

Dr Brandt worked as a consultant for the European Monitoring Centre for Drugs and Drug Addiction between 2013 and 2015 on technical reports and presentations for substances, including *para*-methyl-4-methylaminorex (4,4'-DMAR) and α -pyrrolidinovalerophenone (α -PVP). He is also the United Kingdom of Great Britain and Northern Ireland National Focal Point and Coordinator of the early warning system on NPS for the European Monitoring Centre for Drugs and Drug Addiction.

The disclosed interests were considered by the Expert Committee not to conflict with any issues to be discussed at the meeting or with the recommendations to be issued by the Expert Committee. No other interests declared by members of the Expert Committee were deemed relevant to the work of the group.

The Expert Committee elected a Chair, Co-chair and Rapporteur. The Chair welcomed all participants and the agenda as proposed by the Secretariat was accepted.

1. Work of international bodies concerned with controlled substances

1.1 Update from the International Narcotics Control Board

Dr Viroj Sumyai, Observer for the International Narcotics Control Board (INCB), informed the Committee about the role and functions of INCB. Established by the 1961 Single Convention on Narcotic Drugs, INCB consists of 13 members who are elected by the Economic and Social Council and who serve in their personal capacity, not as government representatives. Three members with medical, pharmacological or pharmaceutical experience are elected from a list of candidates nominated by WHO and 10 members are elected from a list of candidates nominated by governments. Dr Sumyai further recalled the provisions of the treaties on the scheduling procedures foreseen under the 1961 and 1971 conventions and gave an overview of cooperation between INCB and WHO.

In his update on recent developments, particular reference was made to the work of INCB on the availability of internationally controlled drugs for medical and scientific purposes, an area at the core of the Board's mandate. A special report dedicated to this issue would be published in 2016, before the UNGASS on the World Drug Problem, and Dr Sumyai thanked WHO for providing inputs to that report. Dr Sumyai also highlighted the work of INCB on operational aspects of NPS, in particular its Project ION (International Operations on NPS), an international operational initiative supporting national authorities' efforts to prevent non-scheduled NPS of abuse from reaching consumer markets.

1.2 Update from the United Nations Office on Drugs and Crime

Dr Justice Tettey, Observer for the United Nations Office on Drugs and Crime (UNODC) informed the Committee of the Office's role in promoting Member States' understanding of the current emerging drug markets; conducting research to provide the scientific evidence-base for effective policy decisions; and supporting the implementation of the scheduling decisions under the international drug control conventions.

He described the current trends in NPS noting that as of October 2015, more than 600 substances that are not under international control had been reported by 98 countries. Dr Tettey further noted the different patterns in the emergence and persistence of NPS at the

global level, such as the striking heterogeneity at the country level regarding the number and type of NPS and the transient nature of some NPS.

He reported that, pursuant to CND resolutions 57/9 and 58/11, UNODC continued to monitor, analyse and share information on NPS, with its Early Warning Advisory (EWA) on NPS being recognized as the major source of information at the global level. The EWA is a tool used actively by Member States and international organizations, such as WHO and INCB, in the context of evidence-based responses to the problem. Following the joint UNODC-WHO Expert Consultation on New Psychoactive Substances held in Vienna from 9 to 11 December 2014, and further to CND Resolution 58/11, the UNODC EWA had been supporting the ECDD process with information aimed at enabling priority for review to be assigned to the most prevalent, persistent and harmful NPS at the international level.

Dr Tetley noted that identification and detection of substances continues to be a major challenge in terms of monitoring and reporting, and in the implementation of scheduling decisions. In this context, UNODC is supporting Member States through:

- development and dissemination of recommended laboratory methods for analysis of the recently controlled substances;
- provision of chemical reference standards to aid laboratory analysis of these substances in seizures and biological matrices;
- updating of key knowledge products such as the multilingual dictionaries on narcotic drugs, psychotropic substances, precursors and chemicals under international control (5, 6); and
- collection of data on synthetic drugs.

Further challenges highlighted by Dr Tetley included the paucity of data on potential risks and harms of new substances and of other information needed to carry out the risk assessments and the need to improve data exchange between international and regional organizations.

1.3 Update from Management of Substance Abuse Unit, WHO

Dr Vladimir Poznyak, Coordinator, Management of Substance Abuse Unit at the Department of Mental Health and Substance Abuse (MSB/MSD), informed the Committee about the global action plans 2013–2020 for the prevention and control of noncommunicable diseases and mental health where the availability of medicines, including controlled ones, is an

important option for implementation at all levels. The recently approved health target 3.5 “to strengthen the prevention and treatment of substance abuse” in the 2030 agenda for Sustainable Development and the UNGASS on the World Drug Problem to be held in April 2016 create the new context for the international work on drug-related issues. Furthermore, discussion of the public health dimensions of the world drug problem was to be included on the agenda of the 138th meeting of the Executive Board of WHO in January 2016.

A range of activities are being carried out by MSB/MSD, including estimation of drug-attributable disease burden, development of new guidelines and tools for management of disorders resulting from drug use, and production of the report on prevention and treatment resources for substance use disorders. Following the expert meeting in April 2015, the report on health and social consequences of non-medical use of cannabis was being developed. According to the latest WHO survey, after alcohol, cannabis is the second most commonly reported substance at treatment services for substance use disorders worldwide.

The draft version of ICD-11 retains the diagnostic categories of “substance dependence” and “harmful use” and provides additional possibilities for coding and reporting health conditions resulting from drug use, including separate coding for cocaine, 3,4-methylenedioxymethamphetamine (MDMA) and related drugs, dissociative drugs including ketamine and phencyclidine (PCP). Meanwhile an option of coding health conditions caused by use of NPS not covered by existing specified classes of psychoactive substances has to be further explored in the current ICD-11 linearization. Following the field-testing and finalization of ICD-11, an update of the WHO *Lexicon of alcohol and drug terms* (7) is foreseen.

1.4 Update from Essential Medicines and Health Products, WHO

Dr Gilles Forte, Coordinator of the Policy, Access and Use team, in the Department of Essential Medicines and Health Products (EMP) based at WHO headquarters, reported on the EMP Department’s activities related to controlled substances, including substances with medical purpose.

As far as the thirty-seventh meeting of the ECDD was concerned, these included WHO’s work on the collection and analysis of the data on prevalence and on harm to health that are used when selecting substances to be reviewed by the Committee. The second UNODC-WHO Expert Consultation on New Psychoactive Substances, held in Vienna in early December 2014, had discussed mechanisms for improving the collection of data on

NPS together with the development of a strategy for the identification of the most problematic substances through international, regional and national monitoring systems.

EMP is actively involved in improving access to medicines, which is one of the six WHO leadership priorities identified in the 12th General Programme of Work for the period 2014–2019. In May 2015, at the 68th World Health Assembly (WHA), two resolutions that acknowledged the importance of improving access to controlled medicines were adopted by Member States. The first resolution is aimed at strengthening emergency and essential surgical care and anaesthesia as a component of universal health coverage (WHA68.15). The second resolution concerns the global burden of epilepsy and the need for coordinated action at the country level to address its health, social and public knowledge implications (WHA68.20).

Dr Forte explained how EMP collaborates with countries and regional institutions on the development and implementation of balanced policies and regulations aimed at improving access to controlled medicines while preventing abuse and trafficking. It has been involved in the implementation of the Access to Opioid Medication in Europe (ATOME) project to improve access to opioids for analgesia and the treatment of opioid dependence in 12 European countries. EMP also collaborates with UNODC and the Union for International Cancer Control (UICC), in countries where the gaps in access to essential medicines need to be addressed, in particular for the treatment of pain and for palliative care. In 2015, assessments were carried out in Ethiopia, Kenya, Senegal and Uganda to identify barriers to access to controlled medicines and capacity-building needs.

EMP participated in the Ministers' Meeting of the First African Union Specialized Technical Committee Meeting on Health, Population and Drug Control held in Ethiopia in April 2015, where WHO's role in the international drug control system and the importance of maintaining access to ketamine as an essential medicine for anaesthesia and analgesia were discussed.

Representatives from EMP also attended the UNODC Global SMART (Synthetics Monitoring: Analyses, Reporting and Trends) Programme Regional Workshop for East and South-East Asia in mid-September 2015, where challenges associated with NPS were discussed. At this workshop, a special session was held on ketamine use in East- and South-East Asia.

EMP is currently involved in the preparation of WHO's contribution to the UNGASS on the World Drug Problem. A publication on *WHO roles, mandates and activities to counter the world drug problem: a public health perspective* has been issued and comments have

been regularly provided on the UNGASS draft outcome document *UNGASS 2016: Our joint commitment in addressing the world drug problem*. Preparations have also included EMP's participation at UN Missions briefings in Geneva and Vienna, and at inter-sessional meetings of CND on UNGASS.

2. Criteria for assessing new psychoactive substances

The Committee was provided with an overview of the difficulties in assessing NPS as well as an approach for doing so. Several issues regarding the evaluation of NPS were identified, the most notable being the absence of data of the kind that had often been available for drugs evaluated before NPS became a pressing concern. The need for the ECDD to continue its review of NPS to fulfil its role within WHO was discussed. It was suggested that non-traditional sources of data, such as web-based sources, might need tapping into to provide a way to obtain several categories of information typically examined during the ECDD's review process.

Following the presentation, the Committee discussed the challenges associated with the evaluation of NPS. Discussants affirmed that despite these challenges, WHO must continue to assess the seriousness of problems and the scientific evidence associated with use of NPS. The public health implications of NPS were emphasized as being a central focus. During the discussions, approval was expressed that WHO and UNODC had been working in collaboration to prioritize NPS and that this greatly facilitated the drug review process by the ECDD. It was concluded that NPS continue to be a reality requiring constant monitoring, and that additional work is required to refine the criteria associated with reviewing NPS.

3. Terminology

The experts had noted that some criteria and terms used during the critical evaluation of substances by the Committee are somewhat ambiguous. Clearly understood criteria and terms are essential for addressing categories within the structure of the review template and for application during drug reviews. The aim is to operationalize these terms. The Committee supported the formation of a working group to deal with this issue and others that are relevant to the preparations for the meeting, such as inclusion of a glossary.

4. Follow-up on recommendations made by the ECDD at its thirty-sixth meeting

The thirty-sixth meeting of the WHO ECDD took place in Geneva, Switzerland from 16 to 20 June 2014. A total of 24 substances were critically reviewed. The Committee recommended that 12 substances be placed under international control, that 1 substance should not be placed under international control, and recommended that 11 substances be kept under surveillance. As a result, the recommendations on the following substances were conveyed to the Secretary-General of the United Nations and discussed at the fifty-eighth session of the Commission on Narcotic Drugs in March 2015.

4.1 Mephedrone

After a critical review of mephedrone at its thirty-sixth meeting, the ECDD considered that the degree of risk to public health and society associated with the abuse liability of mephedrone is substantial. Therapeutic usefulness has not been recorded. The Committee considered that the evidence of its abuse warranted its placement under international control. As per the *Guidance on the WHO review of psychoactive substances for international control (4)*, higher regard was accorded to the substantial public health risk than to the lack of therapeutic usefulness. The Committee recommended that mephedrone be placed in Schedule II of the 1971 Convention.

This recommendation was conveyed to the UN Secretary-General and subsequently transmitted to Member States by the Secretary-General together with supporting information. At its tenth meeting, on 13 March 2015, the CND decided by 47 votes to none, with 1 abstention to include mephedrone (4-methylmethcathinone) in Schedule II of the Convention on Psychotropic Substances of 1971 (Decision 58/1).

4.2 Ketamine (INN)

After the critical review of ketamine at its thirty-sixth meeting, the ECDD acknowledged the concerns raised by some countries and UN organizations, but noted that ketamine abuse currently does not appear to pose a sufficient public-health risk on a global scale to warrant scheduling. Consequently, the Committee recommended that ketamine should not be placed under international control at this time. Countries with serious abuse problems may decide to

introduce or maintain control measures, but should ensure ready access to ketamine for surgery and anaesthesia for human and veterinary care.

This recommendation was conveyed to the UN Secretary-General and subsequently transmitted to Member States by the Secretary-General together with supporting information. At its tenth meeting, on 13 March 2015, the CND decided by consensus to postpone the consideration of the proposal concerning the recommendation to place ketamine in Schedule IV of the Convention on Psychotropic Substances of 1971 and to request additional information from WHO and other relevant sources (Decision 58/2).

4.3 AH-7921

After a critical review of AH-7921 at its thirty-sixth meeting, the ECDD considered that the degree of risk to public health and society associated with the abuse liability and accompanying evidence warranted its placement under international control. Therapeutic use has not been recorded. The Committee recommended that AH-7921 be placed in Schedule I of the 1961 Single Convention, as amended by the 1972 Protocol.

This recommendation was conveyed to the UN Secretary-General and subsequently transmitted to Member States by the Secretary-General together with supporting information. At its tenth meeting, on 13 March 2015, the CND decided to include AH-7921 in Schedule I of the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol (Decision 58/3).

4.4 Gamma-butyrolactone (GBL)

After a critical review of gamma-butyrolactone (GBL) at its thirty-sixth meeting, the ECDD considered that the degree of risk to public health and society associated with the abuse liability of GBL is especially serious. While the Committee recognized widespread and important industrial use, GBL has no defined therapeutic usefulness. The Committee considered that the evidence of its abuse warranted its placement under international control within Schedule I of the 1971 Convention.

This recommendation was conveyed to the UN Secretary-General and subsequently transmitted to Member States by the Secretary-General together with supporting information. At its tenth meeting, on 13 March 2015, the CND decided by consensus not to include

gamma-butyrolactone (GBL) in Schedule I of the Convention on Psychotropic Substances of 1971 (Decision 58/4).

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

After a critical review of 1,4-butanediol (1,4-BD) at its thirty-sixth meeting, the ECDD considered that the degree of risk to public health and society associated with the abuse liability of 1,4-BD is especially serious. While the Committee recognized its widespread and important industrial use, 1,4-BD has no defined therapeutic usefulness. The Committee considered that the evidence of its abuse warranted its placement under international control within Schedule I of the 1971 Convention.

This recommendation was conveyed to the UN Secretary-General and subsequently transmitted to Member States by the Secretary-General together with supporting information. At its tenth meeting, on 13 March 2015, the CND decided by consensus not to include 1,4-butanediol (1,4-BD) in Schedule I of the Convention on Psychotropic Substances of 1971 (Decision 58/5).

4.6 25B-NBOMe

After a critical review of 25B-NBOMe, at its thirty-sixth meeting, the ECDD considered that the degree of risk to public health and society associated with the abuse liability of 25B-NBOMe is especially serious. While the Committee noted its use in medical research, it has no recorded therapeutic use. The Committee considered that the evidence of its abuse warranted its placement under international control and recommended that 25B-NBOMe be placed in Schedule I of the 1971 Convention.

This recommendation was conveyed to the UN Secretary-General and subsequently transmitted to Member States by the Secretary-General together with supporting information. At its tenth meeting, on 13 March 2015, the CND decided by 46 votes to 1, with 1 abstention, to include 25B-NBOMe (2C-B-NBOMe) in Schedule I of the Convention on Psychotropic Substances of 1971 (Decision 58/6).

4.7 25C-NBOMe

After a critical review of 25C-NBOMe at its thirty-sixth meeting, the ECDD considered that the degree of risk to public health and society associated with the abuse liability of 25C-NBOMe is especially serious. While the Committee noted its use in medical research, it has no recorded therapeutic use. The Committee considered that the evidence of its abuse warranted its placement under international control and recommended that 25C-NBOMe be placed in Schedule I of the 1971 Convention.

This recommendation was conveyed to the UN Secretary-General and subsequently transmitted to Member States by the Secretary-General together with supporting information. At its tenth meeting, on 13 March 2015, the CND decided by 46 votes to 1, with 1 abstention, to include 25C-NBOMe (2C-C-NBOMe) in Schedule I of the Convention on Psychotropic Substances of 1971 (Decision 58/7).

4.8 25I-NBOMe

After a critical review of 25I-NBOMe at its thirty-sixth meeting, the ECDD considered that the degree of risk to public health and society associated with the abuse liability of 25I-NBOMe is especially serious. While the Committee noted its use in medical research, 25I-NBOMe has no recorded therapeutic use. The Committee considered that the evidence of its abuse warranted its placement under international control and recommended that 25I-NBOMe be placed in Schedule I of the 1971 Convention.

This recommendation was conveyed to the UN Secretary-General and subsequently transmitted to Member States by the Secretary-General together with supporting information. At its tenth meeting, on 13 March 2015, the CND decided by 47 votes to 1 to include 25I-NBOMe (2C-I-NBOMe) in Schedule I of the Convention on Psychotropic Substances of 1971 (Decision 58/8).

4.9 N-Benzylpiperazine (BZP)

After a critical review of *N*-benzylpiperazine (BZP) at its thirty-sixth meeting, the ECDD considered that the degree of risk to public health and society associated with the abuse liability of BZP is substantial. Its therapeutic usefulness has been assessed to be little, as it is not currently licensed for use. The Committee considered that the evidence of its abuse warranted its placement under international control. The Committee recommended that BZP be placed in Schedule II of the 1971 Convention.

This recommendation was conveyed to the UN Secretary-General and subsequently transmitted to Member States by the Secretary-General together with supporting information. At its tenth meeting, on 13 March 2015, the CND decided by 48 votes to 1 to include *N*-benzylpiperazine (BZP) in Schedule II of the Convention on Psychotropic Substances of 1971 (Decision 58/9).

4.10 JWH-018

After a critical review of JWH-018 at its thirty-sixth meeting, the ECDD considered that the degree of risk to public health associated with the abuse liability of JWH-018 is substantial. Therapeutic usefulness has not been recorded. As per the *Guidance on the WHO review of psychoactive substances for international control (4)*, higher regard was accorded to the substantial public health risk than to the lack of therapeutic usefulness. The Committee recommended that JWH-018 be placed under international control in Schedule II of the 1971 Convention.

This recommendation was conveyed to the UN Secretary-General and subsequently transmitted to Member States by the Secretary-General together with supporting information. At its tenth meeting, on 13 March 2015, the CND decided by 48 votes to 1, with 1 abstention, to include JWH-018 in Schedule II of the Convention on Psychotropic Substances of 1971 (Decision 58/10).

4.11 AM-2201

After a critical review of AM-2201 at its thirty-sixth meeting, the ECDD considered that the degree of risk to public health associated with the abuse liability of AM-2201 is substantial. Therapeutic usefulness has not been recorded. As per the *Guidance on the WHO review of psychoactive substances for international control (4)*, higher regard was accorded to the substantial public health risk than to the lack of therapeutic usefulness. The Committee recommended that AM-2201 be placed under international control in Schedule II of the 1971 Convention.

This recommendation was conveyed to the UN Secretary-General and subsequently transmitted to Member States by the Secretary-General together with supporting information.

At its tenth meeting, on 13 March 2015, the CND decided by 48 votes to 1 to include AM-2201 in Schedule II of the Convention on Psychotropic Substances of 1971 (Decision 58/11).

4.12 3,4-Methylenedioxypropylone (MDPV)

After a critical review of 3,4-methylenedioxypropylone (MDPV) at its thirty-sixth meeting, the ECDD considered that the degree of risk to public health and society associated with the abuse liability of MDPV is substantial. Therapeutic usefulness has not been recorded. The Committee considered that the evidence of its abuse warranted its placement under international control. As per the *Guidance on the WHO review of psychoactive substances for international control (4)*, higher regard was accorded to the substantial public health risk than to the lack of therapeutic usefulness. The Committee recommended that MDPV be placed in Schedule II of the 1971 Convention.

This recommendation was conveyed to the UN Secretary-General and subsequently transmitted to Member States by the Secretary-General together with supporting information. At its tenth meeting, on 13 March 2015, the CND decided by 48 votes to 1 to include 3,4-methylenedioxypropylone (MDPV) in Schedule II of the Convention on Psychotropic Substances of 1971 (Decision 58/12).

4.13 Methylone (BK-MDMA)

After a critical review of methylone (BK-MDMA) at its thirty-sixth meeting, the ECDD considered that the degree of risk to public health and society associated with the abuse liability of methylone is substantial. Therapeutic usefulness has not been recorded. The Committee considered that the evidence of its abuse warranted its placement under international control. As per the *Guidance on the WHO review of psychoactive substances for international control (4)*, higher regard was accorded to the substantial public health risk than to the lack of therapeutic usefulness. The Committee recommended that methylone be placed in Schedule II of the 1971 Convention.

This recommendation was conveyed to the UN Secretary-General and subsequently transmitted to Member States by the Secretary-General together with supporting information.

At its tenth meeting, on 13 March 2015, the CND decided by 49 votes to 1 to include methylone (beta-keto-MDMA) in Schedule II of the Convention on Psychotropic Substances of 1971 (Decision 58/13).

5. Critical 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. If a preceding meeting of the Committee found that a critical review of a substance is warranted, the Secretariat will prepare such a review for the next meeting of the Committee. However, a pre-review is not always needed and in certain cases a critical review can be undertaken directly.

According to the *Guidance on the WHO review of psychoactive substances for international control* (4) “a critical review is initiated 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 CND to review a substance;
- (3) a pre-review of a substance has resulted in an Expert Committee recommendation for critical review; or
- (4) information is brought to WHO’s attention that a substance is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any Party.

In respect of case (4), if therapeutic use of the substance is confirmed subsequently by any Party, the substance shall be subjected to a pre-review.”

5.1 MT-45

Substance identification

Chemically, MT-45 is 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine. MT-45 has two enantiomers and is commonly available as the racemic mixture.

Previous review

MT-45 has not been previously reviewed by the Committee. A critical review was proposed based on information brought to WHO's attention that MT-45 is clandestinely manufactured, poses a risk to public health and society, and has no recognized therapeutic use by any Party.

Similarity to known substances and effects on the central nervous system

Structurally, MT-45 is somewhat similar to lefetamine (SPA; (*R*)-*N,N*-dimethyl-1,2-diphenylethylamine), a stimulant with analgesic effects, that is controlled as a Schedule IV drug under the UN 1971 Convention on Psychotropic Substances, but conversion into SPA is considered difficult.

MT-45 (the racemate) binds to the μ -, δ -, and κ -opioid receptors and has many of the effects of a classical opioid such as morphine. It inhibits electrically induced contractions of the guinea-pig ileum, it has antinociceptive effects in thermal, mechanical, electrical and chemical pain models. It reduces gastrointestinal transit time, depresses respiration, produces Straub tail in mice, and induces hyperglycaemia. The isomers show subtle differences. The *S*(+)-isomer produces most of the morphine-like effects whereas the *R*(-)-isomer has been reported not to depress respiration, produce Straub tail, or to have hyperglycaemic effects, and it has a 1000-fold higher affinity for both the σ_1 and σ_2 receptors than for the opioid receptors.

Dependence potential

Regarding MT-45's ability to induce *physical dependence*, the mixed opioid agonist-antagonist, nalorphine, is able to precipitate opioid-like withdrawal jumping in MT-45-treated mice, suggestive of physical dependence. MT-45 is also able to attenuate signs of morphine withdrawal in mice thus demonstrating cross-dependency with morphine. Controlled studies examining the potential physical dependence effects of MT-45 in human subjects have not been reported; however, user websites contain reports of withdrawal-like symptoms following use of MT-45.

Actual abuse and/or evidence of likelihood of abuse

MT-45 is being abused for non-medical reasons in several countries, most often apparently for its opioid-like effects. Recognizing the abuse of this drug and its associated toxicity, several European countries have brought MT-45 under some level of regulatory control. Additionally, the Synthetic Drug Control Act of 2015 is currently circulating the United States legislature, and that is also proposing to place MT-45 in the most restrictive schedule under the United States system. Scholarly reports documenting the prevalence and incidence of abuse of MT-45 are not available and neither are any primary preclinical studies pertinent to the prediction of the likelihood of abuse of MT-45 other than to physical dependence. Fatal and non-fatal intoxications involving MT-45 have been reported.

Therapeutic usefulness

There are no known approved human therapeutic applications for MT-45.

Recommendation

MT-45 is a compound with morphine-like effects. The Committee considered that the degree of risk to public health and society associated with the abuse liability and accompanying evidence warranted its placement under international control. Therapeutic use in humans has not been recorded. The Committee recommended that MT-45 be placed in Schedule I of the 1961 Single Convention, as amended by the 1972 Protocol.

5.2 Acetylfentanyl

Substance identification

Chemically, acetylfentanyl is *N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]acetamide. It is in the phenylpiperidine class of synthetic opioids that includes fentanyl, a Schedule I drug under the UN 1961 Single Convention on Narcotic Drugs. Acetylfentanyl has also been referred to as “desmethyl fentanyl”.

Previous review

Acetylfentanyl has not been previously reviewed by the Committee. A critical review was proposed based on information brought to WHO’s attention that acetylfentanyl is clandestinely manufactured, poses a risk to public health and society, and has no recognized therapeutic use by any Party.

Similarity to known substances and effects on the central nervous system

Acetylfentanyl displaces ^3H -etorphine binding in rat cerebral membrane and can completely inhibit the mouse vas deferens stimulated twitch, which is reduced to 29.3 (± 2.1)% levels by the μ -opioid receptor antagonist, beta-funaltrexamine, and reversed by an equimolar concentration of naltrexone. Overall, these data indicate that acetylfentanyl is a μ -opioid receptor agonist similar to morphine. Also similar to morphine-like μ -opioid receptor agonists, it has antinociceptive effects in several rodent models.

Dependence potential

Studies on *physical dependence* in animals have found that acetylfentanyl can relieve signs of withdrawal in morphine-dependent rhesus monkeys and thus demonstrates cross-dependency to morphine. There have been no published reports involving human subjects and acetylfentanyl under controlled conditions on the primary physical dependence-inducing effects, or the cross-dependency effects of acetylfentanyl.

Actual abuse and/or evidence of likelihood of abuse

Published reports involving controlled studies with acetylfentanyl in directly relevant abuse-liability procedures such as self-administration, drug discrimination, intra-cranial self-stimulation, or conditioned place preference are not currently available. Acetylfentanyl is being used for non-medical purposes, although the incidence and prevalence of its abuse cannot be accurately estimated partly because it is not routinely tested for in forensic toxicology. It has been identified in confiscated material being trafficked illicitly in the United States, Europe and Japan where it has been found as a white or pale-beige powder, in tablets and in nasal sprays, and in one report on blotting paper. At least eight countries have brought acetylfentanyl under some level of control as an abused substance. Users have reported using acetylfentanyl via insufflation, smoking, and through the intravenous routes of administration. It is sold over the Internet where it is sometimes promoted as a “research chemical”, and its use is discussed on drug-user websites. Preclinical studies indicate that there is a narrow margin of safety for acetylfentanyl. Over 50 fatal intoxications involving acetylfentanyl have been reported from the United States, across Europe and from Japan.

Therapeutic usefulness

There are no known approved medical products containing acetylfentanyl, nor are there any known industrial uses for the drug.

Recommendation

Acetylfentanyl has effects similar to those of morphine and fentanyl that are included in Schedule I of the 1961 Single Convention on Narcotic Drugs. It has no recorded therapeutic use and its use has resulted in fatalities. Thus, because it meets the required condition of similarity, it is recommended that acetylfentanyl be placed in Schedule I of the Single Convention on Narcotic Drugs, 1961, as consistent with Article 3, paragraph 3 (iii) of that convention in that the substance is liable to similar abuse and productive of similar ill-effects as drugs in Schedule I. In addition, in accordance with Article 3, paragraph 5 of that convention, considering acetylfentanyl is particularly liable to abuse and to produce ill-effects, and its liability is not offset by substantial therapeutic advantages not possessed by substances other than drugs in Schedule IV, it is further recommended it be included in Schedule IV of the Single Convention on Narcotic Drugs, 1961.

5.3 α -Pyrrolidinovalerophenone (α -PVP)

Substance identification

Chemically, α -PVP (α -pyrrolidinovalerophenone) is 1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one. This synthetic cathinone is the desmethyl analogue of pyrovalerone that is listed in Schedule IV of the 1971 United Nations Convention on Psychotropic Substances. α -PVP has two enantiomers and is commonly available as the racemic mixture. α -PVP is closely related to 3',4'-methylenedioxypropylvalerone (MDPV) that has recently been placed in Schedule II of the UN Convention on Psychotropic Substances (1971).

Previous review

α -PVP has not been previously reviewed by the Committee. A direct critical review was proposed based on information brought to WHO's attention that α -PVP is clandestinely manufactured, poses a risk to public health and society, and has no recognized therapeutic use by any Party.

Similarity to known substances and effects on the central nervous system

α -PVP is a potent blocker at the dopamine transporter (DAT) and a moderate blocker at the norepinephrine transporter (NET) with negligible activity at the serotonin transporter (SERT), similar to some other psychostimulants. In many preclinical procedures it demonstrates a psychostimulant-like profile in which it increases locomotion, produces stereotypies, fully substitutes for the discriminative stimulus effects of cocaine and methamphetamine, decreases intracranial self-stimulation thresholds, produces conditioned place preference and is self-administered.

Dependence potential

Research data using human subjects pertinent to α -PVP's dependence potential have not been reported. In preclinical studies, behavioural effects induced by α -PVP are comparable to those produced by other psychomotor stimulants such as cocaine, methamphetamine and MDPV, which predict a stimulant-like dependence potential.

Actual abuse and/or evidence of likelihood of abuse

Several of the nonclinical effects of α -PVP predict a likelihood of abuse for α -PVP in that it decreases intracranial self-stimulation thresholds, produces conditioned place preference, and is self-administered. α -PVP has been sold as a “research chemical”, “bath salt”, “stain remover”, “plant food”, “plant fertilizer”, “insect repellent”, and “jewellery cleaner” and in the form of tablets, suppositories, ampoules, and in liquid formulations. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) identified 65 Internet vendors of α -PVP including some presumably based in China, the European Union, India, the Russian Federation and the United States. α -PVP has been associated with both non-fatal and fatal intoxications. Frequently, when analysed, α -PVP is identified in biofluids, accompanied by other abused substances. In cases where α -PVP use has been established unambiguously, neurological, psychiatric and cardiovascular effects consistent with an extensive psychostimulant toxidrome have been observed, which include cardiotoxicity and violent and psychotic behaviour. More than 130 deaths have been associated with α -PVP, and hospitalizations were required among users with non-fatal acute intoxications.

Therapeutic usefulness

There are no known approved medical products containing α -PVP.

Recommendation

The Committee considered that the degree of risk to public health and society associated with the abuse of α -PVP is substantial. Therapeutic usefulness has not been recorded. Its pharmacological effects are similar to methamphetamine and MDPV, psychostimulants listed in Schedule II of the 1971 Convention. The Committee considered that the evidence of its abuse warranted its placement under international control. As per the *Guidance on the WHO review of psychoactive substances for international control (4)*, higher regard was accorded to the substantial public health risk than to the lack of therapeutic usefulness. The Committee recommended that α -PVP be placed in Schedule II of the 1971 Convention.

5.4 4-Fluoroamphetamine (4-FA)

Substance identification

Chemically, 4-fluoroamphetamine (4-FA) is 1-(4-fluorophenyl)propan-2-amine. 4-FA has two enantiomers and is commonly available as the racemic mixture.

Previous review

4-FA has not been previously reviewed by the Committee. A critical review was proposed based on information brought to WHO's attention that 4-FA is clandestinely manufactured, poses a risk to public health and society, and has no recognized therapeutic use by any Party.

Similarity to known substances and effects on the central nervous system

4-FA is a ring-substituted analogue of amphetamine. Similar to amphetamine, 4-FA functions as a substrate of monoamine transporters and a releasing agent of dopamine (DA), norepinephrine (NE) and 5-hydroxytryptamine (5-HT). Similarly to amphetamine, it increases locomotor activity in rodents and it displays amphetamine-like discriminative stimulus effects.

Dependence potential

There are no data from clinical studies in humans regarding the dependence potential of 4-FA.

Actual abuse and/or evidence of likelihood of abuse

In animal studies, 4-FA occasions the discriminative stimulus effects of amphetamine suggesting that it would be likely to produce amphetamine's subjective effects. 4-FA is also

self-administered by rhesus monkeys but with reportedly lower efficacy than *d*-amphetamine. There are no controlled human studies addressing the abuse potential of 4-FA. 4-FA has been found in seized products in Europe since 2007, in products sold as “ecstasy” tablets and as “amphetamine” powder, as well as as an adulterant in other illicit controlled substances. Although 4-FA has been detected in some fatal and non-fatal instances, other drugs were also present or else data to allow assessment were limited. Therefore evidence for the direct role of 4-FA is not compelling.

Therapeutic usefulness

4-FA has never been marketed as a medicinal product.

Recommendation

Owing to the current insufficiency of data regarding dependence, abuse and risks to public health (including risks to the individual), the Committee recommended that 4-FA not be placed under international control at this time, but be kept under surveillance.

5.5 *para*-Methyl-4-methylaminorex (4,4'-DMAR)

Substance identification

Chemically, 4,4'-DMAR (*para*-methyl-4-methylaminorex) is 4-methyl-5-(4-methylphenyl)-4,5-dihydro-1,3-oxazol-2-amine. 4,4'-DMAR has four enantiomers and exists as racemic *cis*- or *trans*- forms. It is a synthetic substituted oxazoline derivative interpretable as an analogue of 4-methylaminorex (4-MAR) and aminorex, which are psychostimulants listed as Schedule I and Schedule IV substances, respectively, under the 1971 United Nations Convention on Psychotropic Substances.

Previous review

4,4'-DMAR has not been previously reviewed by WHO. A critical review was proposed based on information brought to WHO's attention that 4,4'-DMAR is clandestinely manufactured, poses a risk to public health and society, and has no recognized therapeutic use by any Party.

Similarity to known substances and effects on the central nervous system

In *in vitro* studies, *cis*-4,4'-DMAR demonstrates comparable potency to *d*-amphetamine and aminorex (which are scheduled under the 1971 United Nations Convention on Psychotropic Substances) to induce release of DA and NE, but with greater potency than those compounds to release 5-HT via their respective transporters. *trans*-4,4'-DMAR is also a fully efficacious releasing agent at the DAT and NET, but it acts as an uptake blocker at SERT. Currently, there are no published reports of clinical studies involving 4,4'-DMAR.

Dependence potential

There are no published animal or human studies that have examined the dependence and abuse potential of 4,4'-DMAR.

Actual abuse and/or evidence of likelihood of abuse

A seizure of 4,4'-DMAR was first reported in December 2012 in the Netherlands. Subsequently, use and seizures were reported in a number of other European countries. 4,4'-DMAR has been encountered as a “research chemical”, in powdered and tablet form, and has been surreptitiously sold as “ecstasy” or other psychostimulant drugs. A total of 32 analytically confirmed deaths associated with 4,4'-DMAR have been reported. 4,4'-DMAR was found to contribute to the cause of death in a number of cases, despite the detection of one or more psychoactive substances and/or their metabolites in postmortem biological samples.

Therapeutic usefulness

There are currently no therapeutic applications for 4,4'-DMAR. Patent applications have been filed for some of its isomers that describe their uses as ligands for the trace amine associated receptor 1 (TAAR1) related to a range of potential applications to central nervous system disorders, and the (4*S*, 5*S*)-*trans*-4,4'-DMAR enantiomer has been featured in several patents related to the preparation of a range of phospholipase A2 inhibitors. There are no marketing authorizations (existing, ongoing or suspended) for 4,4'-DMAR.

Recommendation

As per the *Guidance on the WHO review of psychoactive substances for international control* (4), higher regard was accorded to the substantial public health risk than to the lack of therapeutic usefulness. The Committee considered that the degree of risk to public health and

society associated with the abuse of 4,4'-DMAR is substantial. The Committee recommended that 4,4'-DMAR be placed in Schedule II of the 1971 Convention.

5.6 *para*-Methoxymethylamphetamine (PMMA)

Substance identification

Chemically, PMMA (*para*-methoxymethylamphetamine) is 1-(4-methoxyphenyl)-*N*-methylpropan-2-amine. PMMA has two enantiomers and is commonly available as the racemic mixture.

Previous review

PMMA has not been previously reviewed by the Committee. A critical review was proposed based on information brought to WHO's attention that PMMA is clandestinely manufactured, poses a risk to public health and society, and has no recognized therapeutic use by any Party.

Similarity to known substances and effects on the central nervous system

PMMA is a substituted phenethylamine, being a methoxy-derivative of methamphetamine. Methamphetamine is a Schedule II substance under the 1971 United Nations Convention on Psychotropic Substances. PMMA is also related to *para*-methoxyamphetamine (PMA) which is a Schedule I substance under the 1971 United Nations Convention on Psychotropic Substances. PMA is a metabolite of PMMA. At high doses, PMMA can produce sympathomimetic stimulation; its central stimulation is weak, and is weaker than PMA, amphetamine, methamphetamine and MDMA. Overall, the actions of PMMA observed in animals and human users strongly suggest a dominant role for serotonergic activity.

Actual abuse and/or evidence of likelihood of abuse

PMMA has been shown to lack amphetamine-like or hallucinogen-like stimulus properties in animals in drug discrimination studies, but produces MDMA-like discriminative stimulus effects. Indeed, its use and abuse (first noted in the late 1980s) has been associated with the MDMA "ecstasy" culture for which it is often sold as an undisclosed substitute. Use and abuse of PMMA has subsequently been reported worldwide, but particularly in Europe as well as in Asia and Canada. Its use has been associated with deaths that have been increasing with time (1990s, 1 death; 2000s, 40 deaths; and 2010s, 90 deaths). At high doses of PMMA,

some of the effects of MDMA such as stimulation and euphoria are produced. Owing to the slow onset of effects, the user expecting MDMA-like effects may assume that the dose is too low and re-dose, which has been a defining feature of deaths involving PMMA.

Therapeutic usefulness

PMMA has no reported use in medical practice. There are no marketing authorizations (existing, ongoing or suspended) for PMMA.

Recommendation

The Committee considered that the effects of PMMA are similar to PMA, a drug listed in Schedule I of the Convention on Psychotropic Substances of 1971, and the degree of risk to public health and society associated with its abuse is especially serious. The Committee also noted it has no recorded therapeutic use. The Committee considered that the evidence of its abuse warranted its placement under international control and recommended that PMMA be placed in Schedule I of the 1971 Convention.

5.7 Methoxetamine (MXE)

Substance identification

Chemically, methoxetamine (MXE) is 2-(ethylamino)-2-(3-methoxyphenyl)cyclohexanone. It is a synthetic drug and belongs to the arylcyclohexylamine class, like phencyclidine.

Methoxetamine has two enantiomers and is commonly available as the racemic mixture.

Previous review

During its thirty-sixth meeting, the WHO ECDD discussed the critical review report on methoxetamine and concluded that owing to the insufficiency of data regarding dependence, abuse and risks to public health, methoxetamine should not be placed under international control at that time, but be kept under surveillance. In 2014, the European Union decided to bring methoxetamine under control after a risk assessment by the EMCDDA. Furthermore, new information on its abuse potential and more reports of fatal and non-fatal intoxications warranted a critical review at the thirty-seventh meeting of the ECDD.

Similarity to known substances and effects on the central nervous system

Methoxetamine binds to the N-methyl-D-aspartate (NMDA) glutamate receptor similar to ketamine and phencyclidine, but unlike ketamine it also binds to the SERT. It is possible that inhibition of SERT may contribute to both its psychopharmacological profile and its increased risk of toxicity compared to ketamine.

While methoxetamine is classified within the same pharmacological class as PCP and ketamine, its reported effects appear to differ from those of ketamine, suggesting that its actions in the brain may overlap with, but are not the same as, those of ketamine. In addition, the methoxetamine doses that produce the expected and toxic effects overlap, making this compound particularly dangerous.

Dependence potential

No dependence studies have been conducted with methoxetamine. Information from user websites is suggestive. One user reported craving, an escalation in dosage, and feelings of being “detached and sad” during abstinence, but apparently had no withdrawal signs indicative of physical dependence.

Actual abuse and/or evidence of likelihood of abuse

In nonclinical studies, methoxetamine produces conditioned place preference in rats comparable to the effect of ketamine, and is self-administered, but not robustly, suggesting some potential for abuse. Clinical abuse liability studies have not been conducted. Information from other official sources is not available. Some inferences can be made from information on user websites. Desired psychological and behavioural effects reported on such websites include: euphoria, empathy, pleasant intensification of sensory experiences, mild to strong sense of dissociation from the physical body, de-realization, improved social interaction, distorted sense of reality and vivid hallucinations. A total of 120 non-fatal intoxications and 22 deaths associated with methoxetamine have been reported. Methoxetamine use has been reported from an increasing number of countries including: Austria, Belgium, Canada, Estonia, Finland, France, Italy, the Netherlands, Norway, Poland, Russian Federation, Singapore, Spain, Sweden, Ukraine, The United Kingdom of Great Britain and Northern Ireland and the United States.

Therapeutic usefulness

There is no evidence that methoxetamine is used therapeutically.

Recommendation

Methoxetamine has been shown to have effects similar to phencyclidine, a compound listed in Schedule II of the Convention on Psychotropic Substances of 1971. The Committee considered that the degree of risk to public health and society associated with the abuse liability of methoxetamine is substantial. The Committee also noted it has no recorded therapeutic use. The Committee considered that the evidence of its abuse warranted its placement under international control. The Committee therefore recommended that methoxetamine be placed in Schedule II of the 1971 Convention.

6. 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 (second step of the review process). The criterion for the 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 substance, which causes significant health and social problems.

In addition to the Secretariat, any member of the Expert Committee, or any representative of 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-seventh 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.

6.1 Etizolam (INN)

Substance identification

Chemically, etizolam is 4-(2-chlorophenyl)-2-ethyl-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine.

Previous review

The ECDD reviewed etizolam for the first time at its twenty-sixth meeting in 1989. At that time, the Committee rated the abuse liability of etizolam as moderate and the therapeutic usefulness as moderate to high. In view of the lack of clear-cut abuse, and of public health

and social problems associated with its use, the Committee was unable to come to a decision concerning the scheduling of etizolam and recommended that a decision be deferred until its twenty-seventh meeting.

At its twenty-seventh meeting in 1990, the Committee again rated the abuse liability of etizolam as low to moderate and the therapeutic usefulness as moderate to high. The Committee noted few public health and social problems associated with its use at that time and considered that the degree of seriousness of these problems was not great enough to warrant international control. Consequently, the Committee did not recommend scheduling of etizolam in 1990.

Similarity to known substances and effects on the central nervous system

Etizolam has pharmacological effects similar to those of the model benzodiazepine, diazepam that is in Schedule IV of the Convention on Psychotropic Substances of 1971. It behaves as a full benzodiazepine receptor agonist and potentiates the gamma-amino butyric acid (GABA)-induced chloride current, induces muscle relaxation, has anti-convulsive effects, potentiates sleep time, causes a loss of the righting reflex, and occasions the pentobarbital discriminative stimulus, similar to diazepam. In contrast to diazepam, etizolam decreases the turnover and inhibits the uptake of NE in the mouse brain.

Dependence potential

Few human data are available regarding the dependence potential of etizolam. In case reports, one woman was able to be tapered off etizolam without experiencing withdrawal symptoms; in another case, a man was unable to stop etizolam use and during abstinence he experienced withdrawal symptoms characteristic of benzodiazepine withdrawal (palpitations, impaired sleep, agitation and tremors).

Actual abuse and/or evidence of likelihood of abuse

In nonclinical studies, etizolam completely occasions the pentobarbital discriminative stimulus in rhesus monkeys similar to diazepam. This suggests that etizolam would have subjective effects similar to those of the sedative hypnotics and thus, is likely to share their abuse potential. In a Japanese psychiatric hospital survey on drug-related psychiatric disorders, the number of etizolam-abusing patients was 120, followed by flunitrazepam (101), triazolam (95) and zolpidem (53 patients) out of a total of 1579 cases, suggesting that the abuse potential of etizolam is relatively high. There appear to be no data directly pertinent to

the nature and magnitude of the public health problems related to the misuse, abuse and dependence potential of etizolam nor any available data regarding its illicit manufacture and trafficking. However, several publications in the medical literature have commented that etizolam abuse has become a serious problem in Japan, and in September 2014, The Blue Ridge Poison Centre (VA, USA) called etizolam an emerging drug of concern and observed that there is an upward trend in calls to United States poison control centres and in Internet searches regarding this drug.

Therapeutic usefulness

Etizolam has marketing authorizations as a medicinal product in India, Italy and Japan. It is not listed in the WHO Model List of Essential Medicines. In contrast to diazepam and many other benzodiazepines, it decreases the turnover and inhibits the uptake of NE in mouse brain, which may provide anti-depressant activity in addition to conventional benzodiazepine-like anxiolytic activity, but apart from this potential property, it appears that it has no exceptional therapeutic advantages.

Recommendation

Based on the evidence available regarding dependence, abuse and risks to public health, the Committee recommended that a critical review of etizolam is warranted for a future meeting. The Committee noted deficiencies in information and suggested several potential sources that could be helpful in the preparation of the critical review, including those from traffic accident reports, seizure data, user forums, and pharmacovigilance data.

6.2 Phenazepam

Substance identification

Chemically, phenazepam is 7-bromo-5-(2-chlorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one.

Previous review

Phenazepam has not been previously reviewed by the Committee.

Similarity to known substances and effects on the central nervous system

Phenazepam belongs to the 1,4-benzodiazepines, the same family to which diazepam, oxazepam and temazepam belong, and it has a structural resemblance to diazepam, which is in Schedule IV of the Convention on Psychotropic Substances of 1971. Phenazepam and its metabolite, 3-hydroxyphenazepam, bind to the benzodiazepine binding site on the GABA_A receptor. In laboratory animals, phenazepam shows many *in vivo* effects typical of benzodiazepines, including suppression of locomotor activity at moderate to high doses, induction of myorelaxation and anticonvulsant activity, and it can induce sleep. In humans, phenazepam exhibits many of the effects of a sedative.

Dependence potential

In laboratory animals, phenazepam can induce tolerance, and discontinuation of its administration can result in withdrawal effects indicative of physical dependence. Withdrawal signs, measured as an increase in the score of the Hamilton Anxiety Scale following discontinued administration of phenazepam, have been reported in one study.

Actual abuse and/or evidence of likelihood of abuse

User reports from Internet websites indicate that phenazepam may be used to enhance the euphoric effects of opioids (for example, to “boost” methadone doses), to alleviate withdrawal or abstinence syndromes (such as between heroin doses), to temper cocaine highs, and to augment the effects of alcohol. Unauthorized use of phenazepam has been reported over the past few years in Finland, New Zealand, Norway, Turkey, Russian Federation, Sweden, the United Kingdom and the USA. Effects such as psychomotor impairment, respiratory arrest, psychotic experiences, delirium, overdose and deaths have been reported, as well as driving under its influence. Phenazepam can be directly purchased from the Internet and has been sold as a powder, as tablets, and spiked in blotters similar to lysergic acid diethylamide (LSD).

Therapeutic usefulness

Phenazepam has been in clinical use since 1978, primarily in the Russian Federation, to treat epilepsy, insomnia and alcohol withdrawal syndrome, for short-term treatment of anxiety disorders (panic attacks), and as premedication prior to surgery, as it enhances the effects of anaesthetics while reducing anxiety.

Recommendation

The Committee undertook a pre-review of the substance and considered that the information provided in the pre-review report was sufficient and indicated that dependence and harm caused by phenazepam was of such magnitude that proceeding directly into critical review within the meeting was warranted. All procedural requirements for a critical review, including two peer reviews, were fulfilled. Phenazepam has been shown to have effects similar to diazepam that is in Schedule IV of the Convention on Psychotropic Substances of 1971. The Committee considered that the degree of risk to public health and society associated with the abuse of phenazepam is smaller but still significant risk to public health compared to substances in Schedules I–III and has a therapeutic usefulness from little to great. The Committee considered that the evidence of its abuse warranted its placement under international control. The Committee further recommended that phenazepam be placed in Schedule IV of the 1971 Convention.

7. Updates¹

7.1 Ketamine (INN)

Updates on ketamine were presented in which the levels and consequences of its abuse, and new potential medical applications were identified. Levels of ketamine abuse appeared to be declining in many countries worldwide. Potential new therapeutic uses were identified including in depression and refractory status epilepticus. Evaluation of ketamine for treating depression is undergoing Phase III studies. Ketamine is widely used as an anaesthetic agent for human and veterinary use globally. Ketamine is the anaesthetic agent of choice in low-income countries and emergency situations where there are limitations in trained medical personnel, anaesthesia machines, and consistent sources of electricity.

Following its deliberations, the Committee unanimously agreed that it found nothing in the updates, nor that which was disclosed during its deliberations, that would give it reason to recommend a new pre-review or critical review of ketamine with a view to potentially changing its standing recommendation of 2014 that ketamine should not be placed under international control.

¹ In accordance with the *WHO Regulations for Expert Advisory Panels and Committees* and the *WHO Guidance on the WHO review of psychoactive substances for international control*, in consultation with the members and the Secretariat, the Chair decided to hold sessions of the Committee under this agenda item with the members only.

7.2 Cannabis and cannabis resin

The Commission on Narcotic Drugs, in Resolution 52/5, expressed that it “...looks forward to an updated report on cannabis by the Expert Committee, subject to the availability of extra budgetary resources”, and the Report of the International Narcotics Control Board for 2014 reiterated, “... its invitation to WHO to evaluate the potential medical utility of cannabis and the extent to which cannabis poses a risk to human health.” WHO therefore commissioned an update report paper on cannabis and cannabis resin.

An update on the scientific literature on cannabis was presented and reviewed during the session including the pharmacology, toxicology and the claimed therapeutic applications. The Committee then deliberated about the content of the material presented. The Committee requested the Secretariat to begin collecting data towards a pre-review of cannabis, cannabis resin, extracts and tinctures of cannabis at a future meeting. Furthermore, it specifically requested the Secretariat to place emphasis on any therapeutic advantages that they may have relative to other existing therapeutics.

8. Future agenda items

The Committee agreed to establish an informal working group to address issues involving terminology used within its reviews as well as terms that may be included in its guidance document (*Guidance on the WHO review of psychoactive substances for international control*). A report of the results of this working group would be added to the agenda of the next ECDD meeting.

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