

This report presents the recommendations of the thirty-sixth WHO Expert Committee on Drug Dependence (ECDD). The ECDD is responsible for the assessment of therapeutic usefulness, the liability to abuse and dependence and the public health and social harm of each substance under review. After receiving the advice from the Expert Committee to schedule or to amend the scheduling status of a substance, the Director-General of WHO will as appropriate, communicate the recommendations to the United Nations. The report summarizes the review of 26 substances and the Committee's recommendations for scheduling under the international drug control conventions. The report also contains updates from international bodies concerned with controlled substances, a summary of the follow-up on recommendations made at the previous Committee meeting and a summary of the discussion on improving data collection and evidence for prioritization and substance evaluation, in particular for new psychoactive substances. Issues identified for consideration at future Expert Committee meetings are also listed.

WHO Expert Committee on Drug Dependence

Thirty-sixth report



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Thirty-third report

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Thirty-sixth report

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



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Contents

WHO Expert Committee on Drug Dependence	v
Abbreviations	viii
Introduction	1
1. Follow-up on recommendations made by the ECDD at its thirty-fifth meeting	4
1.1 Gamma hydroxybutyric acid (GHB)	4
1.2 Dronabinol (INN)	4
1.3 Ketamine (INN)	5
1.4 ECDD Secretariat follow-up on other matters	5
2. Work of international bodies concerned with controlled substances	7
2.1 Update from the International Narcotics Control Board	7
2.2 Update from the United Nations Office on Drugs and Crime	7
2.3 Update from WHO	8
2.4 Challenges in assessing new psychoactive substances	9
3. Critical review of psychoactive substances	11
3.1 <i>N</i> -Benzylpiperazine (BZP)	11
3.2 Tapentadol (INN)	13
3.3 Gamma-butyrolactone (GBL)	14
3.4 1,4-Butanediol (1,4-BD)	16
3.5 JWH-018	17
3.6 JWH-073	19
3.7 AM-2201	20
3.8 UR-144	21
3.9 APINACA (AKB-48)	23
3.10 RCS-4	24
3.11 JWH-250	25
3.12 Mephedrone	26
3.13 3,4-Methylenedioxypropylvalerone (MDPV)	28
3.14 Methylone (BK-MDMA)	29
3.15 4-Methylethcathinone (4-MEC)	30
3.16 4-Fluoromethcathinone (flephephedrone; 4-FMC)	32
3.17 25B-NBOMe	33
3.18 25C-NBOMe	34
3.19 25I-NBOMe	35
3.20 Alpha-methyltryptamine (AMT)	37
3.21 AH-7921	38
3.22 Methoxetamine	39
3.23 Methiopropamine (MPA)	40
3.24 Ketamine (INN)	42

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4. Pre-review of psychoactive substances	44
4.1 Lisdexamfetamine (INN)	44
4.2 Tramadol (INN)	45
5. Information on exemptions	47
6. Other matters	48
6.1 Improving data collection and evidence base for substance evaluation in cooperation with other agencies	48
6.2 Planning evaluation of cannabis	48
6.3 Future agenda items	49
Acknowledgements	50
References	51

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Geneva, Switzerland, 16–20 June 2014

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Abbreviations

ADHD	attention deficit hyperactivity disorder
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
BK-MDMA	methylone
BZP	<i>N</i> -benzylpiperazine
CB1 and CB2 receptors	cannabinoids receptors type 1 and type 2
CND	Commission on Narcotic Drugs
ECDD	Expert Committee on Drug Dependence
EMP	WHO Department of Essential Medicines and Health Products
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
4-FMC	4-fluoromethcathinone
GBL	gamma-butyrolactone
GHB	gamma-hydroxybutyric acid
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
NPS	new psychoactive substance(s)
PET	positron emission tomography

RCS-4	4-methoxyphenyl(1-pentyl-1 <i>H</i> -indol-3-yl)methanone
SMART	Global Synthetics Monitoring Analyses Reporting and Trends
THC	tetrahydrocannabinol
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-sixth meeting of the WHO Expert Committee on Drug Dependence (ECDD) took place in Geneva, Switzerland from 16 to 20 June 2014.

Mr C. 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 outlined the role and focus of WHO in improving access to quality assured essential medicines and other health technologies, as a contribution to universal health coverage and to the achievement of health-related Millennium Development Goals (MDGs). He noted the adoption of the resolutions of the sixty-seventh World Health Assembly of May 2014 on access to essential medicines (WHA 67.22) and on strengthening of palliative care as a component of comprehensive care throughout the life course (WHA 67.19), which confirm Member States' commitment to improving access to controlled medicines. He acknowledged the critical normative and standard-setting role of WHO expert committees, in particular the ones on drug dependence, on selection and use of essential medicines, and on quality, efficacy and safety of medicines and other health technologies.

The mandate, the roles and activities of WHO within the global framework of substance control were presented. 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 be held 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 ensuring 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: the WHO 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, all members of the Expert Committee and all temporary advisers attending the meeting were requested to declare any conflicts of interest. In this regard, the following interests were declared:

Dr Pennings declared that he is a member of the Risk Assessment Committee on New Drugs of the Netherlands. Dr Elliott and Dr Brandt both declared that they had served as scientific advisers to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Professor Beardsley declared that he had briefly served as an adviser to Grünenthal GmbH for a novel compound, not related to any substance to be discussed at the meeting. Dr Buitrago declared that she had previously acted as a paid consultant for Sanofi-aventis but this company was not involved with any of the medicines under consideration. Dr Walker declared that she had received research funding for mephedrone studies from the US National Institutes of Health. Dr Scholten declared that he had done consultancy work for a company related to lisdexamfetamine. Therefore, Dr Scholten did not participate in the deliberations regarding the pre-review of lisdexamfetamine. The other members and temporary advisers declared that they had no conflicts of interest.

The declared interests, except that of Dr Scholten, 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.

The Expert Committee elected the Chair, Co-chair and Rapporteur. The Chair welcomed all participants and reminded the Expert Committee that it is customary for the Committee to take its decisions by consensus. If the Committee was not unanimous in its findings, any divergent view would be recorded in

or appended to the report. The Expert Committee noted the larger number of compounds to be reviewed over the course of the meeting compared to previous meetings, but was fully aware that the reason for this was the global concern about the increase in use of new psychoactive substances (NPS). A notification to the United Nations (UN) Secretary-General had been made by the United Kingdom of Great Britain and Northern Ireland for mephedrone and by the People's Republic of China for ketamine, resulting in these compounds being critically reviewed as part of the agenda of the thirty-sixth ECDD meeting. The notifications and the additional information related to them were provided and shared with the Committee. In this respect, an amended agenda as proposed by the Secretariat was accepted.

1. Follow-up on recommendations made by the ECDD at its thirty-fifth meeting

1.1 Gamma hydroxybutyric acid (GHB)

After a critical review of γ -hydroxybutyric acid (GHB), by the ECDD at its thirty-fifth meeting, the Committee had come to the conclusion that GHB should be moved from Schedule IV to Schedule II of the 1971 Convention. This recommendation was made on the basis that the abuse liability of GHB was substantial whereas the therapeutic usefulness was little to moderate. This recommendation was conveyed to the UN Secretary-General and subsequently transmitted to Member States by the Secretary-General together with supporting information. During the fifty-sixth session of CND, it was decided by 41 votes to 1, with no abstentions, that GHB be transferred from Schedule IV to Schedule II of the Convention on Psychotropic Substances of 1971 (CND Decision 56/1).

1.2 Dronabinol (INN)

A critical review of dronabinol and its stereoisomers was carried out in March 2006 by the ECDD at its thirty-fourth meeting, which led to a recommendation to move dronabinol from Schedule II to Schedule III of the 1971 Convention. At its fiftieth session, the CND decided not to vote on the recommendation of WHO and requested WHO to reconsider this issue at a future ECDD meeting (CND decision 50/2). At its thirty-fifth meeting, the ECDD discussed whether the recommendations on dronabinol made at its thirty-fourth meeting should be revisited. The ECDD was unaware of any new evidence that was likely to materially alter the scheduling recommendation submitted to the CND at its fiftieth session in March 2007. The ECDD decided that the recommendation it had made at the thirty-fourth meeting to move dronabinol from Schedule II to Schedule III of the 1971 Convention should stand. This recommendation was conveyed to the Secretary-General for further action, but the CND did not take a decision at its fifty-sixth session. During the fifty-seventh session of CND in March 2014, however, a draft decision on dronabinol was proposed on the basis of the recommendation made by the ECDD at its thirty-fifth meeting. After deliberations, the Commission voted on the proposed draft decision. Having received 9 votes in favour, 20 votes against and 12 abstentions, dronabinol was not moved from Schedule II to Schedule III of the 1971 Convention (see reports of the fifty-sixth and fifty-seventh session of the CND, respectively).

1.3 Ketamine (INN)

During the fifty-sixth session of CND, concern was expressed by some countries regarding the decision of the ECDD at its thirty-fifth meeting not to recommend international scheduling of ketamine. Participants acknowledged that further discussion was required and they welcomed the continued work that would be conducted by WHO in relation to ketamine. During the fifty-seventh session of CND, Resolution 57/10 on preventing the diversion of ketamine from legal sources while ensuring its availability for medical use was issued. This Resolution “invites Member States, where the domestic situation so requires, to consider controlling the use of ketamine by placing it on a list of substances controlled under their national legislation, while simultaneously ensuring access to ketamine for medical and scientific purposes, consistent with the international drug control conventions.”

A notification was made by the Government of the People’s Republic of China concerning the proposed recommendation for international control of ketamine and therefore for the ECDD to critically review this substance at its thirty-sixth meeting.

1.4 ECDD Secretariat follow-up on other matters

The Expert Committee was informed by the Secretariat that the four pre-reviewed substances recommended for critical review by the ECDD at its thirty-fifth meeting were on the agenda for the thirty-sixth meeting, i.e. tapentadol, *N*-benzyl piperazine (BZP), γ -butyrolactone (GBL), and 1,4 butanediol (1,4-BD).

Also on the agenda of the thirty-sixth meeting, as recommended by the ECDD at its thirty-fifth meeting, were the critical reviews of mephedrone and of synthetic cannabinoids. With regard to mephedrone, the United Kingdom of Great Britain and Northern Ireland had also made a notification under Article 2, paragraphs 1 and 3 of the 1971 Convention in the meantime. In light of CND Resolution 52/5 on the Exploration of all aspects related to the use of cannabis seeds for illicit purposes, the Secretariat had informed the ECDD at its thirty-fifth meeting that it was likely to propose cannabis for inclusion on the agenda of a future ECDD meeting. In this respect, the Secretariat, presented an information document on cannabis and cannabis resin to the ECDD for consideration at this thirty-sixth meeting.

Since the thirty-fifth meeting of the ECDD, the Secretariat had been working with the WHO Uppsala Monitoring Centre on the collection and analysis of pharmacovigilance data for the assessment of drug abuse and dependence potential that could inform ECDD scheduling decisions, using VigiBase data.

The WHO Secretariat had also continued to advocate for improved access to controlled medicines, while preventing their misuse, and for the appropriate selection and use of medicines for pain and palliative care, through the promotion of WHO policy guidelines and tools e.g. *Ensuring balance in national policies on controlled substances: guidance for availability and accessibility of controlled medicines* (5), *WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses* (6) and the 18th WHO Model List of Essential Medicines (7).

Some recommendations made by the ECDD at its thirty-fifth meeting were deferred to future ECDD meetings. These included the discussion on the use of terms and terminology related to ECDD work that take into account current trends and priorities; the pre-reviews of substances such as zolpidem currently in schedule IV of the 1971 Convention; of ethanol (ethyl alcohol); and the review of levacetylmethadol (LAAM) and its potential role as opioid agonist therapy in the treatment of opioid dependence.

2. Work of international bodies concerned with controlled substances

2.1 Update from the International Narcotics Control Board

Professor Suryawati, Observer for the International Narcotics Control Board (INCB), informed the Committee of the role of the Board. Its mandate is to monitor and promote compliance with the three international drug control conventions. The function of the INCB is to ensure availability of controlled substances for legitimate use and to prevent illicit activities. These functions should be seen in the light of the preambles and articles of the Single Convention on Narcotic Drugs and the Convention on Psychotropic Substances. Professor Suryawati and Mrs Fernandez Santis also gave an overview of the various reports and publications produced by the Board, including technical reports on NPS. Professor Suryawati explained the view of the INCB that international control does not negatively impact on the availability of medicines and that non-availability had other causes (e.g. overly strict domestic legislation). INCB collaborates with WHO to improve information sharing and monitoring of availability of controlled medicines. Future challenges highlighted by the INCB were low accessibility of opioid medications, so-called over-availability of some controlled substances, and the identification of innovative approaches to address NPS challenges.

2.2 Update from the United Nations Office on Drugs and Crime

Dr Justice Tetley, Observer for the United Nations Office on Drugs and Crime (UNODC), highlighted the Organization's role of supporting Member States in their efforts against drugs, crime and terrorism. He presented the mandated activities of the UNODC with regard to NPS noting that 351 substances that are not subject to international control had been notified to the Organization. Particular reference was made to activities carried out since 2010 to improve understanding of the NPS problem through global monitoring and research; promoting international cooperation in responding to the problem; establishment of a global early warning advisory; and provision of support to national drug testing laboratories in the identification of NPS.

He highlighted the contribution of UNODC research outputs such as the Global Synthetics Monitoring, Analyses, Reporting and Trends (SMART) Programme's report of March 2013 entitled *The challenge of new psychoactive substances* (8) and the Early Warning Advisory to support WHO's preparation for the thirty-sixth meeting of the ECDD. Dr Tetley presented UNODC's work in promoting international cooperation, including organizing the first International Expert Consultations on NPS in collaboration with WHO and other international

organizations in 2013. Furthermore, Dr Tettey highlighted the current support to drug testing laboratories, which included publication of recommended methods for the analysis of NPS in seized material, provision of reference materials and implementation of a proficiency testing scheme.

2.3 Update from WHO

Dr Gilles Forte, Coordinator, Policy, Access and Use team, Department of Essential Medicines and Health Products (EMP), WHO, reported on the EMP Department's activities related to the Secretariat functions for the thirty-sixth meeting of the ECDD. These included the collection and analysis of data for carrying out reviews of psychoactive substances, and the coordination and support for the development of critical reviews and pre-reviews of psychoactive substances. EMP is actively involved in the implementation of the WHO access to controlled medicines agenda in line with the resolutions of the sixty-seventh World Health Assembly on access to essential medicines (WHA 67.22) and on strengthening of palliative care as a component of comprehensive care throughout the life course (WHA 67.19). The 18th WHO Model List of Essential Medicines (7) and the 4th WHO Model List of Essential Medicines for Children (9) were revised in April 2013 by the WHO Expert Committee on Selection and Use of Essential Medicines to include a special section on selected medicines for pain and for palliative care. The *WHO guidelines on pharmacological treatment of persisting pain in children with medical illnesses* are being promoted for use in WHO Member States (6). Preparatory work for development of new guidelines for the pharmacological treatment of persisting pain in adults with medical illnesses and for treatment of acute pain is under way. Support is provided to countries for the development and implementation of policies and regulations for a balanced approach that is aimed at improving access to controlled substances while preventing abuse and trafficking. This support is currently provided to 12 countries in Europe through the Access to Opioid Medication in Europe project (ATOME).¹ WHO EMP is also involved in the UN Task Force on Transnational Drug Trafficking and Crime and is actively contributing to the activities building up to the United Nations General Assembly Special Session on the World Drug Problem in 2016 (UNGASS 2016). Collaboration with UNODC is continuing for the development of "Model Legislative Provisions on Drug Control" and for coordinated data collection and analysis for improving prioritization and evaluation of NPS.

Dr Vladimir Poznyak, Coordinator, introduced the Committee to the work of the Management of Substance Abuse team within the Department of Mental Health and Substance Abuse. A range of activities was being carried out, including the development of normative guidance and technical tools, the review

¹ Access to Opioid Medication in Europe project (ATOME) (www.atome-project.eu/).

of evidence of effectiveness of different drug policy options, and the updating and maintenance of the global information system on prevention and treatment resources for substance use disorders. The plan of work for WHO Management of Substance Abuse in 2014–2015 included a special task on contributing to the international drug policy dialogue, which has special relevance to the preparation of the forthcoming UNGASS on the World Drug Problem. Dr Poznyak explained that one of the challenges for WHO and other organizations in addressing the issue of NPS was the nomenclature that is essential to ensure common understanding among the various players involved and efficient coordination of action. The revision of the nomenclature in the area of alcohol and drugs depends on the development of the latest International Classification of Diseases (ICD)-11 for which work was in progress and expected to be completed by 2017.

2.4 Challenges in assessing new psychoactive substances

Dr Elizabeth Mathai, Technical Officer, Policy, Access and Use team, EMP, WHO, explained the role of WHO within the international drug control conventions, the principles and processes of assessment of substances by the ECDD and the actions taken towards evaluation of NPS. Under the Single Convention on Narcotic Drugs 1961 as amended by the 1972 Protocol and the Convention on Psychotropic Substances of 1971, WHO is responsible for the medical, scientific and public health evaluation of psychoactive substances. This mandate is supported by the ECDD, which provides advice to the Director-General of WHO for further recommendations to the UN Secretary-General. The evaluations are carried out according to the guidance provided in the WHO Executive Board approved *Guidance on the WHO review of psychoactive substances for international control (4)*. Article 3 of the 1961 Convention and Article 2 of the 1971 Convention primarily describe the role of WHO in relation to changes in the scope of control of substances.

Twenty-six substances were assessed at the thirty-sixth meeting of the ECDD, of which twenty-four had gone through a critical review and two through a pre-review. Several of these were synthetic NPS. At the time of the thirty-sixth meeting of the ECDD, 351 such substances had been identified by international monitoring systems. These substances belong to different chemical groups and there are many within each group. A major concern for WHO when evaluating this type of substances is the paucity of evidence suitable for carrying out a meaningful evaluation. Data paucity is evident especially for the assessment of dependence potential, abuse liability and both individual and public-health harm from these substances. There are very limited systematic surveys and studies and most of the available information is from case reports; relevant laboratory capacity to identify these substances, especially in the health-care sector, is lacking; data related to criminal activities are also poor and added to this is the

current scenario where multiple substances are used by individual users (poly-substance use), making it difficult to assess the harm attributable to an individual substance.

However, there is evidence to show that at least some of these substances cause significant harm. Also, many of these substances have no legitimate medical use and limited scientific and research use. There is increasing international concern over the proliferation and uncontrolled use of these substances in different parts of the world.

It is in this context that NPS were being evaluated by the ECDD. The WHO Secretariat had shortlisted a few substances for evaluation at the thirty-sixth meeting of the ECDD from the hundreds in existence. This pre-selection was carried out on the basis of data from UNODC and EMCDDA obtained through their early warning systems, which indicated abuse in some parts of the world, and data from some toxicology laboratories that had reported serious harm including deaths from these substances during the past 2 to 3 years. A few frequently abused substances were then selected to represent different chemical groups. Critical review reports were commissioned for each of these substances and these reports were peer-reviewed according to the *Guidance on the WHO review of psychoactive substances for international control* (4).

The Committee discussed how scheduling criteria could be applied in instances of limited data to come to a scheduling decision. The Committee highlighted a need to explore the ability to review a substance where limited data may exist in relation to certain aspects of the current review guidelines. Further discussions on this would take place at the second UNODC-WHO expert consultation on NPS towards the end of 2014 and the establishment of a working group was also proposed to address this issue in more depth. The Committee's view was that the evaluation of the NPS during its thirty-sixth meeting would allow an initial exploration of evidence and help draw relevant lessons for future practical and appropriate review of NPS.

3. 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)*,¹ “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.”

3.1 *N*-Benzylpiperazine (BZP)

Substance identification

N-benzylpiperazine (BZP) is an aryl-substituted piperazine and is chemically 1-benzyl-1,4-diazacyclohexane.

Previous review

BZP was pre-reviewed at the thirty-fifth meeting of the ECDD and based on the reported psychostimulant effects, evidence of abuse and adverse effects, the Expert Committee had concluded that a critical review was warranted.

¹ p.11, paragraph 19.

Similarity to known substances and effects on the central nervous system

BZP stimulates the release and inhibits the reuptake of dopamine, serotonin (5-HT) and noradrenaline, but dopaminergic and serotonergic effects predominate. It is a central nervous system stimulant with amphetamine-like properties demonstrated in both animal and human studies, although with a psychostimulant response potency less than that of dexamfetamine (INN). Like amphetamine, in humans, BZP was found to increase pulse rate, blood pressure (systolic and diastolic) and pupillary dilation. Adverse effects may occur when BZP is co-ingested with other drugs (in particular 3,4-methylenedioxymethamphetamine (MDMA) and other serotonergic/dopaminergic compounds), but toxic effects associated with BZP alone have also been reported. Agitation, tachycardia and seizures have been noted.

Dependence potential

There have been few studies on the dependence potential of BZP and no specific studies have been done in humans. However, a study involving the administration of BZP to people who had been dependent on amphetamine and similar drugs suggested that BZP is liable to abuse. Animal studies found that BZP possessed rewarding properties and reinforcing effects, and substituted for cocaine, amphetamine and S(+)-MDMA in self-administration and discrimination studies.

Actual abuse and/or evidence of likelihood of abuse

BZP abuse and/or seized material has been reported in 18 countries. BZP use appears to be associated with situations similar to that of “ecstasy” (MDMA), or with users who are seeking effects similar to those obtained with ecstasy. BZP has previously been sold as “ecstasy” in powder, capsule, tablet or pellet form via the Internet.

Therapeutic usefulness

BZP has no recorded therapeutic applications or medical use. However, it was synthesized in the early 1940s and it is often reported that BZP was originally developed as a potential anthelmintic for the treatment of intestinal parasitic worms in livestock, but was not licensed as it was found to be relatively ineffective and to cause adverse effects such as seizures in mammals. However, no published or unpublished works confirm these accounts. In the 1980s, BZP was used to manufacture the antidepressant medication piberaline, which was later withdrawn.

Recommendation

BZP has been shown to have effects similar to amphetamine. The Committee 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.

3.2 Tapentadol (INN)

Substance identification

Tapentadol is chemically 3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]-phenol hydrochloride. It has two chiral centres and is manufactured as a single (*R,R*)-stereoisomer.

Previous review

Tapentadol was pre-reviewed during the thirty-fifth meeting of ECDD and a recommendation was made for critical review.

Similarity to known substances and effects on the central nervous system

Tapentadol has some structural similarity to morphine and has shown agonist activity at the μ -opioid receptor and norepinephrine reuptake inhibition. It produces analgesia in acute and chronic pain states similar to that produced by oxycodone or morphine. Most reports of adverse events in humans have come from clinical trials, with nausea, dizziness, vomiting, somnolence and headache being the most commonly reported by patients. Respiratory depression with tapentadol has occurred rarely and had limited clinical relevance.

Dependence potential

Few published preclinical data on dependence potential for tapentadol exist, but animal studies have shown that tolerance and dependence developed in rats. There was a small amount of evidence of withdrawal in clinical studies in humans. Patients taking tapentadol were less likely to have withdrawal symptoms as assessed using the Clinical Opiate Withdrawal Scale than subjects taking oxycodone.

Actual abuse and/or evidence of likelihood of abuse

Based on the preclinical and clinical pharmacology of tapentadol, as well as anecdotal data, the potential for abuse with tapentadol is consistent with that of currently marketed drugs such as hydromorphone, oxycodone, morphine, and tramadol. Tapentadol has been marketed since 2008 without significant events or signs of abuse and currently is dispensed with tamper-resistant coatings. However, tapentadol has not yet appeared in many drug use surveys or surveillance reports, which limits the data regarding tapentadol abuse, dependence, diversion, recreational use, or poison control. Those data that are available suggest the potential for abuse of tapentadol to be similar to that of other μ -opioid agonists or slightly less. While three respondents to the WHO questionnaire confirmed recreational/harmful use of tapentadol, thirteen stated that there was no such use.

Therapeutic usefulness

Tapentadol is primarily prescribed and dispensed on an outpatient basis for osteoarthritis, joint pain or chronic pain states that have not responded to other medications.

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 tapentadol not be placed under international control at this time but be kept under surveillance.

3.3 Gamma-butyrolactone (GBL)

Substance identification

Gamma-butyrolactone (GBL) is chemically oxolan-2-one. GBL can be synthesized from α -hydroxybutyric acid (GHB) or tetrahydrofuran.

Previous review

During the pre-review of GHB at the thirty-fourth meeting of the ECDD, the Committee “noted information relating to the abuse of GBL itself (convertible to GHB in the body) and suggested this substance for pre-review”. Based on the evidence presented in the pre-review of GBL during the thirty-fifth meeting of the ECDD, given its close association with GHB, and the recommendation made by the Committee at its thirty-fifth meeting to reschedule GHB from Schedule

IV to Schedule II of the 1971 Convention, the Committee recommended that a critical review of GBL be undertaken.

Similarity to known substances and effects on the central nervous system

GBL is readily converted, both chemically and in the body, to the Schedule II drug GHB and most of GBL's pharmacological and toxicological effects are mediated through GHB as a metabolite. Nevertheless, pharmacological factors show that GBL tends to be more potent, faster acting and to have a longer duration of activity than GHB. It is a central nervous system depressant with effects that are exacerbated by other central nervous system depressants (including ethanol). There is a steep dose–effect curve between doses producing desired and excessive effects, and there have been numerous published reports of adverse reactions to GBL including fatalities. Signs and symptoms include euphoria, relaxation, reduced inhibition and sedation, progressing to vomiting, urinary and faecal incontinence, agitation, convulsions, bradycardia, respiratory depression, coma and death.

Dependence potential

Reports of animal studies noted a spontaneous and precipitated withdrawal syndrome after chronic administration of GBL. There have been various reports that, in human users, GBL can produce a withdrawal syndrome when the substance is abruptly discontinued following regular chronic use. Withdrawal from GBL appears similar to withdrawal from other sedative–hypnotic drugs such as ethanol and benzodiazepines.

Actual abuse and/or evidence of likelihood of abuse

GBL abuse and/or seized material have been reported in 18 countries. GBL is sold as a liquid, often presented for illicit sale as GHB but also as a so-called cleaning product via the Internet. It is extremely difficult to accurately assess the magnitude of abuse relating specifically to GBL considering the near absence of data explicitly pertaining to GBL rather than GHB or 1,4-butanediol.

Therapeutic usefulness

While GBL was sold in health food shops and athletic venues as a dietary supplement and purported to induce sleep, release growth hormone, enhance sexual activity and athletic performance, there is no recognized therapeutic indication for GBL. However, it has widespread industrial use being a common solvent found in paint strippers, nail polish removers, stain removers and circuit board cleaners. It is also a common intermediate in industrial chemistry including in the manufacture of pyrrolidones and in some pharmaceuticals.

Recommendation

GBL produces its effects in the body through the *in vivo* formation of the scheduled substance GHB. The Committee 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.

3.4 1,4-Butanediol (1,4-BD)

Substance identification

1,4-butanediol (butane-1,4-diol; 1,4-BDO or 1,4-BD) is a colourless, viscous liquid derived from butane by placement of alcohol groups at each end of the chain. It is one of four stable isomers of butanediol.

Previous review

During the discussion of gamma-hydroxybutyric acid (GHB) at its thirty-fourth meeting, the ECDD “noted information relating to the abuse of 1,4-BD itself (convertible to GHB in the body) and suggested this substance for pre-review.” Based on the evidence presented in the pre-review of GBL during its thirty-fifth meeting, given its close association with GHB, and the recommendation made by the Committee to reschedule GHB from Schedule IV to Schedule II of the 1971 Convention, the thirty-fifth meeting of the Committee recommended that a critical review of 1,4-BD be undertaken.

Similarity to known substances and effects on the central nervous system

1,4-BD is readily converted, both chemically and in the body, to the Schedule II drug, GHB, with a T_{\max} of conversion following oral administration of 39.4 (± 11.2) minutes in humans. Most of 1,4-BD's pharmacological and toxicological effects are mediated through GHB as a metabolite, as 1,4-BD itself has no binding affinity to central nervous system receptors. Nevertheless, through GHB, it produces central nervous system depressant effects which may be exacerbated by other central nervous system depressants (including ethanol). There is a steep dose–effect curve between doses producing desired and excessive effects, and there have been various published reports of adverse reactions to 1,4-BD including fatalities. Signs and symptoms include euphoria, relaxation, reduced inhibition and sedation, progressing to vomiting, urinary and faecal incontinence, agitation, convulsions, bradycardia, respiratory depression, coma and death.

Dependence potential

Some animal studies have indicated that 1,4-BD can induce physical dependence. There have been various reports that, in human users, 1,4-BD can produce a withdrawal syndrome when the substance is abruptly discontinued following regular chronic use. Withdrawal from 1,4 BD appears similar to withdrawal from other sedative–hypnotic drugs such as ethanol and benzodiazepines.

Actual abuse and/or evidence of likelihood of abuse

1,4-BD abuse and/or seized material has been reported in 18 countries. There are instances of diversion of the raw substance, and trafficking in dietary supplements containing the compound as well as discrete instances of clandestine manufacture. 1,4-BD is sold under various product and so-called street names. It is extremely difficult to accurately assess the magnitude of abuse relating specifically to 1,4-BD considering the near absence of data explicitly pertaining to 1,4-BD rather than GHB or GBL.

Therapeutic usefulness

1,4-BD has no recognized therapeutic application. However, the dimethanesulfonate form (1,4-butanediol dimethanesulfonate) is available in oral and intravenous formulations for the treatment of chronic myeloid leukaemia but does not produce any adverse effects on the central nervous system. However, 1,4-BD has industrial use as an intermediate chemical for production of tetrahydrofuran and poly(tetramethylene-ether)glycol, polybutylene terephthalate, GBL, polyurethane and other solvents.

Recommendation

1,4-Butanediol produces its effects in the body through the *in vivo* formation of the scheduled substance GHB. The Committee considered that the degree of risk to public health and society associated with the abuse liability of 1,4-butanediol is especially serious. While the Committee recognized its widespread and important industrial use, 1,4-butanediol 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.

3.5 JWH-018

Substance identification

Naphthalen-1-yl(1-pentyl-1*H*-indol-3-yl)methanone, is also referred to as JWH-018.

Previous review

JWH-018 had not been previously pre-reviewed or critically reviewed by the Committee. A direct critical review was proposed based on information brought to WHO's attention that JWH-018 is clandestinely manufactured, poses an especially serious risk to public health and society, and has no recognized therapeutic use by any party. Preliminary data collected from the literature and from different countries indicated that this substance may cause substantial harm and that it has no medical use.

Similarity to known substances and effects on the central nervous system

The aminoalkylindole JWH-018 is a full cannabinoid agonist with low nanomolar binding affinity at cannabinoid receptors type 1 and type 2 (CB1 and CB2 receptors). It also appears that some slight selectivity is observed towards the CB2 receptor. Its interaction with these receptor subtypes correlates with a psychopharmacological profile that is shared with delta-9-tetrahydrocannabinol (THC), which is less potent in a number of assays than JWH-018. Analytically confirmed cases of adverse effects, including non-fatal and fatal intoxications, have been reported in addition to instances of driving under the influence of the substance. Seizures, tachycardia and hypertension have been noted.

Dependence potential

There is some evidence to suggest that synthetic cannabinoid receptor agonists may be able to produce tolerance and withdrawal symptoms when substance use is abruptly discontinued following regular use of high doses. Further detailed studies of these properties of JWH-018 are warranted. The urge for re-dosing has also been associated with JWH-018.

Actual abuse and/or evidence of likelihood of abuse

Reports obtained from animal studies (e.g. drug discrimination) indicate the ability of JWH-018 to mimic effects typically observed with THC. Survey data indicate that JWH-018, like a range of other synthetic cannabinoids, shows THC-like effects in humans. In a WHO survey, 25 Member States confirmed that there was recreational/harmful use of JWH-018.

Therapeutic usefulness

JWH-018 has no recorded therapeutic applications or medical use. Within the research setting, anti-inflammatory and chemopreventive properties of JWH-018 have been reported.

Recommendation

The Committee noted the challenges associated with the evidence base concerning the substance. It also noted analytically confirmed cases of non-fatal and fatal intoxications involving JWH-018. The Committee therefore 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.¹ The Committee recommended that JWH-018 be placed under international control in Schedule II of the 1971 Convention.

3.6 JWH-073

Substance identification

(1-butyl-1*H*-indol-3-yl)(naphthalen-1-yl)methanone, also referred to as JWH-073.

Previous review

JWH-073 had not been previously pre-reviewed or critically reviewed. A direct critical review was proposed based on information brought to WHO's attention that JWH-073 is clandestinely manufactured, poses an especially serious risk to public health and society, and has no recognized therapeutic use by any party. Preliminary data collected from the literature and from different countries indicated that this substance may cause substantial harm and that it has no medical use.

Similarity to known substances and effects on the central nervous system

The aminoalkylindole JWH-073 shows agonist properties at CB1 and CB2 receptors and appears to be equipotent to delta-9-THC. Its interaction with these receptor subtypes correlates with a psychopharmacological profile that is shared with delta-9-THC, although it appears to be shorter acting than the natural product. While there were analytically confirmed cases of non-fatal intoxications (tachycardia and hypertension were noted), these also involved other confirmed synthetic cannabinoids.

Dependence potential

There is some evidence to suggest that synthetic cannabinoid receptor agonists may be able to produce tolerance and withdrawal symptoms when substance use

¹ p. 18, paragraph 56, penultimate sentence.

is abruptly discontinued following regular use of high doses. Further detailed studies on these properties of JWH-073 are warranted.

Actual abuse and/or evidence of likelihood of abuse

Reports obtained from animal studies (e.g. drug discrimination) indicate the ability of JWH-073 to mimic effects typically observed with THC. Survey data indicate that JWH-073, like a range of other synthetic cannabinoids, shows THC-like effects in humans. In a WHO survey, 22 Member States confirmed that there was recreational/harmful use of JWH-073.

Therapeutic usefulness

JWH-073 has no recorded therapeutic applications or medical use.

Recommendation

The Committee noted the challenges associated with the evidence base concerning the substance. Of particular significance was the lack of analytically confirmed cases of non-fatal and fatal intoxications involving solely JWH-073. The Committee recommended that JWH-073 not be placed under international control at this time, but be kept under surveillance.

3.7 AM-2201

Substance identification

AM-2201 is chemically [1-(5-fluoropentyl)-1*H*-indol-3-yl]-naphthalen-1-yl-methanone.

Previous review

AM-2201 had not been previously pre-reviewed or critically reviewed. A direct critical review was proposed based on information brought to WHO's attention that AM-2201 is clandestinely manufactured, poses an especially serious risk to public health and society, and has no recognized therapeutic use by any party. Preliminary data collected from the literature and from different countries indicated that this substance may cause substantial harm and that it has no medical use.

Similarity to known substances and effects on the central nervous system

AM-2201 (the 5-fluoropentyl analogue of JWH-018) is a full cannabinoid agonist with low nanomolar binding affinity at the CB1 receptor. Its interaction with these receptor subtypes correlates with a psychopharmacological profile that is

shared with delta-9-THC. It appears to display a greater potency in vitro than JWH-018. Analytically confirmed cases of adverse effects, including non-fatal and fatal occurrences, have been reported in addition to instances of driving under the influence of the drug. Restlessness, hallucinations and somnolence have been noted.

Dependence potential

There is some evidence to suggest that synthetic cannabinoid receptor agonists may be able to produce tolerance and withdrawal symptoms when substance use is abruptly discontinued following regular use of high doses. Further detailed studies on these properties of AM 2201 are warranted.

Actual abuse and/or evidence of likelihood of abuse

Survey data indicate that AM-2201, like a range of other synthetic cannabinoids, shows THC-like effects in humans. In a WHO survey, 22 Member States confirmed that there was recreational/harmful use of AM-2201.

Therapeutic usefulness

AM-2201 has no recorded therapeutic applications or medical use.

Recommendation

The Committee noted the challenges associated with the evidence base concerning the substance. It also noted analytically confirmed cases of non-fatal and fatal intoxications involving AM-2201. The Committee therefore 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.¹ The Committee recommended that AM-2201 be placed under international control in Schedule II of the 1971 Convention.

3.8 UR-144

Substance identification

UR-144 is chemically: (1-pentyl-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl) methanone.

¹ p. 18, paragraph 56, penultimate sentence.

Previous review

UR-144 had not been previously pre-reviewed or critically reviewed by the Committee. A direct critical review was proposed based on information brought to WHO's attention that UR-144 is clandestinely manufactured, poses an especially serious risk to public health and society, and has no recognized therapeutic use by any party. Preliminary data collected from the literature and from different countries indicated that this substance may cause substantial harm and that it has no medical use.

Similarity to known substances and effects on the central nervous system

UR-144 shows high affinity and selectivity towards the CB2 receptor and shows cannabinoid agonist properties at both CB1 and CB2 receptor subtypes. While there were analytically confirmed cases of non-fatal (nausea, vomiting, seizures and tachycardia) and fatal intoxications these also involved other confirmed synthetic cannabinoids. Detections of UR-144 in instances of driving under the influence of the drug were also reported.

Dependence potential

There is some evidence to suggest that synthetic cannabinoid receptor agonists may be able to produce tolerance and withdrawal symptoms when substance use is abruptly discontinued following regular use of high doses. Further detailed studies on these properties of UR-144 are warranted.

Actual abuse and/or evidence of likelihood of abuse

Survey data indicate that UR-144, like a range of other synthetic cannabinoids, shows THC-like effects in humans. In a WHO survey, 19 Member States confirmed that there was recreational/harmful use of UR-144.

Therapeutic usefulness

UR-144 has no recorded therapeutic applications or medical use.

Recommendation

The Committee noted the challenges associated with the evidence base concerning the substance. Of particular significance was the lack of analytically confirmed cases of non-fatal and fatal intoxications involving solely UR-144. The Committee recommended that UR-144 not be placed under international control at this time but be kept under surveillance.

3.9 APINACA (AKB-48)

Substance identification

APINACA (AKB-48) is chemically *N*-(adamantan-1-yl)-1-pentyl-1*H*-indazole-3-carboxamide.

Previous review

APINACA had not been previously pre-reviewed or critically reviewed by the Committee. A direct critical review was proposed based on information brought to WHO's attention that APINACA is clandestinely manufactured, poses an especially serious risk to public health and society, and has no recognized therapeutic use by any party. Preliminary data collected from the literature and from different countries indicated that this substance may cause substantial harm and that it has no medical use.

Similarity to known substances and effects on the central nervous system

APINACA binds to CB1 and CB2 receptors with twofold higher affinity for the CB2-subtype. However, the binding affinity of APINACA to both receptor subtypes is at least 15-fold lower than that of delta-9-THC.

Dependence potential

There is some evidence to suggest that synthetic cannabinoid receptor agonists may be able to produce tolerance and withdrawal symptoms when substance use is abruptly discontinued following regular use of high doses. Further detailed studies on these properties of APINACA are warranted.

Actual abuse and/or evidence of likelihood of abuse

Survey data indicate that APINACA, like a range of other synthetic cannabinoids, shows THC-like effects in humans. In a WHO survey, 16 Member States confirmed that there was recreational/harmful use of APINACA.

Therapeutic usefulness

APINACA has no recorded therapeutic applications or medical use.

Recommendation

The Committee noted the challenges associated with the evidence base concerning the substance. Of particular significance was the lack of analytically confirmed

cases of non-fatal and fatal intoxications involving APINACA. The Committee recommended that APINACA not be placed under international control at this time but be kept under surveillance.

3.10 RCS-4

Substance identification

RCS-4 is chemically 4-methoxyphenyl(1-pentyl-1*H*-indol-3-yl)methanone.

Previous review

RCS-4 had not been previously pre-reviewed or critically reviewed by the Committee. A direct critical review was proposed based on information brought to WHO's attention that RCS-4 is clandestinely manufactured, poses an especially serious risk to public health and society, and has no recognized therapeutic use by any party. Preliminary data collected from the literature and from different countries indicated that this substance may cause substantial harm and that it has no medical use.

Similarity to known substances and effects on the central nervous system

The affinity of RCS-4 for CB1 and CB2 receptors is not known, but RCS-4 is able to stimulate guanosine triphosphate (GTP) binding to rat brain cortical membranes in a specific CB1 receptor-mediated binding assay. Thus it is conceivable that its effects may show delta-9-THC-like features. While there were analytically confirmed cases of non-fatal intoxications, these also involved other confirmed synthetic cannabinoids. Detections of RCS-4 in instances of driving under the influence of the drug were also reported.

Dependence potential

There is some evidence to suggest that synthetic cannabinoid receptor agonists may be able to produce tolerance and withdrawal symptoms when substance use is abruptly discontinued following regular use of high doses. Further detailed studies on these properties of RCS-4 are warranted.

Actual abuse and/or evidence of likelihood of abuse

Survey data indicate that RCS-4, like a range of other synthetic cannabinoids, shows THC-like effects in humans. In a WHO survey, 19 Member States confirmed that there was recreational/harmful use of RCS-4.

Therapeutic usefulness

RCS-4 has no recorded therapeutic applications or medical use.

Recommendation

The Committee noted the challenges associated with the evidence base concerning the substance. Of particular significance was the lack of analytically confirmed cases of non-fatal and fatal intoxications involving RCS-4. The Committee recommended that RCS-4 not be placed under international control at this time but be kept under surveillance.

3.11 JWH-250

Substance identification

JWH-250 is chemically 2-(2-methoxyphenyl)-1-(1-pentylindol-3-yl)ethanone.

Previous review

JWH-250 had not been previously pre-reviewed or critically reviewed. A direct critical review was proposed based on information brought to WHO's attention that JWH-250 is clandestinely manufactured, poses an especially serious risk to public health and society, and has no recognized therapeutic use by any party. Preliminary data collected from the literature and from different countries indicated that this substance may cause substantial harm and that it has no medical use.

Similarity to known substances and effects on the central nervous system

JWH-250 shows low nanomolar binding affinity at CB1 and CB2 receptors and it also appears to show some slight selectivity towards the CB1 receptor. Its interaction with these receptor subtypes correlates with a psychopharmacological profile that is shared with delta-9-THC. While there were analytically confirmed cases of non-fatal intoxications, these also involved other confirmed synthetic cannabinoids. Detection of JWH-250 in instances of driving under the influence of the substance was also reported.

Dependence potential

There is some evidence to suggest that synthetic cannabinoid receptor agonists may be able to produce tolerance and withdrawal symptoms when substance use is abruptly discontinued following regular use of high doses. Further detailed studies on these properties of JWH-250 are warranted.

Actual abuse and/or evidence of likelihood of abuse

Survey data indicate that JWH-250, like a range of other synthetic cannabinoids, shows THC-like effects in humans. In a WHO survey, 22 Member States confirmed that there was recreational/harmful use of JWH-250.

Therapeutic usefulness

JWH-250 has no recorded therapeutic applications or medical use.

Recommendation

The Committee noted the challenges associated with the evidence base concerning the substance. Of particular significance was the lack of analytically confirmed cases of non-fatal and fatal intoxications involving JWH-250. The Committee recommended that JWH-250 not be placed under international control at this time but be kept under surveillance.

3.12 Mephedrone

Substance identification

Mephedrone (4-methylmethcathinone, 4-MMC) is chemically (*R,S*)-2-(methylamino)-1-(4-methylphenyl)propan-1-one.

Previous review

Mephedrone had not been previously pre-reviewed or critically reviewed by the Committee. A direct critical review was proposed based on information brought to WHO's attention that mephedrone is clandestinely manufactured, poses an especially serious risk to public health and society, and has no recognized therapeutic use by any party. Preliminary data collected from the literature and from different countries indicated that this substance may cause substantial harm. Furthermore, a notification to the Secretary-General had been made by the United Kingdom of Great Britain and Northern Ireland concerning a proposed recommendation for international control of mephedrone (4-methylmethcathinone), under Article 2, paragraphs 1 and 3 of the Convention on Psychotropic Substances, 1971.

Similarity to known substances and effects on the central nervous system

Mephedrone is a ring-substituted analogue of methcathinone. Key features related to the mechanisms of action are comparable with psychostimulants and medicinal products that target the monoaminergic system. In vitro studies indicate that mephedrone may act as a non-selective substrate at transporters

of serotonin, dopamine and norepinephrine, similar to MDMA. Although its catecholamine-related properties appear to be less pronounced than those observed with methamphetamine, the behavioural profile of mephedrone was observed overall to be comparable with amphetamine-type psychostimulants. Mephedrone appears to show a profile with abuse liability. Adverse effects reported in connection with mephedrone use pointed towards the observation of a psychostimulant-type toxidrome and include tachycardia, hypertension, agitation, paranoia, hallucinations and insomnia. Non-fatal and fatal intoxications involving mephedrone have been reported.

Dependence potential

No detailed clinical studies in humans are available. Reports obtained from surveys and casework indicated that mephedrone consumption might be associated with the potential to produce cravings and dependence. Further studies are warranted to elucidate the psychological or physical mechanisms of dependence.

Actual abuse and/or evidence of likelihood of abuse

Self-administration studies in animals indicated a propensity for self-administration and abuse liability. In humans, mephedrone use was reported to show psychostimulant-like effects and an association with binge use (i.e. repeated use of the drug within a short period of time) was noted. In a WHO survey, 21 Member States confirmed recreational/harmful use of mephedrone.

Therapeutic usefulness

Mephedrone has no recorded therapeutic applications or medical use.

Recommendation

The Committee 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.¹ The Committee recommended that mephedrone be placed in Schedule II of the 1971 Convention.

¹ p. 18, paragraph 56, penultimate sentence.

3.13 3,4-Methylenedioxypropylamphetamine (MDPV)

Substance identification

3,4-Methylenedioxypropylamphetamine (MDPV) is chemically (*R,S*)-1-(1,3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl)propan-1-one.

Previous review

MDPV had not been previously pre-reviewed or critically reviewed by the Committee. A direct critical review was proposed based on information brought to WHO's attention that MDPV is clandestinely manufactured, poses an especially serious risk to public health and society, and has no recognized therapeutic use by any party. Preliminary data collected from the literature and from different countries indicated that this substance may cause substantial harm and that it has no medical use.

Similarity to known substances and effects on the central nervous system

MDPV is structurally related to propylamphetamine. Key features related to the mechanisms of action are comparable with cocaine-like psychostimulants, which includes potent dopamine transporter (DAT) and norepinephrine transporter (NET) selective transporter blockage. MDPV is a potent locomotor stimulant in mice, which has also been shown to lead to increases of extracellular dopamine in mesolimbic reward pathways using microdialysis studies. MDPV appears to show a profile of high abuse liability. Adverse effects reported from MDPV use pointed towards the observation of a potent and potentially long-lasting psychostimulant-type toxidrome and include severe agitation, violent behaviour, tachycardia, psychosis, profuse diaphoresis, paranoia and anxiety. Non-fatal and fatal intoxications involving MDPV have been reported.

Dependence potential

No detailed clinical studies in humans are available. Reports obtained from surveys and casework indicated that MDPV consumption might be associated with the potential to produce craving and dependence. Further studies are warranted to elucidate the psychological or physical mechanisms of dependence.

Actual abuse and/or evidence of likelihood of abuse

Self-administration studies in animals indicated a strong propensity for self-administration and abuse liability. In humans, MDPV use was reported to show potent psychostimulant-like effects and a strong association with binge use. In a WHO survey, 22 Member States confirmed recreational/harmful use

of MDPV. MDPV might show abuse liability similar to that of cocaine and methamphetamine, especially in experienced recreational drug users with a history of poly-drug use.

Therapeutic usefulness

MDPV has no recorded therapeutic applications or medical use.

Recommendation

The Committee 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.¹ The Committee recommended that MDPV be placed in Schedule II of the 1971 Convention.

3.14 Methylone (BK-MDMA)

Substance identification

Methylone(beta-keto-MDMA) is chemically (*R,S*)-1-(1,3-benzodioxol-5-yl)-2-(methylamino)propan-1-one.

Previous review

Methylone had not been previously pre-reviewed or critically reviewed by the Committee. A direct critical review was proposed based on information brought to WHO's attention that methylone is clandestinely manufactured, poses an especially serious risk to public health and society, and has no recognized therapeutic use by any party. Preliminary data collected from the literature and from different countries indicated that this substance may cause substantial harm and that it has no medical use.

Similarity to known substances and effects on the central nervous system

Methylone is the beta-keto analogue of MDMA. Key features related to the mechanisms of action are comparable with psychostimulants and medicinal products that target the monoaminergic system. Some of its pharmacological properties overlap with those reported for mephedrone. These include the ability to act as a non-selective substrate at transporters of serotonin, dopamine and

¹ p. 18 paragraph 56, penultimate sentence.

norepinephrine. Although its catecholamine-related properties appear to be less pronounced than those observed with methamphetamine, the behavioural profile of methylone was observed to be similar to that of amphetamine-type psychostimulants. Methylone shows potential for abuse liability. Adverse effects reported in connection with methylone use pointed towards the observation of a psychostimulant-type toxidrome and include tachycardia, hypertension, paranoia, anxiety, bruxism and muscle tension and aching. Non-fatal and fatal intoxications involving methylone have been reported.

Dependence potential

No detailed clinical studies in humans are available.

Actual abuse and/or evidence of likelihood of abuse

Patterns of self-administration in animals and effects on brain reward function suggest that methylone shows potential for abuse liability. In a WHO survey, 23 Member States confirmed recreational/harmful use of methylone.

Therapeutic usefulness

Methylone has no recorded therapeutic applications or medical use.

Recommendation

The Committee 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.¹ The Committee recommended that methylone be placed in Schedule II of the 1971 Convention.

3.15 4-Methylethcathinone (4-MEC)

Substance identification

4-Methylethcathinone (4-MEC) is chemically (*R,S*)-2-(ethylamino)-1-(*p*-tolyl)propan-1-one.

¹ p. 18, paragraph 56, penultimate sentence.

Previous review

4-MEC had not been previously pre-reviewed or critically reviewed by the Committee. A direct critical review was proposed based on information brought to WHO's attention that 4-MEC is clandestinely manufactured, poses an especially serious risk to public health and society, and has no recognized therapeutic use by any party. Preliminary data collected from the literature and from different countries indicated that this substance may cause substantial harm and that it has no medical use.

Similarity to known substances and effects on the central nervous system

4-MEC is a homologue of mephedrone. Key features related to the mechanisms of action are comparable with psychostimulants and medicinal products that target the monoaminergic system. Recent studies have shown that 4-MEC may act as a non-selective inhibitor of serotonin, dopamine and norepinephrine transporters. In addition, it was observed to selectively release serotonin, while locomotor activity in the rat was not observed. Detailed data on adverse effects reported in connection with 4-MEC use are not abundant, but there is some likelihood of encountering a psychostimulant-type toxidrome. However, few non-fatal or fatal intoxications involving 4-MEC have been reported in the literature.

Dependence potential

No detailed clinical studies in humans are available.

Actual abuse and/or evidence of likelihood of abuse

No detailed studies are available. In a WHO survey, 19 Member States confirmed recreational/harmful use of 4-MEC.

Therapeutic usefulness

4-MEC has no recorded therapeutic applications or medical use.

Recommendation

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

3.16 4-Fluoromethcathinone (flephedrone; 4-FMC)

Substance identification

4-Fluoromethcathinone (flephedrone; 4-FMC) is chemically (*R,S*)-1-(4-fluorophenyl)-2-methylaminopropan-1-one.

Previous review

4-FMC had not been previously pre-reviewed or critically reviewed by the Committee. A direct critical review was proposed based on information brought to WHO's attention that 4-FMC is clandestinely manufactured, poses an especially serious risk to public health and society, and has no recognized therapeutic use by any party. Preliminary data collected from the literature and from different countries indicated that this substance may cause substantial harm and that it has no medical use.

Similarity to known substances and effects on the central nervous system

4-FMC is a ring-substituted analogue of methcathinone. Key features related to the mechanisms of action are comparable with psychostimulants and medicinal products that target the monoaminergic system. 4-FMC was observed to function as a catecholamine-selective substrate-type releaser of dopamine and norepinephrine. Similarities to psychomotor stimulants such as cocaine, methcathinone and methamphetamine have been shown, although 4-FMC appears to be less potent. Very few non-fatal and fatal intoxications involving 4-FMC have been reported in the literature.

Dependence potential

No detailed clinical studies in humans are available.

Actual abuse and/or evidence of likelihood of abuse

No detailed clinical studies in humans are available. Preclinical data indicate pharmacological overlaps with some classical psychostimulants suggesting the possibility of abuse liability. Fifteen Member States confirmed recreational/harmful use of 4-FMC.

Therapeutic usefulness

4-FMC has no recorded therapeutic applications or medical use.

Recommendation

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

3.17 25B-NBOMe

Substance identification

25B-NBOMe (2C-B-NBOMe) is chemically 2-(4-bromo-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine.

Previous review

25B-NBOMe had not been previously pre-reviewed or critically reviewed by the Committee. A direct critical review was proposed based on information brought to WHO's attention that 25B-NBOMe is clandestinely manufactured, poses an especially serious risk to public health and society, and has no recognized therapeutic use by any party. Preliminary data collected from the literature and from different countries indicated that this substance may cause substantial harm and that it has no medical use.

Similarity to known substances and effects on the central nervous system

25B-NBOMe is structurally related to the phenethylamine 2C-B (Schedule II 1971 Convention). It has nanomolar affinity for the serotonin 5-HT_{2A} receptor and is a partial agonist, with less affinity for the 5-HT_{2C} receptor. 25B-NBOMe is a central nervous system stimulant with hallucinogenic properties. Adverse effects in a clinical intoxication included tachycardia, hypertension, seizures and hyperpyrexia. Some analytically confirmed non-fatal and fatal intoxications involving 25B-NBOMe have been reported in the literature.

Dependence potential

No studies have examined the dependence potential of 25B-NBOMe *in vitro*, in animals or in humans.

Actual abuse and/or evidence of likelihood of abuse

25B-NBOMe abuse and/or seized material has been reported in 10 countries. It has been sold as a replacement for lysergic acid diethylamide (LSD) or sold as LSD directly on the illicit drug market, including as blotter tabs. It has also been associated with the purchase of so-called research chemicals via the Internet.

Therapeutic usefulness

25B-NBOMe has no recorded therapeutic applications or medical use. However, radiolabelled 25B-NBOMe has been used in medical research as a tool to study the serotonergic system in the brain and as a tracer for positron emission tomography (PET) imaging.

Recommendation

The Committee noted the challenges associated with the evidence base concerning the substance. The Committee 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.

3.18 25C-NBOMe

Substance identification

25C-NBOMe (2C-C-NBOMe) is chemically 2-(4-chloro-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine.

Previous review

25C-NBOMe had not been previously pre-reviewed or critically reviewed by the Committee. A direct critical review was proposed based on information brought to WHO's attention that 25C-NBOMe is clandestinely manufactured, poses an especially serious risk to public health and society, and has no recognized therapeutic use by any party. Preliminary data collected from the literature and from different countries indicated that this substance may cause substantial harm and that it has no medical use.

Similarity to known substances and effects on the central nervous system

25C-NBOMe is structurally related to the phenethylamine 2C-C. It has nanomolar affinity for the serotonin 5-HT_{2A} receptor and is a partial agonist, with less affinity for the 5-HT_{2C} receptor. 25C-NBOMe is a central nervous system stimulant with hallucinogenic properties. Adverse effects in a clinical intoxication included tachycardia, hypertension, seizures and hyperpyrexia. Some analytically confirmed non-fatal and fatal intoxications involving 25C-NBOMe have been reported in the literature.

Dependence potential

No studies have examined the dependence potential of 25C-NBOMe in vitro, in animals or in humans.

Actual abuse and/or evidence of likelihood of abuse

25C-NBOMe abuse and/or seized material has been reported in 13 countries. It has been sold as a replacement for LSD or sold as LSD directly on the illicit drug market, including as blotter tabs. It has also been associated with the purchase of so-called research chemicals via the Internet.

Therapeutic usefulness

25C-NBOMe has no recorded therapeutic applications or medical use. However, radiolabelled 25C-NBOMe has been used in medical research as a tool to study the serotonergic system in the brain and as a tracer for PET imaging.

Recommendation

The Committee noted the challenges associated with the evidence base concerning the substance. The Committee 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.

3.19 25I-NBOMe

Substance identification

25I-NBOMe (2C-I-NBOMe) is chemically 2-(4-iodo-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine.

Previous review

25I-NBOMe had not been previously pre-reviewed or critically reviewed by the Committee. A direct critical review was proposed based on information brought to WHO's attention that 25I-NBOMe is clandestinely manufactured, poses an especially serious risk to public health and society, and has no recognized therapeutic use by any party. Preliminary data collected from the literature and from different countries indicated that this substance may cause substantial harm and that it has no medical use.

Similarity to known substances and effects on the central nervous system

25I-NBOMe is structurally related to the phenethylamine 2C-I. It has nanomolar affinity for the serotonin 5-HT_{2A} receptor and is a full agonist, with less affinity for the 5-HT_{2C} receptor. 25I-NBOMe is a central nervous system stimulant with hallucinogenic properties. Adverse effects in clinical intoxications included tachycardia, hypertension, confusion, agitation, aggression, visual and auditory hallucinations, seizures, hyperpyrexia, clonus, metabolic acidosis, rhabdomyolysis and acute kidney injury. User injury from violent behaviour has also been reported. Various analytically confirmed non-fatal and fatal intoxications involving 25I-NBOMe have been reported in the literature.

Dependence potential

No studies have examined the dependence potential of 25I-NBOMe in vitro, in animals or in humans.

Actual abuse and/or evidence of likelihood of abuse

25I-NBOMe abuse and/or seized material has been reported in 25 countries. It has been sold as a replacement for LSD or sold as LSD directly on the illicit drug market, including as blotter tabs. It has also been associated with the purchase of so-called research chemicals via the Internet.

Therapeutic usefulness

25I-NBOMe has no recorded therapeutic applications or medical use. However, radiolabelled 25I-NBOMe has been used in medical research as a tool to study the serotonergic system in the brain and as a tracer for PET imaging.

Recommendation

The Committee noted the challenges associated with the evidence base concerning the substance. The Committee 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.

3.20 Alpha-methyltryptamine (AMT)

Substance identification

Alpha-methyltryptamine (AMT) is chemically 2-(1*H*-indol-3-yl)-1-methylethylamine with (*R*)- and (*S*)- stereoisomers.

Previous review

AMT had not been previously pre-reviewed or critically reviewed by the Committee. A direct critical review was proposed based on information brought to WHO's attention that AMT is clandestinely manufactured, poses an especially serious risk to public health and society, and has no recognized therapeutic use by any party. Preliminary data collected from the literature and from different countries indicated that this substance may cause substantial harm and that it has no medical use.

Similarity to known substances and effects on the central nervous system

AMT shares several similarities with various scheduled tryptamine hallucinogens such as alpha-ethyltryptamine (AET), *N,N*-dimethyltryptamine (DMT), 5-methoxy-*N,N*-diisopropyltryptamine (5-MeO-DIPT), 5-methoxy-*N,N*-diallyltryptamine (5-MeO-DALT), 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT) and 5-methoxy- α -methyltryptamine (5 MeO-AMT). AMT has a high affinity for the 5-HT (5-hydroxytryptamine or serotonin) transporter and inhibits dopamine, 5 HT and norepinephrine reuptake and monoamine oxidase. It is a central nervous system stimulant with hallucinogenic properties. Adverse effects include mild increases in blood pressure or respiration rate, tachycardia, mydriasis, diaphoresis, salivation, severe nausea, severe vomiting, increased deep tendon reflexes, impaired coordination, visual and auditory disturbances and distortions. Although fatal intoxications involving AMT have been reported in the literature, they have also involved other drugs which may be a feature of the toxicity profile of AMT.

Dependence potential

No studies have examined the dependence potential of AMT in vitro, in animals or in humans.

Actual abuse and/or evidence of likelihood of abuse

AMT abuse and/or seized material has been reported in nine countries. Although the use of tryptamines (including AMT) remains limited, the use appears to have increased over the past five years. AMT has been sold in the form of powders, capsules or pellets via the Internet.

Therapeutic usefulness

Historically, AMT was first developed in the 1960s as an antidepressant and monoamine oxidase inhibitor (MAOI). There is no current legitimate medical or therapeutic use for AMT.

Recommendation

Owing to the current insufficiency of data regarding dependence, abuse and risks to public health, the Committee recommended that AMT not be placed under international control at this time but be kept under surveillance.

3.21 AH-7921

Substance identification

AH-7921 is an *N*-substituted cyclohexylmethylbenzamide and is chemically 3,4-dichloro-*N*-{[1-(dimethylamino)cyclohexyl]methyl}benzamide.

Previous review

AH-7921 had not been previously pre-reviewed or critically reviewed by the Committee. A direct critical review was proposed based on information brought to WHO's attention that AH-7921 is clandestinely manufactured, poses an especially serious risk to public health and society, and has no recognized therapeutic use by any party. Preliminary data collected from the literature and from different countries indicated that this substance may cause substantial harm and that it has no medical use.

Similarity to known substances and effects on the central nervous system

AH-7921 has been shown in animals to be generally equipotent to morphine, exhibiting a steep dose–response curve for respiratory depression. It is a μ -opioid receptor agonist although its analgesic activity may also involve κ -opioid receptors. AH-7921 is a central nervous system depressant. In addition to analgesia, relaxation, euphoria, so-called opiate glow, and alertness, occasional itching, nausea and tremors have been described by self-reporting users. Various analytically confirmed non-fatal and fatal intoxications involving AH-7921 have been reported in the literature.

Dependence potential

No studies have examined the dependence potential of AH-7921 in vitro, in animals or in humans. There have been few studies on the dependence/abuse potential of AH-7921 and no specific studies in humans. However, dependence liability studies in animals showed that AH-7921 produced a withdrawal syndrome similar to that observable for morphine using a similar dose schedule.

Actual abuse and/or evidence of likelihood of abuse

AH-7921 abuse and/or seized material has been reported in nine countries. AH-7921 use appears to be associated with the purchase of so-called research chemicals or equivalent products via the Internet.

Therapeutic usefulness

Although investigated as an opioid for analgesia, AH-7921 has no recorded therapeutic applications or medical use.

Recommendation

AH-7921 is an opioid 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 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.

3.22 Methoxetamine

Substance identification

Methoxetamine is an arylcyclohexylamine and is chemically 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone. It has two enantiomers and is commonly available as the racemic mixture.

Previous review

Methoxetamine had not been previously pre-reviewed or critically reviewed by the Committee. A direct critical review was proposed based on information brought to WHO’s attention that methoxetamine is clandestinely manufactured, poses an especially serious risk to public health and society, and has no recognized therapeutic use by any party. Preliminary data collected from the literature and from different countries indicated that this substance may cause substantial harm and that it has no medical use.

Similarity to known substances and effects on the central nervous system

Methoxetamine shows some structural and pharmacological similarities to ketamine. Data suggest that methoxetamine has *N*-methyl-*D*-aspartate (NMDA) receptor antagonistic activity, similar to ketamine, and functions as a dopamine and serotonin reuptake inhibitor. It is reported to have longer lasting and more powerful adverse effects than ketamine but with weaker analgesic and anaesthetic effects. Specifically, although not formally profiled, methoxetamine is described as a dissociative anaesthetic with hallucinogenic effects also like those of ketamine. Adverse effects following methoxetamine consumption have been reported to be vomiting, nausea, diarrhoea, hypertension, tachycardia and, in some cases, central nervous system depression. Although various non-fatal and fatal intoxications involving methoxetamine have been reported in the literature, they have also involved other drugs and manners of death.

Dependence potential

No studies have examined the dependence potential of methoxetamine *in vitro*, in animals or in humans.

Actual abuse and/or evidence of likelihood of abuse

Methoxetamine abuse and/or seized material has been reported in 14 countries. Methoxetamine use appears to be associated with the purchase of so-called research chemicals or equivalent products via the Internet.

Therapeutic usefulness

Methoxetamine has no recorded therapeutic applications or medical use.

Recommendation

Owing to the current insufficiency of data regarding dependence, abuse and risks to public health, the Committee recommended that methoxetamine not be placed under international control at this time but be kept under surveillance.

3.23 Methiopropamine (MPA)

Substance identification

Methiopropamine (MPA) is chemically 1-(thiophen-2-yl)-2-methylaminopropane, which is a structural analogue of methamphetamine in which the phenyl group has been replaced with a thiophene ring.

Previous review

MPA had not been previously pre-reviewed or critically reviewed by the Committee. A direct critical review was proposed based on information brought to WHO's attention that MPA is clandestinely manufactured, poses an especially serious risk to public health and society, and has no recognized therapeutic use by any party. Preliminary data collected from the literature and from different countries indicated that this substance may cause substantial harm and that it has no medical use.

Similarity to known substances and effects on the central nervous system

MPA shows some structural and pharmacological similarities to methamphetamine. It functions primarily as a norepinephrine and dopamine reuptake inhibitor and, secondarily, as a serotonin reuptake inhibitor. MPA is a central nervous system stimulant and displays methamphetamine-like properties including stimulation, alertness and increase of focus and energy. Side-effects following administration that have been reported are tachycardia, anxiety, panic attacks, perspiration, headache, nausea, difficulty in breathing, vomiting, difficulty urinating and sexual dysfunction. Although some non-fatal and fatal intoxications involving MPA have been reported in the literature, they have also involved other drugs or else data to allow assessment have been limited.

Dependence potential

No studies have examined the dependence potential of MPA in vitro, in animals or in humans.

Actual abuse and/or evidence of likelihood of abuse

MPA abuse and/or seized material has been reported in 10 countries. MPA use appears to be associated with the purchase of so-called research chemicals or equivalent products via the Internet.

Therapeutic usefulness

MPA has no recorded therapeutic applications or medical use.

Recommendation

Owing to the current insufficiency of data regarding dependence, abuse and risks to public health, the Committee recommended that MPA not be placed under international control at this time but be kept under surveillance.

3.24 Ketamine (INN)

Substance identification

Ketamine 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 review

Ketamine had been pre-reviewed by the ECDD at its thirty-third meeting, at which a recommendation was made for a critical review. At its thirty-fourth meeting, the ECDD carried out a critical review of ketamine and concluded that the information available was not sufficient to warrant scheduling. Also in view of the activities of the Commission on Narcotic Drugs regarding ketamine in its forty-ninth session held in March 2006, at the thirty-fourth meeting, the ECDD requested the Secretariat to produce an updated version of the critical review and present it to the next Committee meeting. At its thirty-fifth meeting, and on the basis of the critical review undertaken, the Committee decided that bringing ketamine under international control was not appropriate. At its fifty-seventh session in March 2014, the Commission on Narcotic Drugs adopted Resolution 57/10 on preventing the diversion of ketamine from legal sources while ensuring its availability for medical use. The Commission stated a concern regarding the threat to the well-being of people and society posed by the diversion of ketamine and by the rising trend in the abuse and trafficking of that substance. A notification was made by the Government of the People's Republic of China, under Article 2, paragraph 1 of the Convention on Psychotropic Substances (1971), concerning the proposed recommendation for international control of ketamine. The information provided by China with its notification to the Secretary-General was brought to the Expert Committee's attention.

Similarity to known substances and effects on the central nervous system

Ketamine is an anaesthetic that binds to the so-called phencyclidine (PCP)-binding site of the NMDA-receptor complex as a non-competitive antagonist. Several studies indicate that opioid receptors are also involved in the pharmacological analgesic effects of ketamine. In non-fatal intoxications, anxiety (especially in first-time users), agitation, changes of perception (e.g. loss of notion of danger or visual disturbances), disorientation and impairment of motor function, such as ataxia and dystonic reaction have been described. Reported intoxications typically involve other drugs and ketamine was the sole intoxicant in only a very limited number of fatalities.

Dependence potential

Ketamine may produce dependence in animal models, but reports of dependence in humans are rare. 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 and/or evidence of likelihood of abuse

In many countries, levels of abuse in the general population appear to be low. However, some countries report higher levels of abuse. There are reports on ketamine abuse in certain groups with access to the substance (e.g. medical and veterinarian professionals) and by people who use drugs. Ketamine is difficult to synthesize, so illicit manufacture is rare in most countries. The INCB and UNODC have reported that illicit manufacture of ketamine is of increasing concern in east and south-east Asia. Information supplied by China with its notification to the Secretary-General stated that in China “illegal ketamine production is becoming increasingly serious”.

Therapeutic usefulness

Ketamine is widely used as an anaesthetic in humans and is the anaesthetic of choice in veterinary medicine. Ketamine is included in the WHO Model List of essential medicines (7) and the WHO Model List of essential medicines for children (9) as well as in many national lists of essential medicines. Ketamine has analgesic, hypnotic and short-term memory loss (amnesic) effects and is useful for induction of anaesthesia, procedural sedation and analgesia. Compelling evidence was presented about the prominent place of ketamine as an anaesthetic in developing countries and crisis situations. The ease of parenteral administration gives ketamine a major advantage when anaesthetic gases are impossible to use owing to limited equipment and a lack of appropriately trained specialists.

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 Committee acknowledged the concerns raised by some countries and UN organizations, ketamine abuse currently does not appear to pose a sufficient public-health risk of global scale to warrant scheduling. Consequently, the Committee recommended that ketamine 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.

4. Pre-review of psychoactive substances

As mentioned at the beginning of section 3, 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-sixth 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 Lisdexamfetamine (INN)

Lisdexamfetamine, chemical name (2*S*)-2,6-diamino-*N*-[(2*S*)-1-phenylpropan-2-yl]hexanamide, (2*S*)-2,6-diamino-*N*-[(1*S*)-1-methyl-2-phenylethyl]hexanamidedimethanesulfonate, had not previously been reviewed by the Committee.

As a central nervous system stimulant, lisdexamfetamine is used as an adjunct in the treatment of attention deficit hyperactivity disorder (ADHD). As a pro-drug, lisdexamfetamine was specifically designed as an abuse-resistant product. After oral administration and absorption, enzyme hydrolysis following contact with red blood cells will break lisdexamfetamine into lysine, a naturally occurring essential amino acid, and active dexamfetamine, which is responsible for the substance's pharmacological activity. The safety and efficacy of lisdexamfetamine in the treatment of ADHD in children and adults has been established and the toxicology and adverse effect profile appears similar to other stimulant drugs for this indication. Although lisdexamfetamine self-administration is limited in preclinical and clinical studies, lisdexamfetamine does produce similar subjective and discriminative effects to those of dexamfetamine in humans and animals, respectively. The observation in preclinical studies that lisdexamfetamine produces substantial and sustained increases in catecholaminergic neurotransmission in the prefrontal cortex and striatum without inducing locomotor activation is consistent with the clinical observations that lisdexamfetamine has a long duration of action and

a reasonable separation between its beneficial effects in treating ADHD and the induction of psychostimulant adverse events. To date, there appears to be little evidence of non-medical use of lisdexamfetamine based on data from DAWN Live (Drug Abuse Warning Network¹), Internet and media monitoring, supply-chain monitoring, post-marketing adverse event reports, and Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS[®]) especially in comparison to immediate-release stimulant medicines for ADHD. Nevertheless, the fact that lisdexamfetamine is a pro-drug of dexamfetamine implies a need for similar clinical oversight and precautions for the monitoring and scheduling of this central nervous system stimulant.

Recommendation

Based on the evidence available regarding dependence, abuse and risks to public health, the Committee recommended that a critical review for lisdexamfetamine is not warranted at this time.

4.2 Tramadol (INN)

Tramadol is (\pm)-*trans*-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol. Tramadol was pre-reviewed for the first time at the twenty-eighth meeting of the ECDD in 1992. The Committee did not recommend a critical review on the basis of its low abuse liability as indicated by human studies on its subjective effects and the absence of significant abuse. At the thirty-second meeting of the ECDD in 2000, tramadol was again pre-reviewed. The Committee noted significant numbers of cases of withdrawal syndrome and dependence reported as adverse drug reactions, as well as its potential to produce dependence of the morphine type, and recommended critical review of tramadol. At its thirty-third meeting in 2002, the Committee decided that the information was not sufficient to recommend international control of tramadol, but was adequate to recommend that WHO keep the substance under surveillance. Subsequently, tramadol was pre-reviewed at the thirty-fourth ECDD meeting in 2006. Considering that tramadol continued to show a low level of abuse, even following the major increase in the extent of its therapeutic use, the Committee concluded that there was not sufficient evidence to justify a critical review. Following the adoption of the CND Resolution 56/14 in 2013 regarding “strengthening international cooperation in addressing the non-medical use and abuse, the illicit manufacture and the illicit domestic and international distribution of tramadol”, the substance was presented by the WHO Secretariat for pre-review at the present meeting.

¹ The Drug Abuse Warning Network (DAWN) is a public health surveillance system that monitors drug-related hospital emergency department visits in order to report on the impact of drug use, misuse, and abuse in metropolitan areas and across the United States of America.

Tramadol is an analgesic with a multimode of action. It acts on serotonergic and noradrenergic nociception, while its metabolite *O*-desmethyltramadol acts on the μ -opioid receptor. Its analgesic potency is claimed to be about one tenth that of morphine. Tramadol is used to treat both acute and chronic pain of moderate to (moderately) severe intensity. Tramadol monotherapy does not usually provide adequate analgesia. In treating chronic non-cancer pain, there is little evidence for the use of tramadol for more than three months. Tramadol is considered to be a relatively safe analgesic. The main adverse reactions to tramadol therapy are nausea, dizziness, and vomiting, particularly at the start of the therapy. At therapeutic doses, tramadol does not cause clinically relevant respiratory depression. Tramadol is contraindicated, however, in patients with diminished respiratory function. Tramadol is generally considered as a medicine with a low potential for dependence relative to morphine. Nevertheless, tramadol dependence may occur when it is used for prolonged periods (more than several weeks to months). Dependence on tramadol may occur when used within the recommended dose range but especially when used at supra-therapeutic doses. In many individuals with tramadol dependence, a substance abuse history is found. Orally administered tramadol can produce opioid-like effects (both mental and physical) but these effects are mild and not produced following parenteral administration. Tramadol is generally considered as a medicine with a low abuse potential relative to morphine, and this potential is associated with high-dose oral tramadol. At supra-therapeutic doses, and rarely at therapeutic doses, intoxications may occur. Symptoms of tramadol intoxication are similar to those of other opioid analgesics but may include serotonergic and noradrenergic components. Symptoms include central nervous system depression and coma, tachycardia, cardiovascular collapse, seizures, and respiratory depression up to respiratory arrest. Fatal intoxications are rare and appear to be associated with large overdoses of tramadol and co-ingestion of other drugs (including alcohol).

Tramadol is used worldwide and is listed in many medical guidelines for pain treatment. Tramadol is also included on several national essential medicines lists. It is, however, not included in the 18th WHO Model List of Essential Medicines (April 2013) (7). It is mentioned as a step-2 analgesic in the WHO guidelines on cancer pain relief (10). There is growing evidence of abuse of tramadol in some African and Asian countries where there have been large seizures of such preparations. Tramadol is widely available via the Internet without a prescription. Websites provide many user reports on the non-medicinal use of tramadol. The legal status of tramadol differs internationally. In most countries, it is a prescription-only medicine.

Recommendation

Based on the evidence available regarding dependence, abuse and risks to public health, the Committee recommended that a critical review of tramadol is not warranted at this time.

5. Information on exemptions

The Secretariat was notified by the Secretary-General, United Nations, of the exemption by the Government of Ukraine, pursuant to Article 3, paragraph 3, of the Convention on Psychotropic Substances, 1971, of 12 preparations containing phenobarbital, a psychotropic substance included in Schedule IV of the Convention, from licensing by the competent authority for the control of narcotic drugs, psychotropic substances and precursors as far as domestic trade and distribution are concerned, with the exception of licensing related to the manufacture of the given preparations. The Committee noted the notification.

6. Other matters

6.1 Improving data collection and evidence base for substance evaluation in cooperation with other agencies

The Secretariat presented the challenges in evaluating NPS and potential options for addressing them. The Committee discussed the importance of having reliable and sufficient data that could inform the NPS review process and acknowledged that robust criteria will have to be defined for prioritizing NPS to be reviewed by the Committee. UNODC and WHO mentioned the value of collaboration between international and regional agencies to prevent duplication of data collection efforts while at the same time improving the quality and quantity of data. UNODC and WHO proposed to hold a meeting towards the end of 2014 in order to help identify relevant criteria for the selection of NPS to be reviewed by the Committee and agree on a coordinated approach for data collection. At this meeting, indicators, methods and tools for collection of data on NPS from WHO, EMCDDA and UNODC would be reviewed and proposals for alignment would be made. The Secretariat referred to the importance of continuing and expanding the use of relevant pharmacovigilance data for the assessment of abuse and dependence potential using, among others, the Uppsala Monitoring Centre's VigiBase database. It was proposed at the meeting that data from treatment centres and from poison control centres would also be an important source of information. WHO thanked UNODC, INCB and EMCDDA for sharing information on some of the substances evaluated during the thirty-sixth meeting of the ECDD.

6.2 Planning evaluation of cannabis

The Secretariat presented an information document on cannabis and cannabis resin to the Committee. The document was intended to provide background and relevant information for use by the ECDD when discussing a possible review of cannabis and cannabis resin. The information document included sections on the history of the review and control of cannabis and cannabis resin; procedural aspects of such a review; considerations regarding the current level of control; ECDD assessment requirements (including aspects that need specific attention); and some other considerations. When the Committee evaluates cannabis and its resin, it is recommended that it reviews all aspects listed in the *Guidance on the*

WHO review of psychoactive substances for international control (4), giving special attention to:

- a) its toxicity and adverse reactions in humans;
- b) its abuse and dependence potential;
- c) the medical use of cannabis; and
- d) current controls and their impact.

6.3 Future agenda items

The Committee agreed to include in the agenda of the next meeting of the ECDD proposed methods for improving data collection and the evidence base for substance evaluation that include levels and quality of evidence and criteria for review, which are important for the Committee's decision-making, particularly in view of the challenge posed by NPS.

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