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WHO Expert Committee on Drug Dependence

Thirty-ninth report



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WHO Expert Committee on Drug Dependence

Thirty-ninth 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



**World Health
Organization**

WHO Expert Committee on Drug Dependence: Thirty-ninth report

(WHO Technical Report Series, No. 1009)

ISBN 978-92-4-121018-8

ISSN 0512-3054

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Suggested citation. WHO Expert Committee on Drug Dependence, thirty-ninth report. Geneva: World Health Organization; 2018 (WHO Technical Report Series, No. 1009). Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at <http://apps.who.int/iris>.

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Layout L'IV Com Sàrl, Villars-sous-Yens, Switzerland.
Printed in France.

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Geneva, Switzerland, 6–10 November 2017

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General terms

CND	Commission on Narcotic Drugs
ECDD	Expert Committee on Drug Dependence
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EWA	Early Warning Advisory
INCB	International Narcotics Control Board
INN	International Nonproprietary Name
NPS	new psychoactive substances
SCRA	synthetic cannabinoid receptor agonist
SDG	Sustainable Development Goals
SMART	Synthetics Monitoring: Analysis, Reporting and Trends
THC	tetrahydrocannabinol
UNGASS	United Nations General Assembly Special Session
UNODC	United Nations Office on Drugs and Crime
WHO	World Health Organization



Chemical names

4-FA	4-;1-(4-Fluorophenyl)propan-2-amine
4-FIBF	4-Fluoroisobutyrfentanyl; <i>N</i> -(4-Fluorophenyl)-2-methyl- <i>N</i> -[1-(2-phenylethyl)piperidin-4-yl]propanamide
5F-ADB / 5F-MDMB- PINACA	Methyl (2 <i>S</i>)-2-{{1-(5-fluoropentyl)-1 <i>H</i> -indazole-3-carbonyl}amino}-3,3-dimethylbutanoate
5F-PB-22	Quinolin-8-yl 1-(5-fluoropentyl)-1 <i>H</i> -indole-3-carboxylate
AB-CHMINACA	<i>N</i> -[(2 <i>S</i>)-1-Amino-3-methyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)-1 <i>H</i> -indazole-3-carboxamide
AB-PINACA	<i>N</i> -[(2 <i>S</i>)-1-Amino-3-methyl-1-oxobutan-2-yl]-1-pentyl-1 <i>H</i> -indazole-3-carboxamide
Acryloylfentanyl	<i>N</i> -Phenyl- <i>N</i> -[1-(2-phenylethyl)piperidin-4-yl]prop-2-enamide
Carfentanil	Methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate
CBD	Cannabidiol; (1' <i>R</i> ,2' <i>R</i>)-5'-Methyl-4-pentyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol
Etizolam	4-(2-Chlorophenyl)-2-ethyl-9-methyl-6 <i>H</i> -thieno[3,2- <i>f</i>][1,2,4]triazolo[4,3- α][1,4]diazepine
Furanyl fentanyl	<i>N</i> -Phenyl- <i>N</i> -[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide
Ocfentanil	<i>N</i> -(2-Fluorophenyl)-2-methoxy- <i>N</i> -[1-(2-phenylethyl)piperidin-4-yl]acetamide
Pregabalin	(3 <i>S</i>)-3-(Aminomethyl)-5-methylhexanoic acid
THF-F	Tetrahydrofuranylfentanyl; <i>N</i> -Phenyl- <i>N</i> -[1-(2-phenylethyl)piperidin-4-yl]oxolane-2-carboxamide
tramadol	rac-(1 <i>R</i> ,2 <i>R</i>)-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexan-1-ol
UR-144	(1-Pentyl-1 <i>H</i> -indol-3-yl) (2,2,3,3-tetramethylcyclopropyl)methanone

Introduction

The thirty-ninth meeting of the World Health Organization (WHO) Expert Committee on Drug Dependence (ECDD) took place in Geneva, Switzerland from 6 to 10 November 2017. Dr Suzanne Hill, Director, WHO Department of Essential Medicines and Health Products (EMP), opened the meeting by welcoming all participants on behalf of the WHO Director-General.

Dr Mariângela Simão, Assistant Director-General for Access to Medicines, Vaccines and Pharmaceuticals, thanked the ECDD members for the time and effort they had dedicated to the review of the substances on the agenda of this ECDD meeting. Dr Simão reiterated the mandate of WHO under the 1961 Single Convention on Narcotic Drugs (1) and the 1971 Convention on Psychotropic Substances (2) to undertake the assessment of psychoactive substances with potential for abuse and dependence and that cause harm to health. Where relevant, the importance of therapeutic use of these substances is also assessed. She emphasized that evidence-based assessment of psychoactive substances as mandated by the international drug control conventions is central to the work of the ECDD.

Dr Simão explained that at its thirty-ninth meeting, the ECDD would review 16 substances including several new psychoactive substances (NPS). Particular attention was to be paid to a group of NPS known as fentanyl analogues owing to their association with sharp increases in fatal overdoses.

Dr Simão also discussed the ECDD's pre-review of cannabidiol, a cannabinoid compound found in the cannabis plant, which would pave the way for pre-reviews of cannabis and other cannabis-related substances at the fortieth ECDD meeting in May 2018. A pre-review had been initiated in response to increased interest from Member States in the use of cannabis for medical indications. Furthermore, cannabis had never been reviewed by the ECDD and this prompted the collection of robust scientific evidence and guidance on the safe and effective use of cannabis.

Finally, Dr Simão outlined WHO's work to fulfil its mandates of developing a sustainable surveillance and rapid alert system for substances that present substantial or serious risk to public health. She described WHO's efforts to implement a robust prioritization process to identify the most prevalent, persistent and harmful substances so that they could be assessed by the ECDD. She expressed appreciation of the active participation of Member States, and their critical role in gathering information to support future scheduling decisions concerning NPS. In line with the recommendations of the United Nations General Assembly Special Session (UNGASS), WHO is also actively collaborating with

the United Nations Office on Drugs and Crime (UNODC) and the International Narcotics Control Board (INCB), to reduce the problem associated with the abuse of psychoactive substances and thus contribute to better health.

Dr Gilles Forte, Coordinator of EMP, reminded the members of the Committee of their roles and the expectations held. Mr Jakob Quirin, of the WHO Office of the Legal Counsel, then reminded the members that the Expert Committee is convened under and in accordance with WHO's *Regulations for expert advisory panels* (3) and the *Guidance on the WHO review of psychoactive substances for international control* (4). In accordance with this guidance document, the functions of the ECDD are to review information available to it on substances being considered for international control and for exemptions, and to advise the Director-General on such control.

Declarations of interest

Before the opening of the meeting and in accordance with WHO policy, all members of the Expert Committee and all temporary advisers attending the meeting disclosed potential conflicts of interest that may affect, or may be reasonably perceived to affect, their objectivity and independence in relation to the subject matter of the meeting. Ms Alma Alic, Ethics Officer with the Office of Compliance, Risk Management and Ethics reported the interests that had been declared to the Secretariat of the thirty-ninth ECDD.

Professor Patrick Beardsley, Expert Panel Member, declared that he had received contract support from the National Institute on Drug Abuse to evaluate cannabidiol for treating heroin dependency. Professor Beardsley also declared that he had served as a consultant for abuse-deterrent analgesics for Endo Pharmaceuticals Inc. and Intellipharmaceutics Inc. Finally, Professor Beardsley had recently been awarded a contract from the United States Drug Enforcement Agency to test synthetic opioids, including fentanyl derivatives, to help gather data for their regulatory decisions.

Dr Simon Elliott, Expert Panel Member, declared that he had been a consultant and technical adviser to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) regarding acryloylfentanyl for technical reports and risk assessment in 2016.

Professor Sandra D. Comer, Temporary Adviser, had performed consulting services for Pfizer Inc. up until May 2016. Professor Comer had consulted on two substances, pregabalin and tramadol, which were to be reviewed by the ECDD at its thirty-ninth meeting. Therefore, to prevent a conflict of interest, Professor Comer was recused from these discussions.

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

The members of the Expert Committee elected a chair, co-chair and rapporteur. The chair welcomed all participants and the agenda, as proposed by the Secretariat, was approved.

1. Briefings from international organizations on their work on the public health element of the world drug problem

1.1 Update from the International Narcotics Control Board

Professor Sevil Atasoy, Observer for the International Narcotics Control Board (INCB), informed the Committee about the role and functions of INCB. Established by the 1961 Single Convention on Narcotic Drugs (1), INCB consists of 13 members who are elected by the Economic and Social Council and serve in their personal capacity. Three members with medical, pharmacological or pharmaceutical experience are elected from a list of candidates nominated by WHO and 10 members are elected from a list of candidates nominated by governments.

In the update, Professor Atasoy referred to the recently published annual report of INCB and its thematic chapter on women and drugs, which was prepared in response to the recently adopted Sustainable Development Goals (SDGs) and, in particular, SDG 5 on achieving gender equality and empowering all women and girls. The chapter stressed the importance of considering the specificities and complexities of gender in the design and implementation of drug policy. To implement effective and comprehensive policies to address the drug problem, the needs of women must be targeted and the obstacles preventing them from accessing health care services and treatment must be addressed. Currently, this is not the case. Although one third of global drug users are women, they comprise only one fifth of recipients of treatment for drug dependence. In addition, women are significantly more likely than men to be prescribed narcotics and anti-anxiety medications. There are disproportionately more drug overdoses among women than men. An increasing number of women are being arrested for drug-related crimes. Female prison inmates, along with sex workers, are at particular risk of drug abuse.

Professor Atasoy concluded his statement on the work of INCB by asserting that drug policy must protect the rights of women who use drugs or who have committed drug-related offences as well as the rights of their families. To this end, INCB encourages governments to collect data disaggregated by age, sex and other relevant factors, which will allow for better informed policies and more efficient allocation of resources. Priority should be given to providing easily accessible health care for drug-dependent women. Governments are also encouraged to give high priority to eliminating the stigma associated with drug dependence, particularly among women.

1.2 Update from the United Nations Office on Drugs and Crime

Mr Justice Tettey, Observer for the United Nations Office on Drugs and Crime (UNODC) provided an update to the Committee. The mandate of UNODC is to support Member States in their efforts against drugs, crime and terrorism. UNODC has country and regional field offices in 21 locations around the world, covering more than 150 countries. The three pillars of UNODC work are *research and analytical work*; *normative work* to assist states in the ratification and implementation of the relevant international treaties; and *field-based technical cooperation projects* to enhance the capacity of Member States to counteract illicit drugs, crime and terrorism.

Over the past few years, countries all over the world have had to deal with the threat of NPS. Reports from more than 105 countries have documented the emergence of almost 750 NPS since 2009. Overall, the size of the market for NPS compared to that of the traditional drug markets is still relatively small. However, NPS have been associated with increasing abuse leading to fatal and nonfatal cases of intoxication. The Commission on Narcotic Drugs (CND), following recommendations from WHO and the INCB, has placed several NPS and their precursor chemicals under international control.

UNODC's research and analysis has focused on increasing knowledge and understanding of NPS and expanding the evidence base for policy and operational decisions. The UNODC Early Warning Advisory on NPS (EWA) continues to be the main source of information on NPS at the global level. It represents a key resource for prioritization of substances for review by Member States and WHO, a platform for sharing laboratory and chemical information on NPS, and a compendium of national legislative responses to NPS. In early 2018, the planned addition of a new module on toxic events due to NPS will place the EWA in the best position to fulfil one of the major operational recommendations from the 2016 UNGASS Outcome Document – *identification of the most harmful, prevalent and persistent NPS* (5).

Some key UNODC research outputs in 2017, designed to increase knowledge and understanding of NPS, included the Global Synthetics Monitoring: Analyses, Reporting and Trends (SMART) update on *Fentanyl and its analogues – 50 years on* (March 2017) (6), *World drug report* (June 2017) (7), the Global SMART update on *Non-medical use of benzodiazepines: a growing threat to public health?* (September 2017) (8) and the *Global synthetic drugs assessment: amphetamine-type stimulants and new psychoactive substances* (October 2017) (9).

In terms of normative work to support Member States in the implementation of recent scheduling decisions, UNODC has continued developing and disseminating a series of best practice guidelines and manuals.

These include recommended laboratory methods of analyses of scheduled substances, for example, *Recommended methods for the identification and analysis of fentanyl and its analogues in biological specimens* (November 2017) (10); a supplement to the *Multilingual dictionaries of narcotic drugs and psychotropic substances under international control* (11), and an update to the manual on *Clandestine manufacture of substances under international control* (12). The UNODC national forensic laboratory proficiency-testing programme, the “International Collaborative Exercises”, currently supports 235 laboratories in 74 countries and provided more than 903 units of chemical reference materials, including recently scheduled NPS, to forensic institutions in 55 countries in 2017.

Technical assistance to countries over the past year has addressed gaps in monitoring and reporting on synthetic drugs, including NPS and served to enhance law enforcement and forensic laboratory capacity to detect and identify these substances. Through the Global SMART programme, regional awareness and capacity-building activities have started in Latin America and the Caribbean, the Pacific island states and south-east Asia. In strengthening law enforcement capacity to deal with the dynamic NPS phenomenon, modern detection technologies, including Raman handheld devices have been introduced in UNODC’s drug and precursor field-testing training programme worldwide. In 2018, UNODC will embark on an extensive collaboration with several countries in Latin America and the Caribbean to develop early warning systems on NPS and further enhance law enforcement and forensic laboratory capacity to detect them.

UNODC continues to work closely with WHO on options for responses to the NPS problem. This includes collaboration on developing guidelines for management of NPS use in the clinical setting and the annual UNODC–WHO Expert Consultations on NPS, last held in Vienna, Austria in October 2017.

1.3 Update from the Department of Essential Medicines and Health Products (WHO)

Dr Gilles Forte, Coordinator, Policy, Governance and Knowledge Management, Department of Essential Medicines and Health Products, provided an update on the activities of the department to the Committee.

Dr Forte stated that the United Nations General Assembly Resolution S-30/1, adopted on 19 April 2016 underscores that the availability of internationally controlled drugs for medical and scientific purposes remains low to non-existent in many countries and emphasizes the need for international cooperation to improve access to these medicines. Approximately 96% of the worldwide use of opioid analgesics is in countries in which only 15% of the world population lives.

At the same time, 75% of the world's population, predominantly in lower-income countries, is left with limited or no access to proper pain relief. Fewer than 8% of people in need of palliative care have access to it.

The importance of access to controlled medicines for public health has also been emphasized in several World Health Assembly resolutions. These resolutions reflect Member States' commitment to access to controlled medicines for palliative care (WHA67.19), for emergency and essential surgical care and anaesthesia (WHA68.15) and for epilepsy (WHA68.20). These resolutions also provide WHO with a strong mandate for supporting Member States' efforts to remove barriers to access to these medicines.

Dr Forte discussed the various barriers to access to controlled medicines, which include insufficient knowledge and training on efficacy and safety profiles, inappropriate use or no use, and inaccurate quantification of needs. Many countries also have stricter rules than required by the international drug control conventions, sometimes not contributing to the prevention of substance misuse, but rather creating a barrier to patient access. The perceptions about barriers have changed over time and differ by region.

In line with the international drug control conventions, the WHO approach is to strive for policies and programmes that balance access to essential controlled medicines for all people in need with minimizing misuse or diversion of these medicines. As part of its standard-setting mandate, WHO carries out regular reviews of the efficacy and safety of medicines and updates the WHO Model List of Essential Medicines accordingly. A number of controlled medicines are included in the WHO Model List and are considered essential to alleviate pain and suffering, enable surgery, treat mental health conditions, support dignified and comfortable end-of-life care, help people to overcome addiction and to save lives. Examples of controlled medicines on this list include opioid analgesics (morphine, codeine), long-lasting opioid agonists (methadone, buprenorphine), benzodiazepines and phenobarbital. WHO has also recently developed guidelines for the management of persisting pain in children and is currently developing new guidelines for the management of cancer pain in adults.

In addition to its normative mandate, WHO collaborates with and supports 15 countries in Africa to improve access to medicines, including controlled medicines. This work focuses on monitoring the availability and prices of medicines at health facility level, improving forecasting and quantification, capacity-building of prescribers and dispensers, and on development of balanced policies and legislation.

WHO also works closely with UNODC and INCB. WHO is actively contributing to the INCB Learning Project and is part of the Joint Global Programme (in collaboration with UNODC and the Union for International

Cancer Control) on access to controlled medicines for the management of pain. This programme is currently supported by Australia and Belgium and implemented in East Timor and Democratic Republic of the Congo. It aims to support countries to identify gaps and barriers to access, examine and improve policies, legislation and the supply chain, and support the development of good practices and of capacity-building.

1.4 Update from the Department of Mental Health and Substance Abuse (WHO)

Dr Vladimir Poznyak, Coordinator, Management of Substance Abuse at the Department of Mental Health and Substance Abuse, informed the Committee about the discussions held during the meetings of the WHO governing bodies on public health dimensions of the world drug problem. This included the decision of the seventieth World Health Assembly that requested the Director-General to continue efforts to improve coordination and collaboration of WHO with UNODC and INCB, within their existing mandates, in addressing and countering the world drug problem, and to report on the implementation of this decision at future World Health Assemblies. Dr Poznyak highlighted the new Memorandum of Understanding between WHO and UNODC. It was signed in early 2017 to strengthen collaboration in implementation of the operational recommendations endorsed by the 2016 UNGASS on the world drug problem. It also covered activities needed to reach SDG 3 health target 3.5 on strengthening prevention and treatment of substance abuse.

Dr Poznyak informed the Committee about recent activities in the cluster of Noncommunicable Diseases and Mental Health, focusing on prevention, identification and management of substance use and substance use disorders as well as about the ongoing work on the development of WHO guidelines for the management of cancer pain in adults.

The first WHO Forum on alcohol, drugs and addictive behaviours was organized in Geneva in June 2017. It will serve as a platform for discussions of the most pertinent public health issues by governmental officials, representatives of UN agencies, academia and nongovernmental organizations.

An update was provided on the work on the eleventh revision of the International Classification of Diseases (ICD) with regard to disorders and health conditions due to psychoactive substance use, and the plans for an update of the WHO lexicon on alcohol and drug terms.

1.5 Update from the Department of HIV/AIDS

Dr Andrew Ball, Senior Adviser on Strategy, Policy and Equity in the WHO Department of HIV and the Global Hepatitis Programme provided a brief overview of the public health impact of, and responses to, human immunodeficiency virus (HIV) and viral hepatitis epidemics associated with injecting and other drug use. In October 2017, new global estimates of injecting drug use were published in *the Lancet*, with support from WHO. The article reported that 18% of the estimated 15.6 million people who inject drugs globally are living with HIV, 52% are hepatitis C virus antibody positive and 9% are hepatitis B virus surface antigen positive. Whereas the coverage of high-impact HIV prevention services for people who inject drugs is expanding in a range of countries, less than 1% of people who inject drugs live in countries with high coverage of needle and syringe programmes and opioid substitution therapy.

The Global Health Sector Strategy on HIV and the Global Health Sector Strategy on Viral Hepatitis, 2016–2021, endorsed by the World Health Assembly in 2016, recommends countries to implement a comprehensive set of harm reduction interventions if they are to achieve the elimination of acquired immunodeficiency syndrome (AIDS) and viral hepatitis epidemics as public health threats. WHO has produced a broad range of policy documents, guidelines and implementation tools to guide national programmes on HIV and viral hepatitis prevention, testing, treatment, chronic care and monitoring and evaluation among people who use drugs. In 2017, hepatitis testing guidelines were launched and an update of the guidelines on hepatitis C treatment and care will be released in 2018. Over the past year WHO has intensified its technical support to countries to help them to adapt and implement these policies and guidelines. Countries are being assisted to assess the coverage, quality and impact of their HIV services for people who inject drugs so that services can be tailored to the local context and different populations.

Whereas considerable experience had been gained in developing and implementing harm reduction services for preventing and managing HIV epidemics among people who inject drugs, such interventions and approaches may be inadequate to prevent and control hepatitis C epidemics. In the past three years access to direct-acting antivirals for the treatment of chronic hepatitis C infection, with cure rates exceeding 95%, has shown the potential to transform hepatitis responses. WHO guidelines recommend that all populations, including people who inject drugs, should have equitable access to both HIV and viral hepatitis treatment. Ending the epidemics of HIV and hepatitis will require a renewed focus on people who use drugs, the promotion of supportive policies and laws, and adequate human and financial resources.

2. Update from the second Informal Working Group of the ECDD

Dr Gilles Forte (Secretary of the ECDD) provided an overview of the activities of the second Informal Working Group of the ECDD, which met in Geneva, Switzerland, from 8 to 10 May 2017. Dr Forte explained that the working group was composed of seven members of the thirty-eighth ECDD and was balanced both geographically and by gender.

At that meeting, the Secretariat had supplied the working group with a shortlist of 24 substances that had been identified by Member States and other organizations as possible candidates for review by the ECDD at its thirty-ninth meeting. The working group assessed the evidence base to identify the most prevalent, persistent and harmful of these substances. From the initial list, the working group recommended the inclusion of 14 substances on the agenda of the thirty-ninth meeting of the ECDD.

The Informal Working Group discussed the role of unpublished data in the proceedings of the ECDD. It was highlighted that unpublished data, although considered low-quality evidence, can be informative during the meeting proceedings. The working group recommended that any unpublished information be made available, through the Secretariat, for consideration by the authors of the critical reviews and pre-reviews. The working group also expressed a desire to expand collaborations with Member States, and with international and regional agencies to share data on NPS.

Following an informal proposal from a Member State, the working group also recommended inclusion of an item on the agenda for the thirty-ninth meeting of the ECDD to discuss the exemption clause for preparations containing low doses of codeine in Schedule III of the 1961 Convention. The Informal Working Group also recommended that a discussion on the global opioid crisis be included on the agenda for the thirty-ninth meeting of the ECDD, to review the current information and determine the steps the ECDD could take to help address the issue.

The working group discussed the five upcoming pre-reviews of cannabis and cannabis-related compounds. It was proposed that the Secretariat review the WHO Member States questionnaire and possibly refine the questions to ensure that relevant information specific to cannabis is captured. Also, it was recommended that the cannabidiol pre-review be included in the agenda for the thirty-ninth ECDD meeting on the basis of cannabidiol's potential therapeutic usefulness. The working group then discussed how the remaining four pre-reviews should

be prepared. For each pre-review, six areas of expertise are required: chemistry, pharmacology, toxicology, therapeutic use, epidemiology and scheduling status. To maintain consistency between the reviews, it was decided that an external author with a certain area of expertise (e.g. chemistry) would write the relevant sections for that area of expertise (for example, chemistry sections 1–3) for the four pre-reviews.

The working group developed and further refined the WHO list of substances under surveillance. Previously, the surveillance list had only contained substances that were recommended for surveillance following their review at an ECDD meeting. However, a new surveillance list was developed that contains both ECDD-reviewed substances and other substances that are considered to cause harm to public health but have yet to be reviewed by the ECDD. This surveillance list will be updated regularly to provide Member States with information about the actual or potential dangers associated with particular substances. The members of the working group also provided feedback on the proposed WHO surveillance system. This system will focus on public health and on obtaining data on the adverse effects of NPS (e.g. deaths, poisonings, driving under the influence of drugs and admissions to emergency departments).

The working group also addressed a number of questions that had been submitted to the Secretariat about procedural matters concerning the ECDD.

3. Follow-up on recommendations made by the ECDD at its thirty-eighth meeting

Ms Dilkushi Poovendran gave an overview of the follow-up to the thirty-eighth meeting of the ECDD and informed the Committee about the decisions of the Commission on Narcotic Drugs (CND) (2017). The thirty-eighth meeting of the WHO ECDD had taken place in Geneva, Switzerland, from 14 to 18 November 2016 and the Committee had recommended that ten of the 12 substances it had critically reviewed be placed under international control, that one substance (JWH-073) be kept under surveillance, and one substance (3-MMC) be subject to critical review at a subsequent ECDD meeting.

The recommendations on the following substances to be placed under international control were conveyed to the Secretary-General of the United Nations and discussed at the sixtieth session of the CND in March 2017.

3.1 U-47700

As recommended by the ECDD at its thirty-eighth meeting, on 16 March 2017 the CND decided to include U-47700 in Schedule I of the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol (Decision 60/2).

3.2 Butyrfentanyl

As recommended by the ECDD at its thirty-eighth meeting, on 16 March 2017 the CND decided to include butyrfentanyl in Schedule I of the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol (Decision 60/3).

3.3 4-MEC

As recommended by the ECDD at its thirty-eighth meeting, on 16 March 2017 the CND decided to include 4-MEC in Schedule II of the Convention on Psychotropic Substances of 1971 (Decision 60/4).

3.4 Ethylone

As recommended by the ECDD at its thirty-eighth meeting, on 16 March 2017 the CND decided to include ethylone in Schedule II of the Convention on Psychotropic Substances of 1971 (Decision 60/5).

3.5 Pentedrone

As recommended by the ECDD at its thirty-eighth meeting, on 16 March 2017 the CND decided to include pentedrone in Schedule II of the Convention on Psychotropic Substances of 1971 (Decision 60/6).

3.6 Ethylphenidate

As recommended by the ECDD at its thirty-eighth meeting, on 16 March 2017 the CND decided to include ethylphenidate in Schedule II of the Convention on Psychotropic Substances of 1971 (Decision 60/7).

3.7 Methiopropamine (MPA)

As recommended by the ECDD at its thirty-eighth meeting, on 16 March 2017 the CND decided to include methiopropamine (MPA) in Schedule II of the Convention on Psychotropic Substances of 1971 (Decision 60/8).

3.8 MDMA-CHMICA

As recommended by the ECDD at its thirty-eighth meeting, on 16 March 2017 the CND decided to include MDMA-CHMICA in Schedule II of the Convention on Psychotropic Substances of 1971 (Decision 60/9).

3.9 5F-APINACA

As recommended by the ECDD at its thirty-eighth meeting, on 16 March 2017 the CND decided to include 5F-APINACA in Schedule II of the Convention on Psychotropic Substances of 1971 (Decision 60/10).

3.10 XLR-11

As recommended by the ECDD at its thirty-eighth meeting, on 16 March 2017 the CND decided to include XLR-11 in Schedule II of the Convention on Psychotropic Substances of 1971 (Decision 60/11).

4. Proposed WHO surveillance system for new psychoactive substances (NPS)

Ms Dilkushi Poovendran, Technical Officer, Innovation, Access and Use, Department of Essential Medicines and Health Products, briefed the Committee and the observers on a proposed WHO surveillance system for NPS. Ms Poovendran referred to the recent CND Resolution 60/4, entitled “Preventing and responding to the adverse health consequences and risks associated with the use of new psychoactive substances”, which invited the,

World Health Organization, with the support of Member States, the United Nations Office on Drugs and Crime and other relevant international and regional organizations, to enhance its surveillance of new psychoactive substances of concern, to regularly update its surveillance list and disseminate it to Member States and relevant international and regional organizations and to issue voluntary public health alerts where there is sufficient evidence that a substance poses a significant risk to public health and safety.

Ms Poovendran described a proposed WHO surveillance system that would increase the number of substances assessed in the prioritization process through a collaborative data-sharing arrangement with multiple bodies including UNODC and EMCDDA. The role of WHO would be to collate health-related information and provide expertise in its evaluation. WHO would use these data to update its surveillance list and disseminate information to Member States through an alert system.

5. Review of psychoactive substances

WHO carries out the review of psychoactive substances 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 a fully documented review (critical review) of the substance is required. If a preceding meeting of the Committee found that a critical review of a substance is warranted, the Secretariat will prepare such a review for the next meeting of the Committee. However, a pre-review is not always needed and in certain cases a critical review can be undertaken directly.

According to the *Guidance on the WHO review of psychoactive substances for international control* (4) a critical review is initiated by the Expert Committee in any of the following cases:

- (1) There has been notification from a Party to the 1961 Single Convention on Narcotic Drugs and the 1971 Convention on Psychotropic Substances concerning the scheduling of a substance.
- (2) There has been an explicit request from CND to review a substance.
- (3) A pre-review of a substance has resulted in an Expert Committee recommendation for critical review.
- (4) Information was brought to WHO's attention that a substance is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any Party.

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

5.1 AB-CHMINACA

Substance identification

Chemically, AB-CHMINACA is *N*-[(2*S*)-1-Amino-3-methyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide. AB-CHMINACA contains a chiral centre at the C-2 carbon of the oxobutan-2-yl side chain, so that two enantiomers exist: (*R*)-AB-CHMINACA and (*S*)-AB-CHMINACA. Based on the literature and the most likely precursors to be used, an (*S*)-configuration of the stereocentre should be expected.

Previous review

AB-CHMINACA has not been previously pre-reviewed or critically reviewed. A direct critical review was proposed based on information brought to WHO's attention that AB-CHMINACA is clandestinely manufactured, poses serious

risk to public health and society, and has no recognized therapeutic use by any Party. Preliminary information collected from various sources 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

AB-CHMINACA binds to the cannabinoid CB1 receptor and demonstrates *in vitro* functional agonist activity at the receptor site. It demonstrates activity in all four components of the cannabinoid tetrad assay in mice (activity, catalepsy, hypothermia and analgesia). Across these four components, AB-CHMINACA is 11- to 58-fold more potent than tetrahydrocannabinol (THC) itself. These effects of AB-CHMINACA can be antagonized by the cannabinoid CB1 receptor antagonist, rimonabant. Users of AB-CHMINACA report cannabimimetic effects after smoking the drug. AB-CHMINACA is not readily converted into other internationally controlled substances.

Dependence potential

No controlled, experimental studies examining the dependence potential of AB-CHMINACA in human subjects or laboratory animals were available.

Actual abuse and/or evidence of likelihood of abuse

AB-CHMINACA produces complete, dose-dependent substitution for the discriminative stimulus effects of THC in mice, and is 16 times more potent than THC in this respect, suggesting that it can produce at least some of the subjective and abuse potential effects of synthetic cannabinoid receptor agonists (SCRAs).

AB-CHMINACA is sold and used as a “legal” substitute for cannabis. It is most commonly smoked, or vaped through an e-cigarette. Between 2014 and 2016, seven acute cases of intoxication of people with confirmed exposure to AB-CHMINACA were reported to the EMCDDA. Where details were provided, the clinical features of the poisoning were typical of those reported for SCRAs. Effects of AB-CHMINACA are consistent with those of SCRAs. They include relaxation, euphoria, lethargy, depersonalization, distorted perception of time, impaired motor performance, hallucinations, paranoia, confusion, fear, anxiety, dry mouth, conjunctival injection (“red eyes”), tachycardia, and nausea and vomiting. During a period of less than two weeks in which there was an outbreak of SCRA usage in Florida, the presence of AB-CHMINACA or one of its predicted metabolites, was confirmed in 15 of 21 cases. Some of the patients had acute delirium and seizures. Between 2014 and 2017 a total of 31 deaths of people with confirmed exposure to AB-CHMINACA were reported to the EMCDDA. In at least seven cases, AB-CHMINACA was the cause of death or contributed to the death. In a recent fatal case, in which it was the predominant SCRA present, use of AB-CHMINACA was associated with non-cardiogenic pulmonary oedema.

AB-CHMINACA has also been associated with several instances of impaired driving reported from Hungary, Japan and the United States of America (USA). For instance, in the USA in 2014, AB-CHMINACA was detected in 33 out of 58 people stopped for impaired driving who had tested positive for SCRA. In recognition of its abuse and associated harm, AB-CHMINACA has been placed under national control in a number of countries in several different regions.

Therapeutic usefulness

There are currently no approved medical or veterinary uses of AB-CHMINACA.

Recommendation

AB-CHMINACA is a synthetic cannabinoid receptor agonist. It is clandestinely manufactured and sold under a variety of brand names. It has cannabimimetic effects that are more potent than those of THC, which is listed as a Schedule II substance in accordance with the Convention on Psychotropic Substances of 1971. Its mode of action suggests the potential for dependence and likelihood of misuse. There is evidence of an increase in the number of people using AB-CHMINACA in many countries and of fatal and nonfatal cases. This substance causes substantial harm and has no therapeutic usefulness. AB-CHMINACA shows similar abuse and similar ill effects to other SCRA already scheduled in Schedule II of the 1971 Convention. The Committee recommended that AB-CHMINACA (*N*-[(2*S*)-1-Amino-3-methyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide) be placed in Schedule II under the UN Convention on Psychotropic Substances of 1971.

5.2 5F-ADB/5F-MDMB-PINACA

Substance identification

Chemically, 5F-ADB (also known as 5F-MDMB-PINACA) is methyl (2*S*)-2-[[1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl]amino]-3,3-dimethylbutanoate. 5F-ADB contains a chiral centre at the C-2 carbon of the oxobutan-2-yl side chain, so that two enantiomers exist: (*R*)-5F-ADB and (*S*)-5F-ADB.

Previous review

5F-ADB has not been previously pre-reviewed or critically reviewed. A direct critical review was proposed based on information brought to WHO's attention that 5F-ADB is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any Party. Preliminary information collected from various sources 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

5F-ADB is a synthetic cannabinoid receptor agonist. It has an indazole core, which is a common structural feature in a number of the SCRA. 5F-ADB has potent binding affinity for the CB1 receptor, and a greater potency than THC and MDMB-CHMICA, both of which are listed as Schedule II substances in the UN Convention on Psychotropic Substances 1971. 5F-ADB significantly increases the spontaneous firing rate of dopaminergic neurons, an effect that is blocked when the CB1 antagonist AM251 is present, indicating a CB1 receptor-mediated increase in dopaminergic activity.

5F-ADB appears to have similar effects to other SCRA substances in the individual user. In 2016, 35 cases of acute intoxication of people with confirmed exposure to 5F-ADB were reported to the EMCDDA. In five additional published cases of nonfatal intoxication, in which 5F-ADB was analytically confirmed, central nervous system effects including psychomotor agitation, confusion, altered consciousness, vomiting, headache, dizziness, dilated pupils, acute psychosis and anxiety were observed.

Dependence potential

No controlled, experimental studies directly pertinent to the dependence potential of 5F-ADB in either laboratory animals or human subjects are available.

Actual abuse and/or evidence of likelihood of abuse

Similar to other SCRA, 5F-ADB is found as a constituent in herbal mixtures that are sold under a variety of product names as legal alternatives to cannabis. The most common way of using it is by smoking or vaping through an e-cigarette.

5F-ADB has been widely available on the European market since 2014. The compound has been seized in the form of powder, herbal material, liquids and blotters. More than 1700 seizures have been reported in Europe alone. 5F-ADB seizures have also been reported from Indonesia, Japan, Kazakhstan, the Russian Federation and Ukraine.

Thirty-five cases of acute intoxication and 28 deaths were reported to the EMCDDA following confirmed exposure to 5F-ADB, either alone or in combination with other substances. In at least 20 of the 28 deaths, 5F-ADB was either the cause of death or contributed to death. Cases of impaired driving and deaths involving 5F-ADB have also been reported from Japan.

Therapeutic usefulness

5F-ADB has no approved medical or veterinary use.

Recommendation

5F-ADB is a synthetic cannabinoid receptor agonist. It has cannabimimetic effects that are more potent than those of THC and MDMB-CHMICA, which are listed as Schedule II substances in accordance with the Convention on Psychotropic Substances of 1971. Its mode of action suggests the potential for dependence and likelihood of abuse. There is evidence of an increase in the number of people using 5F-ADB in many countries and fatal and nonfatal intoxication has resulted. This substance causes substantial harm and has no therapeutic usefulness. The Committee recommended that 5F-ADB, also known as 5F-MDMB-PINACA (Methyl (2S)-2-{{1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl}amino}-3,3-dimethylbutanoate) be placed in Schedule II under the UN Convention on Psychotropic Substances of 1971.

5.3 4-Fluoroamphetamine (4-FA)

Substance identification

The chemical name of 4-FA is 1-(4-Fluorophenyl)propan-2-amine. The presence of a chiral centre at the α -carbon of the side chain gives rise to the enantiomeric pair of (*S*)-4-FA and (*R*)-4-FA. 4-FA is most likely to be available as the racemic mixture.

Previous review

4-FA underwent a critical review by the ECDD in 2015. At that time, the Committee recommended that 4-FA not be placed under international control due to insufficient evidence regarding dependence, abuse and risks to public health. However, it was kept under surveillance. Preliminary information collected from various sources indicated that this substance may cause substantial harm and that it has no medical use, thereby warranting an updated critical review.

Similarity to known substances and effects on the central nervous system

4-FA is a ring-substituted derivative of amphetamine, which is listed in Schedule II of the United Nations 1971 Convention on Psychotropic Substances. 4-FA shares some effects of psychostimulants and of the entactogens. Similar to amphetamine-like stimulants, 4-FA releases dopamine, noradrenaline and serotonin, and displays amphetamine-like features in a number of *in vivo* and *in vitro* assays, including the induction of locomotor activity and associated dopamine release in the striatum and nucleus accumbens (regions of the brain linked to the rewarding effects of drugs). 4-FA differs from (+)-amphetamine in its ability to increase extracellular serotonin concentrations in the rat nucleus accumbens.

Some users report that 4-FA promotes pro-social effects that might overlap with those of 3,4-methylenedioxy-methamphetamine (MDMA). Recent studies, including a systematic survey of users, confirmed that the effects of 4-FA were consistent with a psychomotor/entactogen stimulant profile. Some adverse reactions in users have been reported that required hospitalization and others have resulted in death. The clinical features associated with 4-FA intoxication include agitation, tachycardia, hypertension, hyperthermia, cardiovascular toxicity and cerebrovascular complications such as severe headaches and cerebral haemorrhage.

Dependence potential

No reports from controlled, experimental studies pertinent to the possible physical dependence effects of 4-FA in laboratory animals and humans are available.

Actual abuse and/or evidence of likelihood of abuse

In nonclinical studies in rodents, 4-FA shows classic features associated with amphetamine-like stimulants that are predictive of abuse liability. These include release of dopamine, induction of locomotor activity and substitution for the discriminative stimulus effects of (+)-amphetamine. It is also self-administered by rhesus monkeys.

The presence of 4-FA in Europe has been observed at least since 2007. Over the years, it has been found in products sold as “ecstasy”/MDMA tablets, amphetamine powder and also as an adulterant present in other controlled substances. 4-FA is also available online or from offline retailers as a single substance under its own name. 4-FA can be taken orally or insufflated. It is rarely injected.

Most reports of 4-FA use so far are from European countries. Seizures have been documented in a number of European countries and 4-FA is controlled through national legislation in several countries.

Therapeutic usefulness

There are no known approved medical or veterinary applications of 4-FA.

Recommendation

4-FA is a ring-substituted derivative of amphetamine, which is listed in Schedule II of the United Nations Convention on Psychotropic Substances of 1971. In nonclinical studies, 4-FA has been found to share several effects produced by psychostimulants that are predictive of abuse liability. These include activation of locomotion, substitution for the amphetamine discriminative stimulus, and

self-administration. Users report effects of 4-FA that are consistent with a psychomotor/entactogen stimulant profile. It has been found in products sold as “ecstasy”/MDMA tablets, amphetamine powder, as an adulterant present in other controlled substances, and is sold in its own right. Seizures of 4-FA have occurred in more than 20 countries, and several countries have placed it under national control. Some adverse reactions have been reported that required hospitalization and others that have resulted in death.

The Committee considered that the degree of risk to public health and society associated with the abuse of 4-FA is substantial. Therapeutic usefulness has not been recorded. The Committee recognized that 4-FA has similar abuse potential and similar ill effects to substances in Schedule II of the UN Convention on Psychotropic Substances of 1971. The Committee considered that there is sufficient evidence that 4-FA is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. The Committee recommended that 4-FA (1-(4-Fluorophenyl)propan-2-amine) be placed in Schedule II under the UN Convention on Psychotropic Substances of 1971.

5.4 AB-PINACA

Substance identification

Chemically, AB-PINACA is *N*-[(2*S*)-1-Amino-3-methyl-1-oxobutan-2-yl]-1-pentyl-1*H*-indazole-3-carboxamide. AB-PINACA has stereoisomers.

Previous review

AB-PINACA has not been previously pre-reviewed or critically reviewed. A direct critical review was proposed based on information brought to WHO’s attention that AB-PINACA is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any Party. Preliminary information collected from various sources 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

AB-PINACA shows high affinity to cannabinoid CB₁ receptors and differs from a number of other SCRAs in demonstrating greater selectivity towards the CB₂ receptors. AB-PINACA induces responses in animals that are also observed with THC and internationally controlled SCRAs. For instance, it produces all the effects characteristic of cannabinoids in the cannabinoid tetrad assay including the suppression of locomotor activity, reduction of body temperature and production of antinociception and catalepsy with a 2- to 14-fold greater potency

than THC. These effects are reversible by the cannabinoid receptor antagonist rimonabant.

Dependence potential

No reports of controlled, experimental studies using human or laboratory animal subjects directly pertinent to the dependence potential of AB-PINACA are available.

Actual abuse and/or evidence of likelihood of abuse

AB-PINACA is sold in the form of herbal mixtures for smoking. AB-PINACA products have been implicated in cases of impaired driving and motor vehicle collisions.

Reports received from the European Early Warning System on NPS indicate that AB-PINACA has been found in herbal mixtures and powders in several countries. AB-PINACA detections have also been reported in the USA since 2013. Data from law enforcement agencies suggest that AB-PINACA was one of the most commonly reported substances used in the USA in 2014. Japan was the first country to identify AB-PINACA and an increasing number of countries have since reported its use.

Therapeutic usefulness

AB-PINACA is not known to have any approved therapeutic applications.

Recommendation

AB-PINACA is a synthetic cannabinoid receptor agonist and is clandestinely manufactured. It induces similar effects to other SCRA and THC, which are listed as Schedule II substances in accordance with the Convention on Psychotropic Substances of 1971. Adverse effects associated with AB-PINACA use include loss of consciousness, convulsions and death. Ingestion of AB-PINACA products has been implicated in cases of impaired driving and motor vehicle collisions. Reports of AB-PINACA's use have occurred in more than 20 countries.

The Committee considered that the degree of risk to public health and society associated with the abuse of AB-PINACA is substantial. Therapeutic usefulness has not been recorded. It recognized that AB-PINACA has similar abuse liability and similar ill effects to other SCRA in Schedule II of the UN Convention on Psychotropic Substances of 1971. The Committee considered that there is sufficient evidence that AB-PINACA is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. The Committee recommended that AB-PINACA (*N*-[(2*S*)-1-Amino-3-methyl-1-oxobutan-2-yl]-1-pentyl-1*H*-

indazole-3-carboxamide) be placed in Schedule II under the UN Convention on Psychotropic Substances of 1971.

5.5 Ocfentanil

Substance identification

Chemically, ocfentanil is *N*-(2-Fluorophenyl)-2-methoxy-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide. It has no stereoisomers.

Previous review

Ocfentanil has not been previously pre-reviewed or critically reviewed. A direct critical review was proposed based on information brought to the attention of WHO that ocfentanil is clandestinely manufactured, poses a risk to public health and society, and has no recognized therapeutic use by any Party. Preliminary information collected from various sources 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

Chemically, ocfentanil comprises two modifications to fentanyl: replacement of the propionamide group with a methoxyacetamide and the addition of ortho-fluorine to the *N*-phenyl ring. The pharmacodynamic effects of ocfentanil appear to be similar to those of fentanyl, a potent agonist at the μ subtype of opioid receptors and a Schedule I drug under the 1961 Convention. In rodents, ocfentanil was 2.3 times more potent as an analgesic than fentanyl, and its duration of action was shorter. In human subjects, ocfentanil produces a dose-related increase in analgesia and a decrease in respiration. Clinical research conducted on its use as a supplement to general anaesthesia describes a similar potency of ocfentanil and fentanyl and it had no clear advantage over the latter in terms of safety. Ocfentanil has also been reported to produce other typical opioid effects such as itching, nausea and sedation. Ocfentanil-related deaths have been reported in some European and North American countries.

Dependence potential

No data regarding the dependence and abuse potential of ocfentanil from controlled, human or laboratory animal studies are available.

Actual abuse and/or evidence of likelihood of abuse

Ocfentanil is sold online as heroin. Users of material containing analytically confirmed ocfentanil have reported effects similar to those of heroin including

euphoria with stimulation. Epidemiological estimates of use are not available. Ocfentanil is a regulated substance in a number of countries.

Therapeutic usefulness

Ocfentanil is not used therapeutically. It was investigated for therapeutic purposes but found to have a similar clinical profile to fentanyl so further development was discontinued.

Recommendation

Ocfentanil is an opioid that is structurally related to fentanyl, which is regulated under Schedule I of the 1961 Single Convention on Narcotic Drugs. It produces opioid effects including analgesia, euphoria, sedation and potentially serious respiratory depression. Ocfentanil-related deaths have been reported, and it has been brought under national control in several countries in various regions of the world.

Ocfentanil is a compound liable to similar abuse and with similar ill effects to controlled opioids such as fentanyl, which are included in Schedule I of the Single Convention on Narcotic Drugs of 1961. It has no recorded therapeutic use, and its use has been associated with fatalities. There is sufficient evidence that it is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. Thus, because it meets the required condition of similarity, it is recommended that ocfentanil (*N*-(2-Fluorophenyl)-2-methoxy-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide) be placed in Schedule I of the Single Convention on Narcotic Drugs, 1961, as consistent with Article 3, paragraph 3 (iii) of that Convention in that the substance is liable to similar abuse and productive of similar ill effects to drugs in Schedule I.

5.6 Furanyl fentanyl

Substance identification

Furanyl fentanyl is chemically known as *N*-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide. Furanyl fentanyl has no stereoisomers.

Previous review

Furanyl fentanyl has not been previously pre-reviewed or critically reviewed. A direct critical review was proposed based on information brought to WHO's attention that furanyl fentanyl is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any

Party. Preliminary information collected from various sources 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

Furanyl fentanyl is a synthetic opioid that is an analogue of fentanyl. The methods developed for the synthesis of fentanyl are applicable to the synthesis of furanyl fentanyl as it relies on similar precursors and synthetic methods. It is a μ -opioid receptor agonist and produces typical opioid effects including analgesia, miosis, sedation and respiratory depression.

Dependence potential

No information on controlled experimental studies in laboratory animals or humans directly pertinent to the dependence or abuse potential of furanyl fentanyl are currently available.

Actual abuse and/or evidence of likelihood of abuse

The EMCDDA-Europol report noted 113 seizures across a number of European countries. The United States Centers for Disease Control reported 244 drug submissions testing positive for furanyl fentanyl in the first seven months of 2016. Authorities in the USA reported a total of 607 drug samples in which furanyl fentanyl was identified in forensic laboratories between December 2015 and September 2016. Deaths and cases of intoxication associated with furanyl fentanyl usage have been reported from Europe and North America between 2015 and 2017. The US Drug Enforcement Agency reported 128 confirmed fatalities associated with the drug. Canada reported 43 overdose events caused by crack cocaine contaminated with furanyl fentanyl. Serious adverse events (10 cases of acute intoxication and 19 deaths) have been associated with furanyl fentanyl use in Europe.

Therapeutic usefulness

There are no approved therapeutic applications nor any marketing authorizations for furanyl fentanyl.

Recommendation

Furanyl fentanyl is a compound liable to similar abuse and with similar ill effects to controlled opioids such as fentanyl, which are included in Schedule I of the Single Convention on Narcotic Drugs of 1961. It has no recorded therapeutic use and its use has been associated with fatalities. There is sufficient evidence that it is being or is likely to be abused so as to constitute a public health and social

problem warranting the placing of the substance under international control. Thus, because it meets the required condition of similarity, it is recommended that furanyl fentanyl (*N*-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide) be placed in Schedule I of the Single Convention on Narcotic Drugs, 1961, as consistent with Article 3, paragraph 3 (iii) of that Convention in that the substance is liable to similar abuse and productive of similar ill effects to drugs in Schedule I.

5.7 Acryloylfentanyl (Acrylfentanyl)

Substance identification

Chemically, acryloylfentanyl is *N*-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]prop-2-enamide. It has no stereoisomers.

Previous review

Acryloylfentanyl has not been previously pre-reviewed or critically reviewed. A direct critical review was proposed based on information brought to WHO's attention that acryloylfentanyl is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any Party. Preliminary information collected from various sources 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

Acryloylfentanyl is a μ -opioid receptor agonist with a potency similar to fentanyl. In mice, it produces antinociception and has a longer duration of action than fentanyl. In humans, miosis, decreased consciousness and respiratory depression have been associated with acryloylfentanyl use. These effects were reversed by naloxone.

Dependence potential

No controlled, experimental studies that have investigated the dependence potential of acryloylfentanyl in laboratory animals or humans are available. However, the limited information obtainable from user websites suggests that some users of acryloylfentanyl report an urge to re-dose as well as having symptoms suggestive of withdrawal.

Actual abuse and/or evidence of likelihood of abuse

No controlled, experimental studies that have investigated the abuse potential of acryloylfentanyl in laboratory animals or humans are available. Acryloylfentanyl

use has been reported in several European countries and in North America. Data in Europe suggest that the substance is sold online, typically as a powder and as ready-to-use nasal sprays. Acryloylfentanyl is often described as a “research chemical” on such websites. There have been 130 reported deaths associated with acryloylfentanyl use in Europe and North America. Acryloylfentanyl is controlled in a number of countries in different regions of the world.

Therapeutic usefulness

There is no evidence that acryloylfentanyl has been used therapeutically.

Recommendation

The available evidence shows that acryloylfentanyl is an opioid receptor agonist and its pharmacodynamics and clinical effects are similar to those of controlled fentanyls. It binds to opioid receptors and produces antinociception, decreased consciousness, miosis and respiratory depression that can be fatal. The substance has been detected in samples from people who have died and in cases of nonfatal intoxication and its use is a significant concern in a number of countries.

Acryloylfentanyl is a compound liable to similar abuse and with similar ill effects to controlled opioids such as fentanyl, which are included in Schedule I of the Single Convention on Narcotic Drugs of 1961. It has no recorded therapeutic use, and its use has been associated with fatalities. There is sufficient evidence that it is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. Thus, because it meets the required condition of similarity, it is recommended that acryloylfentanyl (N N-Phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]prop-2-enamide) be placed in Schedule I of the Single Convention on Narcotic Drugs, 1961, as consistent with Article 3, paragraph 3 (iii) of that Convention in that the substance is liable to similar abuse and productive of similar ill effects to drugs in Schedule I.

5.8 Carfentanil

Substance identification

Chemically, carfentanil is Methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate. Carfentanil has no stereoisomers.

Previous review

Carfentanil has not been previously pre-reviewed or critically reviewed. A critical review was initiated due to a notification from a Party to the Conventions concerning the scheduling of a substance.

Similarity to known substances and effects on the central nervous system

Carfentanil contains a carboxymethyl group in the fourth position of the piperidine ring of fentanyl, a drug regulated under Schedule I of the 1961 Single Convention on Narcotic Drugs. Carfentanil can be easily converted into sufentanil and alfentanil, which are Schedule I drugs under the 1961 Convention on Narcotic Drugs. Carfentanil binds with high affinity to μ -opioid receptors, and less so to δ - and κ -opioid receptors. Similar to other μ -opioid agonists, it depresses the respiratory centre, produces analgesia, and causes drowsiness, nausea, miosis and sedation. As an analgesic, carfentanil is approximately 10 000 times more potent than morphine. The pharmacodynamic effects of carfentanil can be reversed by opioid antagonists, such as naloxone and naltrexone although re-narcotization can occur.

Dependence potential

Carfentanil has been demonstrated to prevent and alleviate signs of withdrawal in the morphine-dependent rhesus monkey indicating its cross-dependency with morphine. No controlled dependence studies in human subjects have been reported.

Actual abuse and/or evidence of likelihood of abuse

No controlled experimental studies have been conducted investigating the abuse potential of carfentanil. In vitro and in vivo studies present carfentanil as a typical μ -opioid agonist, similar in its pharmacology to the controlled substance, fentanyl. Its pharmacokinetic properties account for its easy and rapid absorption, rapid onset of action and extreme potency. The latter is related to its serious hazardousness to human health, because carfentanil has a qualitative potency 10 000 times that of morphine and 100 times that of fentanyl.

Carfentanil has been detected in powder form in 618 seizures in Europe, amounting to nearly 2.7 kg of seized material (equivalent to 27 000 kg of morphine). It has also been identified in seizures in North America, where it has been sold as counterfeit oxycodone or alprazolam tablets. Carfentanil is used as an adulterant of other controlled substances such as heroin, cocaine and metamfetamine. Carfentanil has been associated with hundreds of deaths in North America and in Europe. Estimates of its lethality are challenging because carfentanil is not always routinely tested for following overdose and because the concentrations are typically extremely low in biological samples. Carfentanil has been placed under some form of national regulation by numerous countries in different regions.

Therapeutic usefulness

Carfentanil has been used in veterinary medicine since 1986, primarily for immobilizing large animals, because of its extreme potency. Etorphine, another opioid compound used in veterinary medicine for immobilizing large animals, is in Schedule I and IV of the Single Convention on Narcotic Drugs, 1961, but is less dangerously potent than carfentanil. Labelled carfentanil ([¹¹C]-carfentanil) is used as a positron emission tomography (PET) radiotracer. It has no approved therapeutic use in humans.

Recommendation

Carfentanil is convertible into sufentanil and alfentanil, two very potent opioid analgesics controlled as Schedule I drugs under the 1961 Convention on Narcotic Drugs. It is a μ -opioid receptor agonist, and its pharmacodynamic and clinical effects are similar to those of fentanyl but it is about 100 times more potent. It binds to opioid receptors, and produces respiratory depression, decreased consciousness, antinociception and miosis. The substance has been associated with hundreds of deaths and nonfatal intoxications globally, and is a significant concern in a number of countries. Due to the extremely small doses that induce lethal effects, it poses a particularly serious threat to public health.

Carfentanil is a compound liable to similar abuse and with similar ill effects to controlled opioids such as fentanyl that are included in Schedule I of the Single Convention on Narcotic Drugs of 1961. There is sufficient evidence that it is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. Thus, because it meets the required condition of similarity, it is recommended that carfentanil (Methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate) be placed in Schedule I of the Single Convention on Narcotic Drugs, 1961, as consistent with Article 3, paragraph 3 (iii) of that Convention in that the substance is liable to similar abuse and productive of similar ill effects to drugs in Schedule I.

The Committee recognized the impact that international scheduling could have on veterinary access to carfentanil in relation to its therapeutic use in large animals. However, the Committee was particularly concerned about the extreme potency of the substance and the serious risk to public health. The Committee felt that the therapeutic advantages did not offset the severe threat to human health. As such, and taking into consideration that substances in Schedule IV afford Parties the opportunity to adopt special measures for drugs with particularly dangerous properties, the Committee recommended that carfentanil (Methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate) be placed in Schedule IV of the UN Single Convention on Narcotic Drugs, 1961.

5.9 4-Fluoroisobutyrfentanyl (4-FIBF, pFIBF)

Substance identification

Chemically, 4-fluoroisobutyrfentanyl (4-FIBF, pFIBF) is *N*-(4-Fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide: 4-Fluoroisobutyryfentanyl is the positional isomer of 4-fluoro-butiryfentanyl (4-FIBF).

Previous review

4-Fluoroisobutyrfentanyl has not been previously pre-reviewed or critically reviewed. A direct critical review was proposed based on information brought to WHO's attention that it is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any Party. Preliminary information collected from various sources 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-Fluoroisobutyryfentanyl is similar to fentanyl, a drug in Schedule I of the 1961 Single Convention on Narcotic Drugs. It is manufactured using precursors and synthetic methods similar to those used to manufacture the pharmaceutical, fentanyl.

4-Fluoroisobutyryfentanyl potently and preferentially binds to the μ -opioid receptor relative to the κ - and δ -opioid receptors. It also preferentially activates the μ -opioid receptor relative to the other opioid receptors. This *in vitro* profile is similar to that of fentanyl. Similar to fentanyl and morphine, 4-fluoroisobutyryfentanyl produces antinociception in laboratory animals that is blocked with naloxone. Consistent with clinical effects involving fentanyl analogues and derivatives, typical opioid overdose symptoms of central nervous system and respiratory depression, decreased consciousness and miotic pupils have been observed with 4-fluoroisobutyryfentanyl, but its use has also been associated with tachycardia and hypertension. Two countries have reported deaths associated with 4-fluoroisobutyryfentanyl use.

Dependence potential

No controlled, experimental studies of either laboratory animals or human subjects that are directly pertinent to the dependence potential of 4-fluoroisobutyryfentanyl are currently available.

Actual abuse and/or evidence of likelihood of abuse

Evidence of abuse of 4-Fluoroisobutyrfentanyl is available. It is currently sold

online and through illicit markets as a nonscheduled substitute for illicit opioids and/or prescription opioids. It has been discussed on user forums where it is described as having typical opioid effects.

4-Fluoroisobutyrylfentanyl has been encountered as a single substance, seized as a liquid, in powder form, and as tablets or in mixtures with heroin, fentanyl, furanyl fentanyl, metamfetamine and cocaine. Based on forensic reports and paraphernalia found at overdose sites, routes of administration appear to be intravenous, oral and as a nasal spray. 4-Fluoroisobutyrylfentanyl has been connected to fatal overdoses in which intravenous and insufflation routes of administration were confirmed. One country reported that 62 overdose deaths involving 4-fluoroisobutyrylfentanyl abuse had occurred in 2016 alone. Seizures of the compound have been reported from Europe and North America.

Therapeutic usefulness

No countries have approved 4-fluoroisobutyrylfentanyl for either medical or veterinary use.

Recommendation

4-Fluoroisobutyrylfentanyl is an opioid that has similar in vitro and in vivo effects to those of fentanyl and other fentanyl analogues that are included in Schedule I of the 1961 Single Convention on Narcotic Drugs. It potently and preferentially binds to, and activates the μ -opioid receptor more than the κ - and δ -opioid receptors. Similar to fentanyl and morphine, 4-fluoroisobutyrylfentanyl produces antinociception in laboratory animals, which is antagonized by naloxone. It is currently sold online and through illicit markets as a non-controlled substitute for illicit opioids and/or prescription opioids. Consistent with clinical effects involving fentanyl analogues and derivatives, typical opioid overdose symptoms of central nervous system and respiratory depression, decreased consciousness and miotic pupils have been observed with 4-fluoroisobutyrylfentanyl.

4-Fluoroisobutyrylfentanyl is a compound liable to similar abuse and with similar ill effects to controlled opioids such as fentanyl, which are included in Schedule I of the Single Convention on Narcotic Drugs of 1961. It has no recorded therapeutic use, and its use has been associated with fatalities. There is sufficient evidence that it is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. Thus, because it meets the required condition of similarity, it is recommended that 4-fluoroisobutyrylfentanyl (*N*-(4-Fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide) be placed in Schedule I of the Single Convention on Narcotic Drugs, 1961, as consistent with Article 3, paragraph 3 (iii) of that Convention in that the substance is liable to similar abuse and productive of similar ill effects to drugs in Schedule I.

5.10 Tetrahydrofuranyl fentanyl (THF-F)

Substance identification

Chemically, tetrahydrofuranyl fentanyl is *N*-Phenylphenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]oxolane-2-carboxamide. Tetrahydrofuranyl fentanyl contains a stereogenic centre allowing for the existence of a pair of enantiomers, (*S*)-tetrahydrofuranyl fentanyl and (*R*)-tetrahydrofuranyl fentanyl. There is no information on the actual enantiomers found on the illicit drug market at the time of the report.

Previous review

Tetrahydrofuranyl fentanyl has not been previously pre-reviewed or critically reviewed. A direct critical review was proposed based on information brought to WHO's attention that tetrahydrofuranyl fentanyl is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any Party. Preliminary information collected from various sources 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

Similar to controlled opioids such as fentanyl, tetrahydrofuranyl fentanyl selectively binds to and activates the μ -opioid receptor and does so with greater potency and efficacy than with the δ - and κ -opioid receptors. A male with analytically confirmed tetrahydrofuranyl fentanyl intoxication suffered reduced consciousness, respiratory depression and miotic pupils, all effects associated with fentanyl.

Dependence potential

Currently, there are no controlled laboratory animal or human studies available that are directly pertinent to the dependence or abuse potential of tetrahydrofuranyl fentanyl.

Actual abuse and/or evidence of likelihood of abuse

Tetrahydrofuranyl fentanyl is currently sold online and through illicit markets as a nonscheduled substitute for illicit opioids and/or prescription opioids. Tetrahydrofuranyl fentanyl has been seized in the form of a liquid, in powder form and as disk-shaped tablets. Based on forensic reports and paraphernalia found at overdose sites, routes of administration appear to be intravenous, oral and as a nasal spray. Seizures of tetrahydrofuranyl fentanyl have been reported

from Europe and North America. One country reported a total of 14 deaths of people with confirmed exposure to tetrahydrofuranlyl fentanyl between 2016 and 2017. In at least 12 cases, tetrahydrofuranlyl fentanyl was the cause of death or contributed to the death. Another country reported two confirmed deaths associated with tetrahydrofuranlyl fentanyl. A number of countries in different regions have controlled tetrahydrofuranlyl fentanyl under national legislation.

Therapeutic usefulness

There are currently no approved therapeutic applications or recorded medical uses for tetrahydrofuranlyl fentanyl.

Recommendation

Controlled in vitro studies indicate that tetrahydrofuranlyl fentanyl has affinity and efficacy as an agonist at the μ -opioid receptor, findings which are consistent with the pharmacological effects observed with use of controlled opioid drugs such as morphine and fentanyl. An analytically confirmed case of tetrahydrofuranlyl fentanyl intoxication indicated effects that were also consistent with other opioid drugs. Several deaths have been associated with tetrahydrofuranlyl fentanyl use. Seizures of the drug have occurred in at least three countries, and it is sold on the Internet.

Tetrahydrofuranlyl fentanyl is a compound liable to similar abuse and with similar ill effects to controlled opioids such as fentanyl that are included in Schedule I of the Single Convention on Narcotic Drugs of 1961. It has no recorded therapeutic use, and its use has been associated with fatalities. There is sufficient evidence that it is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. Thus, because it meets the required condition of similarity, it is recommended that tetrahydrofuranlyl fentanyl (*N*-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]oxolane-2-carboxamide) be placed in Schedule I of the Single Convention on Narcotic Drugs, 1961, as consistent with Article 3, paragraph 3 (iii) of that Convention in that the substance is liable to similar abuse and productive of similar ill effects to drugs in Schedule I.

5.11 UR-144

Substance identification

Chemically, UR-144 is (1-Pentyl-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl) methanone. It has no stereoisomers.

Previous review

UR-144 was previously critically reviewed at the thirty-sixth ECDD meeting in 2014. The Committee had recommended that UR-144 not be placed under international control at that time but be kept under surveillance. Of particular significance to the Committee was the lack of analytically confirmed cases of nonfatal and fatal intoxications involving solely UR-144. Subsequent data collected from the literature and from different countries indicating that this substance may cause substantial harm and that it has no medical use warranted an updated critical review.

Similarity to known substances and effects on the central nervous system

UR-144 is a metabolite of XLR-11, a drug in Schedule II under the UN Convention on Psychotropic Substances of 1971. UR-144 binds to both cannabinoid CB₁ and CB₂ receptors, and has a 1.4 times higher binding affinity to the CB₁ receptor than that of THC. It acts as a full agonist at these receptors in *in vitro* assays. UR-144 produces a complete cannabinoid profile in the mouse tetrad assay. The pyrolysed form of UR-144 (UR-144 degradant) shows a four-fold higher agonist activity at the CB₁ receptor and augments the hypothermic and akinetic actions in mice compared to the parent, indicating that smoking the drug may augment the pharmacological effects on the central nervous system. In other animal studies, UR-144 substitutes for the discriminative stimulus effects of THC in rats, and also in mice, effects which are blocked by the CB₁ receptor antagonist, rimonabant.

Dependence potential

Currently, there are no controlled human or other animal studies available that document the dependence potential of UR-144.

Actual abuse and/or evidence of likelihood of abuse

UR-144 produces several effects similar to other SCRA, which are predictive of the likelihood of a similar abuse potential. Nonmedical use has been reported in numerous countries. Seizures of products containing UR-144 have been reported from East Asia, Europe and North America. UR-144 was one of the most frequently seized synthetic cannabinoids in Europe in 2015. More than 5000 reports identified UR-144 use in one country. Several reports have analytically identified UR-144 in cases of impaired driving, including some involving accidents. The most common clinical effects observed were slurred speech and dilated pupils; others included poor coordination, unsteady gait and difficulty standing, as well as abnormal pupillary reaction. Acute kidney injury requiring haemodialysis following UR-144 use has been described. Numerous countries have brought UR-144 under national legislation.

Therapeutic usefulness

UR-144 has no current therapeutic use, and there are no ongoing applications for medical use.

Recommendation

UR-144 produces cannabimimetic effects similar to other SCRAs and THC, drugs controlled under Schedule II of the UN Convention on Psychotropic Substances of 1971. UR-144 binds to, and functions as a full agonist at both cannabinoid CB₁ and CB₂ receptors. UR-144 substitutes for the discriminative stimulus effects of THC in laboratory animals. Nonmedical use of UR-144 has been reported in more than a dozen countries and has been analytically confirmed in samples from people involved in impaired driving instances. In 2015, UR-144 was one of the most frequently seized synthetic cannabinoids. UR-144 appears to constitute a substantial threat to public health and poses a social problem. There is insufficient evidence to draw a conclusion regarding its capacity to produce dependence-like effects. However, there is sufficient evidence to conclude that it has the capacity to produce similar effects to controlled SCRAs.

The Committee considered that the degree of risk to public health and society associated with the abuse of UR-144 is substantial. Therapeutic usefulness has not been recorded. It recognized that UR-144 has similar abuse potential and similar ill effects to other SCRAs in Schedule II of the UN Convention on Psychotropic Substances of 1971. The Committee considered that there is sufficient evidence that UR-144 is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. The Committee recommended that UR-144 ((1-Pentyl-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone) be placed in Schedule II under the UN Convention on Psychotropic Substances of 1971.

5.12 5F-PB-22

Substance identification

Chemically, 5F-PB-22 is Quinolin-8-yl 1-(5-fluoropentyl)-1*H*-indole-3-carboxylate. It has no stereoisomers.

Previous review

5F-PB-22 has not been previously pre-reviewed or critically reviewed. A direct critical review was proposed based on information brought to WHO's attention that 5F-PB-22 is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any Party. Preliminary

information collected from various sources 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

In vitro and in vivo studies indicate that 5F-PB-22 binds to and activates the CB₁ receptor, and induces a number of biological responses that are also triggered by THC and other SCRA. 5F-PB-22 binds to the CB₁ receptor and activates it as a full agonist, and does so with greater potency than XLR-11 and THC. It also suppresses locomotor activity and reduces body temperature (typical cannabinoid effects). 5F-PB-22 completely substitutes for the discriminative stimulus effects of THC in rats with a 22-fold greater potency than THC itself.

Dependence potential

No information from controlled, experimental studies evaluating the dependence potential of 5F-PB-22 in laboratory animals is available. There is, however, some indication of dependency in users. Six users of herbal mixtures containing 5F-AKB-48 and 5F-PB-22 reported abstinence-related symptoms including agitation and suicidal and self-harm ideation. The urge to re-dose has also been reported by users.

Actual abuse and/or evidence of likelihood of abuse

Nonclinical studies indicate that 5F-PB-22 has effects predictive of abuse potential associated with SCRA. It activates CB₁ receptors, depresses locomotor activity and decreases core temperature. 5F-PB-22 completely substitutes for the discriminative stimulus effects of THC in rats with a 22-fold greater potency, suggesting it may induce at least some of the subjective effects of THC, and consequently possesses SCRA-like abuse potential.

5F-PB-22 is sold in the form of herbal mixtures designed for smoking. Intoxication with 5F-PB-22 is commonly associated with seizures, cardiac toxicity, agitation and unconsciousness. Several fatal and nonfatal cases of intoxication associated with 5F-PB-22 use have been reported from Europe and North America since 2013. In some cases, 5F-PB-22 was the only drug found in the biological specimens. Several cases of driving under the influence of 5F-PB-22 have resulted in accidents and injuries since 2012. Seizures of 5F-PB-22 have been reported from many European countries since 2013. Cases of 5F-PB-22 use have also been reported to UNODC's Early Warning Advisory from about 30 countries since 2013. 5F-PB-22 is a controlled substance in several countries.

Therapeutic usefulness

There are no currently approved therapeutic human or veterinary uses of 5F-PB-22.

Recommendation

5F-PB-22 binds to and activates CB₁ receptors, and it induces a number of biological responses that are also triggered by SCRA and THC. It produces some cannabimimetic effects in laboratory animals, including the suppression of locomotor activity and reduction of core temperature. It also substitutes for the THC discriminative stimulus. Its dependence or abuse potential has yet not been elucidated in controlled, laboratory studies, although there is some indication of dependency in users. Intoxication with 5F-PB-22 is commonly associated with convulsions, cardiac toxicity, agitation and unconsciousness. Several fatal and nonfatal cases of intoxication associated with 5F-PB-22 use have been reported. Seizures of 5F-PB-22 have been reported in many countries, and it is a controlled substance in a number of countries.

The Committee considered that the degree of risk to public health and society associated with the abuse of 5F-PB-22 is substantial. Therapeutic usefulness has not been recorded. It recognized that 5F-PB-22 has similar abuse liability and has similar ill effects to other SCRA in Schedule II of the UN Convention on Psychotropic Substances of 1971. The Committee considered that there is sufficient evidence that 5F-PB-22 is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. The Committee recommended that 5F-PB-22 (Quinolin-8-yl 1-(5-fluoropentyl)-1*H*-indole-3-carboxylate) be placed in Schedule II under the UN Convention on Psychotropic Substances of 1971.

5.13 Etizolam (INN)

Substance identification

Chemically, etizolam is 4-(2-Chlorophenyl)-2-ethyl-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3- α][1,4]diazepine. It does not have stereoisomers.

Previous review

The ECDD reviewed etizolam at its twenty-sixth meeting (1989) and its twenty-seventh meeting (1990). At its thirty-seventh meeting in 2015, the Committee pre-reviewed etizolam and recommended that a critical review was warranted for a future meeting. The Committee noted deficiencies in the information and suggested several potential sources that could be helpful in the preparation of the critical review, including traffic accident reports, seizure data, user forums and pharmacovigilance data.

Similarity to known substances and effects on the central nervous system

Etizolam is a thienodiazepine derivative, with high affinity for the benzodiazepine

site in GABA_A receptors. It also has pharmacological effects similar to those of the model benzodiazepine, diazepam, which is in Schedule IV of the Convention on Psychotropic Substances of 1971. It behaves as a full benzodiazepine receptor agonist and allosterically potentiates the gamma-amino butyric acid (GABA)-induced chloride current. In animals, it induces muscle relaxation, has anticonvulsive effects, potentiates sleep time, causes a loss of the righting reflex, and substitutes for the pentobarbital discriminative stimulus, similar to diazepam.

Dependence potential

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

Actual abuse and/or evidence of likelihood of abuse

In nonclinical studies, etizolam completely substitutes for the pentobarbital discriminative stimulus in rhesus monkeys suggesting that etizolam would have subjective effects similar to those of the sedative hypnotics and probably a similar abuse potential. Reports have indicated that etizolam abuse has become a serious problem in a few countries. Etizolam has reportedly become the predominant benzodiazepine abused in one country and has been implicated in several deaths. Although toxicology reports showed evidence of etizolam in these drug-related deaths, there was also laboratory evidence of multiple drug use in all of the cases. Etizolam is under national controls in several countries.

Therapeutic usefulness

Etizolam has marketing authorizations as a medicinal product in several countries. It is not listed in the 20th WHO Model List of Essential Medicines or the 6th WHO Model List of Essential Medicines for Children. Etizolam has been used clinically to attenuate the recurrence of chronic subdural hematoma after neurosurgery. It is also used to treat some psychiatric conditions, including anxiety disorders.

Recommendation

Etizolam has some effects similar to those of diazepam (and other classical benzodiazepines), which is included in Schedule IV of the 1971 UN Convention on Psychotropic Substances. It induces muscle relaxation, has anticonvulsive

effects, potentiates sleep time, causes ataxia and substitutes for the pentobarbital discriminative stimulus, similar to diazepam. Data on the misuse and abuse of etizolam are still minimal, and it is difficult to describe its liability to abuse as constituting “a significant risk to public health”. The risks of etizolam abuse appear to be relatively low. Furthermore, there continue to be minimal preclinical and clinical data obtained using established methods for assessing the abuse and dependence liability of etizolam.

Owing to the lack of significantly more information since the pre-review conducted by the ECDD at its thirty-seventh meeting in 2015, and considering the current insufficiency of data regarding dependence, abuse and risks to public health (including risks to the individual), the Committee recommended that etizolam (4-(2-Chlorophenyl)-2-ethyl-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3- α][1,4]diazepine) be kept under surveillance. The Committee asked the Secretariat to request more data from Member States that may be affected by the misuse of etizolam, and which could facilitate a future review.

5.14 Pregabalin

Substance identification

Chemically, pregabalin is (3S)-3-(Aminomethyl)-5-methylhexanoic acid. Pregabalin is the (S)-(+)-isomer of 3-isobutyl-GABA.

Previous review

Pregabalin has not been previously pre-reviewed or critically reviewed. A pre-review of was proposed based on information received by the WHO Secretariat regarding the misuse of pregabalin.

Similarity to known substances and effects on the central nervous system

Pregabalin, a gabapentinoid, is an analogue of GABA. Pregabalin does not bind to benzodiazepine or opioid receptors. Despite similarities to GABA, it does not act at GABA receptors or synapses. Various drugs that are GABAergic are under international control and pregabalin has been found to produce a number of effects that are similar to those of some controlled substances.

Dependence potential

Evidence suggests that pregabalin can induce physical dependence. Discontinuation-emergent symptoms from short- and long-term psychiatric studies were more frequent in pregabalin-treated patients than in placebo-treated patients. Withdrawal

signs included insomnia, headache, nausea, infections, diarrhoea and chills. Analysis of two pharmacokinetic studies also showed discontinuation-emergent symptoms from pregabalin of headache, nausea and diarrhoea.

Actual abuse and/or evidence of likelihood of abuse

Four studies in monkeys showed that pregabalin was self-administered during initial access to the drug. Putative tolerance to the euphoric effects of pregabalin developed, as suggested by a decrease in self-administration after one week. There are also phase 2/3 clinical studies in humans supporting the development of tolerance to its euphoric effects. Other preclinical conditioned place preference studies in mice, and self-administration or drug discrimination studies in monkeys, have yielded conflicting results, which have been attributed to varying study conditions. In human subjects, relatively low doses of pregabalin did not increase ratings of “like drug” or “take drug again” indicating low abuse liability. In another study, a higher dose of pregabalin administered to recreational users of alcohol or sedative/hypnotic drugs (n=15) was rated similar to diazepam, indicative of abuse liability. In some clinical trials, euphoria was reported as an adverse effect and it was dose-dependent and transient.

Pregabalin abuse and misuse is increasing rapidly in some countries. Abuse and misuse of pregabalin have been reported from several European countries and countries in other regions. One country reported an escalation in pregabalin-related deaths from 2010–2012.

No data regarding illicit trade, its scope and magnitude are available. However, there is evidence of illicit marketing of pregabalin for recreational uses through online pharmacies. There are anecdotal reports of widespread distribution in prisons in some countries. Pregabalin is under national legislation in several countries in different regions of the world.

Therapeutic usefulness

Pregabalin has approved indications for the treatment of partial seizures, post-herpetic neuralgia, diabetic neuropathy, fibromyalgia, spinal cord injury, neuropathic pain and generalized anxiety disorder. Pregabalin has also been used off-label in the treatment of drug and alcohol withdrawal. Pregabalin is not listed on the 20th WHO Model List of Essential Medicines or the 6th WHO Model List of Essential Medicines for Children.

Recommendation

Pregabalin, a gabapentinoid, is an analogue of GABA, but does not bind to benzodiazepine or opioid receptors, nor does it act at GABA receptors or synapses. Pregabalin has therapeutic uses. The increasing evidence of misuse and abuse in many countries is becoming a growing cause for concern. Pregabalin

has been shown to have the capacity to produce a state of dependence. On this basis, the Committee recommended that pregabalin ((3S)-3-(Aminomethyl)-5-methylhexanoic acid) be subject to a future critical review. The Committee requested that the Secretariat collect further data to support such a review.

5.15 Cannabidiol (CBD)

Substance identification

Chemically, cannabidiol is (1'R,2'R)-5'-Methyl-4-pentyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol. Cannabidiol (CBD) is normally taken to refer to the naturally occurring (-)-enantiomer.

Previous review

Cannabidiol had not been previously pre-reviewed or critically reviewed by the ECDD. The current review was based on the recommendation made at the thirty-eighth meeting of the ECDD that pre-review documentation on cannabis-related substances, including cannabidiol, be prepared and evaluated at a subsequent Committee meeting.

Similarity to known substances and effects on the central nervous system

CBD does not appreciably bind to the CB₁ receptor, which mediates the behavioural activity of THC. Across a range of measures in humans and animals, CBD has been shown to have very different effects from those of THC. In mice, CBD fails to produce the behavioural characteristics associated with CB₁ receptor activation that THC generates (for example, suppression of locomotor activity, hypothermia and antinociception). It does not substitute for the discriminative stimulus effects of THC in rats or pigeons. Neuroimaging studies in humans and animals have shown that CBD has effects that are generally opposite to those of THC. In contrast to THC, CBD has no effect on heart rate or blood pressure under normal conditions, but in animal models of stress it reduces heart rate and blood pressure. It is not clear which mechanisms are responsible for any of CBD's potential clinical or other effects. CBD has no effect on a wide range of physiological and biochemical parameters, nor does it have significant effects on animal behaviour.

Dependence potential

No controlled, experimental studies directly pertinent to the potential physical dependence effects of CBD could be identified. Tolerance to CBD, a phenomenon associated with dependence, has not been observed.

Actual abuse and/or evidence of likelihood of abuse

Several laboratory animal studies indicate that CBD does not produce effects common to many drugs of abuse, nor more specifically to THC. It elevates intracranial self-stimulation thresholds in rats, unlike cocaine, metamfetamine and opioids that decrease these thresholds. Unlike THC, CBD does not increase the firing rate of dopaminergic cells of the mesolimbic ventral tegmental area – nucleus accumbens pathway. CBD has little effect on conditioned place preference and does not substitute for the discriminative stimulus effects of THC.

While the number of studies is limited, the evidence from well-controlled human experimental research indicates that CBD is not associated with abuse potential. Single oral-dose administrations of up to 600 mg CBD had placebo-like effects when evaluated in healthy volunteers according to physiological measures and on the scales of the Addiction Research Centre Inventory. In a randomized, double-blind, within-subject laboratory study in recreational cannabis users, oral administration of up to 800 mg CBD produced no significant psychoactive, cardiovascular or other effects. Together, these studies indicate a low likelihood of abuse of CBD.

At present, there are no case reports of abuse or dependence relating to the use of CBD. There are also no published statistics on non-medical use of CBD. No public health problems (e.g. impaired driving) have been associated with the use of CBD.

Therapeutic usefulness

CBD is present in nabiximols, which are marketed in several countries for the treatment of spasticity due to multiple sclerosis. There are no currently approved CBD-only products; however, CBD is being actively explored for a range of indications consistent with its potential neuroprotective, antiepileptic, anxiolytic, antipsychotic, analgesic, anti-inflammatory, anti-asthmatic and antitumor properties. Importantly, CBD has demonstrated effectiveness in the treatment of at least some forms of epilepsy, with one CBD product currently in advanced clinical development. In 2015, the US Food and Drug Administration granted Fast Track designation for intravenous CBD to treat neonatal hypoxic-ischemic encephalopathy. The European Commission also granted orphan designation for CBD to be used in the treatment of perinatal asphyxia. Currently there are no other treatments available for these conditions, but there is evidence of the effectiveness of CBD in animal models.

Recommendation

In a variety of laboratory animal and human models, preparations containing almost exclusively CBD do not have effects typical of abuse potential. In animals,

CBD increases intracranial self-stimulation thresholds, suggestive of diminished reward activity, and does not produce conditioned place preference. Importantly, it has placebo-like effects when tested for its abuse liability in human subjects. Furthermore, CBD does not have effects characteristic of THC. It does not produce the cannabimimetic effects in the tetrad battery in mice, and does not substitute for the discriminative stimulus effects of THC in rats. At present, there are no case reports of abuse or dependence relating to the use of CBD. Furthermore, no public health problems (e.g. impaired driving) have been associated with the use of CBD.

CBD is not specifically listed in the schedules of the 1961, 1971 or 1988 United Nations International Drug Control Conventions. There is no evidence that CBD as a substance is liable to similar abuse and produces similar ill effects to substances in the 1961 or 1971 Conventions (including cannabis and dronabinol (THC), respectively). The purpose of the pre-review was to determine whether current information justifies a critical review by the Expert Committee of information that may justify the scheduling or a change in the scheduling of the substance in the 1961 or 1971 Conventions. As CBD is not currently a scheduled substance in its own right (only as a component of cannabis extracts), current information does not justify a change in this scheduling status nor does it justify scheduling of the substance.

However, where CBD is produced for pharmaceutical purposes as an extract of cannabis, cannabis extracts and tinctures are included in the 1961 UN Single Convention on Narcotic Drugs. The pre-review of cannabis extracts and tinctures will take place at the fortieth ECDD meeting in May 2018. Therefore it is also recommended that extracts or preparations containing almost exclusively CBD (cannabidiol; (1*R*,2*R*)-5'-Methyl-4-pentyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol) be subject to critical review at that meeting.

5.16 Tramadol

Substance identification

Chemically, tramadol is rac-(1*R*,2*R*)-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexan-1-ol. Tramadol has two chiral centres in the cyclohexane ring, consequently, four different stereoisomers exist: (1*R*,2*R*), (1*S*,2*S*), (1*R*,2*S*), and the (1*S*,2*R*) stereoisomer.

Previous review

Tramadol has been considered by the ECDD five times: in 1992, 2000, 2002, 2006 and 2014. The Committee reviewed tramadol most recently at its thirty-sixth meeting in 2014, and based on the evidence available regarding dependence,

abuse and risks to public health, it recommended that a critical review of tramadol was not warranted at that time. A pre-review of tramadol was recommended at the thirty-ninth ECDD based on information received by the WHO Secretariat regarding the misuse of tramadol.

Similarity to known substances and effects on the central nervous system

Tramadol inhibits serotonin and noradrenaline reuptake, and as a serotonin releaser whereas the *O*-desmethyl metabolite of tramadol (known as M1 or ODT) acts on the μ -opioid receptor. This implies that the mechanism of action of tramadol includes both non-opioid components – that is, noradrenergic and serotonergic components – and opioid components. Intravenous naloxone has been successfully used to reverse the opioid-related respiratory depressant effects of tramadol overdose.

Symptoms following tramadol intoxication are similar to those of other opioid analgesics. These include CNS depression including coma, nausea and vomiting, tachycardia, cardiovascular collapse, seizures and respiratory depression up to respiratory arrest. Moreover, in combination with serotonergic agents (for example, selective serotonin reuptake inhibitors and monoamine oxidase inhibitors), tramadol may induce serotonin syndrome. The hyperthermia in serotonin syndrome is potentially fatal. Because of the μ -opioid agonist activity of *O*-desmethyltramadol, tramadol may lower the respiratory rate and potentially lead to severe respiratory depression.

Dependence potential

Physical dependence on tramadol may occur. This has been shown in animal studies, although this is not consistently seen in all studies. In rhesus monkeys, only mild to moderate withdrawal signs have been reported. Studies show that tramadol may lead to physical dependence in humans when used daily for more than a few weeks. Withdrawal reactions can include restlessness, agitation, anxiety, sweating, insomnia, hyperkinesia, tremor, paraesthesia and gastrointestinal symptoms, consistent with opioid withdrawal. Naloxone can precipitate withdrawal effects in tramadol-dependent subjects. In dependent opioid abusers, intramuscular tramadol was shown to act as a mild opioid agonist, able to suppress opioid withdrawal symptoms, although not to a statistically significant degree, comparable to hydromorphone.

Actual abuse and/or evidence of likelihood of abuse

Based on animal studies, tramadol is an atypical opioid analgesic with mild opioid-like effects. Tramadol is weakly self-administered by monkeys and rats, and less robustly than morphine. Animal studies of tramadol are of uncertain

value as they have used predominantly parenteral routes of administration and the extent of formation of the *O*-desmethyl metabolite across species is not known. Controlled, human laboratory studies indicate that tramadol has a low abuse potential relative to morphine. Moreover, mild opioid-like effects are seen following oral administration of tramadol, but are not produced by parenteral administration. Overall, tramadol appears to have a low abuse potential relative to the prototypic opioid, morphine.

Few cases of fatal poisoning due to tramadol alone have been reported. Most cases of intoxication involved co-ingestion of other drugs or alcohol. Symptoms following tramadol intoxication are similar to those of other opioid analgesics.

There is growing abuse of tramadol in some African and west Asian countries, as evidenced by large seizures, predominantly of tablets, in north and west Africa. Abuse of tramadol has become a serious problem in several Middle-Eastern countries. Data provided by the UNODC (July 2017) on global tramadol seizures show a steady rise in seizures between 2007 and 2015. Several countries have brought tramadol under some form of national legislation.

Therapeutic usefulness

Tramadol is used to treat both acute and chronic pain of moderate to severe intensity. Tramadol is available worldwide as a medicine. It is mentioned as a step-2 analgesic in the WHO guidelines for cancer pain relief. Tramadol is listed on several national essential medicines lists, but it is not listed on the 20th WHO Model List of Essential Medicines or the 6th WHO Model List of Essential Medicines for Children.

Recommendation

Tramadol is used as a medication for controlling moderate acute and chronic painful conditions, and it is listed in several national essential medicines lists. It produces opioid-like effects predominantly through the conversion of tramadol into its active metabolite. There is growing evidence of abuse of tramadol in many countries, in some cases serious, accompanied by adverse reactions and tramadol-associated deaths. The Committee recommended that tramadol ((*rac*-(1*R*,2*R*)-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexan-1-ol) be subject to a critical review at a subsequent meeting. The Committee requested the Secretariat to collect additional data for the critical review, including engagement with Member States to obtain information on the extent of problems associated with tramadol misuse. Also, the Committee asked for information on the medical use of tramadol including the extent to which developing countries, and aid and relief agencies, use and possibly rely on tramadol for provision of analgesia.

6. Cannabis pre-reviews: update on progress of planned reviews for 2018

Ms Dilkushi Poovendran provided an update on the fortieth meeting of the ECDD to be held in May 2018. She informed the Committee that four substances will be subject to pre-review, as recommended by the ECDD at its thirty-eighth meeting in November 2016:

- cannabis plant and cannabis resin
- extracts and tinctures of cannabis
- delta-9-tetrahydrocannabinol (THC)
- isomers of THC.

Ms Poovendran described the inclusion and exclusion criteria that had been developed for each of the pre-reviews. She also reported that the Secretariat had made a public call for experts to author pre-reviews in each of the required areas: chemistry, toxicology, pharmacology, epidemiology and therapeutic use.

Professor Sevil Atasoy, Observer for the INCB commented that cannabis poses one of the big challenges to the international drug control system. She stated that INCB welcomed the ECDD discussion on CBD and especially the upcoming pre-review of cannabis plant and resin, extracts and tinctures, THC and isomers, planned for the ECDD meeting in May 2018. She said that it is important that these pre-reviews also address the terminology used in this area. Cannabis, its various preparations and active ingredients are listed in different schedules of the 1961 and 1971 conventions. Countries are using different terms to refer to the medical use of cannabis and cannabinoids, which may translate differently across different languages. INCB considers it important to use clear and consistent terminology that precisely describes what is meant and that avoids misleading concepts.

INCB expressed its readiness to work with WHO and other partners on this, in the spirit of increased collaboration under the umbrella of the UNGASS resolution on the world drug problem adopted in 2016.

7. Other priorities for the ECDD

7.1 Exemptions related to opioids in Schedule 3 of the 1961 Convention

The Committee acknowledged the concerns that have been raised regarding the exemption for codeine preparations in Schedule 3 of the 1961 Convention. The Committee also recognized the exemptions applying to other opioid preparations in the same schedule and undertook to review the exemptions applying to opioids at the next meeting of the working group.

7.2 Global opioid crisis: role of the ECDD

The Committee discussed the recommendations for addressing the international opioid crisis. While the extent of the opioid crisis has been well-documented in North America, much less is known about what is happening in the broader global context. The Committee recognized the need for a mapping exercise to determine the extent and nature of opioid abuse in low and middle income countries. The Committee also recommended increased provision of training and guidance on the use of pain medications in low and middle income countries. In addition, the Committee considered mechanisms to increase the number of synthetic opioids being monitored in an NPS surveillance system.

7.3 Future agenda items

The Committee agreed that it would request the Secretariat to arrange a critical review of cannabidiol for the fortieth Expert Committee meeting in May 2018. In addition, the Committee requested that the Secretariat collect further data to support critical reviews for pregabalin and tramadol for a subsequent Expert Committee meeting.

Acknowledgements

The Committee wishes to thank Mrs Véronique Bruniquel and Mrs Magdalena Rabini from the WHO Department of Essential Medicines and Health Products, for their administrative support in the planning and the organization of the thirty-ninth meeting of the Expert Committee on Drug Dependence. Thanks are also due to Ms Swathi Iyengar, Technical Officer, Innovation, Access and Use team, Department of Essential Medicines and Health Products, for development of the online questionnaires to Member States. Finally, thanks go to Dr Stephanie Kershaw, Consultant, Adelaide, Australia for her organizational and technical support to the Secretariat, including the editing of technical documents and preparing questionnaire reports.

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Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence

World Health Organization, Geneva, 2009, ISBN 978 92 4 154754 3 (129 pages)



This report presents the recommendations of the thirty-ninth WHO Expert Committee on Drug Dependence (ECDD). The ECDD is responsible for the assessment of psychoactive substances for possible scheduling under the international drug control conventions. The ECDD reviews the therapeutic usefulness, the liability for abuse and dependence, and the public health and social harm of each substance. The ECDD will advise the Director-General of WHO, to schedule or to amend the scheduling status of a substance. The Director General will, as appropriate, communicate the recommendations to the Secretary-General of the United Nations, who will in turn communicate the advice to the Commission on Narcotic Drugs (CND).

The report summarizes the review of 16 substances and the ECDD recommendations for the scheduling of 12 substances. The report also contains updates from international bodies concerned with controlled substances, as well as summaries of the follow-up on the recommendations made at the previous Committee meeting. Issues identified for consideration at future Expert Committee meetings are also covered.

ISBN 978 92 4 121018 8



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