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Agenda item 5(a)

**Implementation of the international drug control
treaties: changes in the scope of control of
substances**

**Summary of assessments, findings and recommendations
of the 44th World Health Organization's (WHO)
Expert Committee on Drug Dependence (ECDD),
11–15 October 2021***

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Summary of assessments, findings and recommendations of the 44th ECDD, 11-15 October 2021

To be added to Schedule I of the Single Convention on Narcotic Drugs (1961):	3
➤ Brorphine	3
➤ Metonitazene	4
To be added to Schedule II of the Convention on Psychotropic Substances (1971):	5
➤ Eutylone (3,4-methylenedioxy-<i>alpha</i>-ethylamino butiophenone)	5
To be kept under surveillance:	6
➤ 4F-MDMB-BICA (4F-MDMB-BUTICA)	6
➤ Benzylone (3,4-Methylenedioxy-N-benzylcathinone)	7
➤ Kratom, mitragynine, 7-hydroxymitragynine	7
➤ Phenibut (4-amino-3-phenyl-butyric acid)	9

Substances to be added to Schedule I of the Single Convention on Narcotic Drugs (1961):**Brorphine****Substance identification**

Brorphine (IUPAC chemical name: 1-[1-[1-(4-bromophenyl)ethyl]-piperidin-4-yl]-1,3-dihydro-2*H*-imidazol-2-one) has a chemical structure similar to bezitramide, an opioid listed in Schedule I of the 1961 Convention. Brorphine freebase has been described as a white or off-white solid, and the hydrochloride salt as a neat solid, with seized samples described as white, yellowish, gray, purple, or white powder, or in crystal form. It is also found in tablets and capsules as falsified opioid medicines. It is reported to be used by the oral, inhalation, and intravenous routes of administration.

WHO review history

Brorphine has not been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is manufactured clandestinely, poses a risk to public health, and is of no recognized therapeutic use.

Similarity to known substances and effects on central nervous system

Brorphine is a full agonist at the μ -opioid receptor, with greater potency than morphine, and less potency than fentanyl. It has analgesic effects that are reversed by an opioid antagonist and, based on its mechanism of action, it would be expected to produce other typical opioid effects such as respiratory depression and sedation. Brorphine may be convertible to bezitramide, which is an opioid listed in Schedule I of the 1961 Single Convention on Narcotic Drugs.

Dependence potential

No controlled animal or human studies have examined the dependence potential of brorphine. As a potent μ -opioid agonist, it would be expected to produce dependence similar to other opioid substances. Unverified online reports describe tolerance and withdrawal following repeated brorphine use.

Actual abuse and/or evidence of likelihood of abuse

In an animal model predictive of abuse potential, brorphine was shown to produce effects similar to morphine and fentanyl.

Deaths involving brorphine have been reported in several countries. Deaths commonly occur after use of brorphine in combination with other opioids or with benzodiazepines such as flualprazolam. Brorphine has been identified in falsified opioid medicines, suggesting that sometimes its use may be unintentional. Fatal and non-fatal intoxications due to brorphine share features with intoxications due to other opioids, such as pulmonary oedema. Brorphine has been detected with other substances in biological fluids in cases of driving under the influence.

Seizures have been reported in multiple countries and regions.

Therapeutic usefulness

Brorphine is not known to have any therapeutic use.

Recommendation

The mechanism of action of brorphine indicates that it is liable to have similar abuse potential and ill effects as opioids that are controlled under Schedule I of the 1961 Single Convention on Narcotic Drugs. Its use has been reported in a number of countries and has been associated with adverse effects, including death. It has no known therapeutic use and is likely to cause substantial harm.

Recommendation: The Committee recommended that buprenorphine (IUPAC chemical name: 1-[1-[1-(4-Bromophenyl)ethyl]-piperidin-4-yl]-1,3-dihydro-2H-imidazol-2-one) be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

Metonitazene

Substance identification

Metonitazene (IUPAC chemical name: *N,N*-Diethyl-2-(2-(4-methoxybenzyl)-5-nitro-1*H*-benzo[*d*]imidazol-1-yl)ethan-1-amine) belongs to the series of 2-benzylbenzimidazole opioid compounds. It is a white or off-white/beige or coloured powder, and is sometimes crystalline in consistency. Reports suggest that it is used intranasally and by intravenous injection.

WHO review history

Metonitazene has not been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is manufactured clandestinely, poses a risk to public health, and has no recognized therapeutic use.

Similarity to known substances and effects on central nervous system

Metonitazene is a chemical analogue of etonitazene and isotonitazene, both of which are Schedule I compounds under the Single Convention on Narcotic Drugs, 1961. Metonitazene is a potent opioid analgesic with a rapid onset of action and greater potency than fentanyl and hydromorphone. Limited early clinical research demonstrated that metonitazene produces analgesia and typical opioid adverse effects including sedation, respiratory depression, nausea, and vomiting. The effects of metonitazene have been shown to be reversed by an opioid antagonist.

Dependence potential

Animal studies have demonstrated that metonitazene suppresses opioid withdrawal and has potent μ -opioid agonist effects. No controlled human studies have reported on the dependence potential of metonitazene, but as a potent μ -opioid agonist, it would be expected to produce dependence similar to other opioids.

Actual abuse and/or evidence of likelihood of abuse

No controlled studies have been reported on the abuse potential of metonitazene, but as it is a potent μ -opioid receptor agonist, it would be expected to have high abuse liability. Online reports from people who report use of metonitazene describe its euphoric and opioid-like effects.

A number of deaths have been reported in association with use of metonitazene. In many of these cases metonitazene has been used in combination with other opioids or benzodiazepines. However, in some fatalities, metonitazene was the sole substance identified in the analysed biological samples.

Trafficking and use of metonitazene have been reported from a number of countries across several regions.

Therapeutic usefulness

Metonitazene is not known to have any therapeutic use.

Recommendation

The mechanism of action and effects of metonitazene indicate that it is liable to have similar abuse potential and ill effects as opioids that are controlled under Schedule I of the 1961 Single Convention on Narcotic Drugs. Its use has been reported in a number of countries and been associated with adverse effects, including death. Metonitazene has no known therapeutic use and is likely to cause substantial harm.

Recommendation: The Committee recommended that metonitazene (IUPAC chemical name: *N,N*-Diethyl-2-(2-(4-methoxybenzyl)-5-nitro-1*H*-benzo[*d*]imidazol-1-yl)ethan-1-amine) be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

Substances to be added to Schedule II of the Convention on Psychotropic Substances (1971):

Eutylone (3,4-methylenedioxy-*alpha*-ethylamino butiophenone)

Substance identification

Eutylone (IUPAC chemical name: 1-(Benzo[*d*][1,3]dioxol-5-yl)-2- (ethylamino)butan-1-one) is a synthetic cathinone of the phenethylamine class. The hydrochloride salt of eutylone has been described as a crystalline solid. Eutylone is mostly found as tablets, capsules, and crystals. It is used orally and intranasally.

WHO review history

Eutylone has not been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is manufactured clandestinely, poses a risk to public health, and has no recognized therapeutic use.

Similarity to known substances and effects on central nervous system

Eutylone is a synthetic cathinone with a mechanism of action and effects similar to other cathinones and to stimulants such as methamphetamine. Related cathinones, such as methylone and *N*-ethylnorpentylone, are listed under Schedule II of the Convention on Psychotropic Substances of 1971. The clinical features described are similar to other cathinones, including sympathomimetic effects and psychostimulant effects such as euphoria, insomnia, tachycardia, agitation, anxiety, delirium and psychosis.

Dependence potential

No animal or human studies have been conducted on the dependence potential of eutylone. Based on its overall profile of effects, eutylone would be expected to produce dependence similar to other psychostimulants.

Actual abuse and/or evidence of likelihood of abuse

In an animal model predictive of abuse potential, eutylone has been shown to produce effects similar to those of methamphetamine. Online reports from people reporting use of eutylone suggest that it has high abuse potential.

Eutylone has been detected in biological samples from forensic, post-mortem, and driving under the influence cases. Published case reports describe fatalities as a result of eutylone use. In addition to the effects described above, reported adverse events in these cases have included rhabdomyolysis, hyperthermia, hypertension, and seizures.

Eutylone has been detected in seized materials in multiple countries across several regions.

Therapeutic usefulness

Eutylone is not known to have any therapeutic use.

Recommendation

Eutylone has effects similar to those of related cathinones listed under Schedule II of the Convention on Psychotropic Substances of 1971.

There is evidence that this substance is used in multiple countries in various regions. Eutylone causes substantial harm, including severe adverse events and fatal intoxications. Its mode of action suggests a likelihood of abuse and it poses a substantial risk to public health. It has no known therapeutic usefulness.

Recommendation: The Committee recommended that eutylone (IUPAC chemical name: 1-(Benzo[d][1,3]dioxol-5-yl)-2- (ethylamino)butan-1-one) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

Substances to be kept under surveillance:

4F-MDMB-BICA (4F-MDMB-BUTICA)

Substance identification

4F-MDMB-BICA (IUPAC chemical name: Methyl 2-([1-(4-fluorobutyl)-1*H*-indol-3-yl]carbonyl)amino)-3,3-dimethylbutanoate) has a chemical structure similar to a number of synthetic cannabinoids. It has been identified in seized materials as a white, off-white, brown or orange powder, and has been identified in herbal blends, vaping solutions, and infused onto paper. It is also available as a reference material as crystalline solid.

WHO review history

4F-MDMB-BICA has not been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is manufactured clandestinely, poses a risk to public health, and has no recognized therapeutic use.

Similarity to known substances and effects on central nervous system

4F-MDMB-BICA is a synthetic cannabinoid, structurally related to 5F-MDMB-PICA, a synthetic cannabinoid which is included in Schedule II of the United Nations Single Convention on Psychotropic Substances of 1971. Some data suggest that 4F-MDMB-BICA has activity at the cannabinoid CB1 receptor, but this action may not be identical to that exerted by other CB1 agonists. No animal or human studies have evaluated the effects of 4F-MDMB-BICA, and there is insufficient data on 4F-MDMB-BICA overdose cases to confirm that it has typical cannabinoid effects.

Dependence potential

No studies have been reported in animals or humans on the dependence potential of 4F-MDMB-BICA.

Actual abuse and/or evidence of likelihood of abuse

No studies have been reported in animals or humans to indicate the likelihood of abuse of 4F-MDMB-BICA. A number of countries in various regions have reported use of 4F-MDMB-BICA. Its use has been associated with multiple deaths and emergency department visits, although multiple substances have been present in analysed biological samples, and the relationship between 4F-MDMB-BICA exposure and cause of death is not established.

Therapeutic usefulness

4F-MDMB-BICA is not known to have any therapeutic use.

Recommendation

4F-MDMB-BICA has a structure similar to other synthetic cannabinoids, but its mechanism of action has yet to be confirmed. The magnitude of harm due to 4F-MDMB-BICA alone is unclear, and no animal or human studies have examined the effects or abuse potential of 4F-MDMB-BICA. Based on the limited information available concerning abuse, dependence and risks to public health, there is insufficient evidence to justify placing 4F-MDMB-BICA under international control.

Recommendation: The Committee recommended that 4F-MDMB-BICA (IUPAC chemical name: Methyl 2-([1-(4-fluorobutyl)-1*H*-indol-3-yl]carbonyl)amino)-3,3-dimethylbutanoate) be kept under surveillance by the WHO Secretariat.

Benzylone (3,4-Methylenedioxy-N-benzylcathinone)

Substance identification

Benzylone (IUPAC chemical name: 1-(Benzo[d][1,3]dioxol-5-yl)-2- (benzylamino)propan-1-one) is a ring-substituted synthetic cathinone. Benzylone is a white powder. The hydrochloride salt of benzylone is a crystalline solid.

WHO review history

Benzylone has not been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is manufactured clandestinely, poses a risk to public health, and has no recognized therapeutic use.

Similarity to known substances and effects on central nervous system

Benzylone has a mode of action suggestive of stimulant effects similar to other cathinones. However, these effects are relatively weak and it fails to produce stimulant effects in animal models.

Limited information is available on its effects in humans.

Dependence potential

There is no information available on the dependence potential of benzylone in animals or humans

Actual abuse and/or evidence of likelihood of abuse

In an animal model predictive of abuse potential, benzylone did not produce effects similar to MDMA, and its similarity to methamphetamine is unclear. No human studies have been conducted to assess abuse liability.

Benzylone has been detected in seized materials in multiple countries across several regions.

There is little information concerning the adverse effects of benzylone. Although it has been detected in post-mortem samples along with other substances, there is no significant evidence of benzylone playing a causative role in deaths.

Therapeutic usefulness

Benzylone is not known to have any therapeutic use.

Recommendation

Benzylone is a synthetic cathinone that has some effects in common with substances listed under Schedule II of the Convention on Psychotropic Substances of 1971. However, its effects are relatively weak and there is no consistent evidence supporting the likelihood of abuse or dependence. In addition, there is no consistent evidence of the extent of public health and social problems related to use of benzylone.

Recommendation: The Committee recommended that benzylone (IUPAC chemical name: 1-(Benzo[d][1,3]dioxol-5-yl)-2- (benzylamino)propan-1-one) be kept under surveillance by the WHO Secretariat.

Kratom, mitragynine, 7-hydroxymitragynine

Substance identification

Kratom is the common term for *Mitragyna speciosa*, a tree native to Southeast Asia. Kratom use is almost exclusively oral, typically by chewing the leaves, ingesting powdered leaf, or drinking a kratom infusion or decoction, or by ingesting powdered leaf as a capsule or pill or dissolved in a beverage. Other forms such as extracts and resins are also used.

Several alkaloids have been detected in kratom plants. The main known psychoactive components of kratom are mitragynine and 7-hydroxymitragynine, both of which are found in the leaves of *Mitragyna speciosa*. Mitragynine

is the most abundant alkaloid in kratom. Whilst 7-hydroxymitragynine is a minor alkaloid, it is also a metabolite of mitragynine.

WHO review history

Kratom has been under ECDD surveillance since 2020 due to a country level report indicating the potential for abuse, dependence, and harm to public health from mitragynine and 7-hydroxymitragynine, and a report from an international organization regarding documented fatalities associated with kratom use. A pre-review on kratom, mitragynine, and 7-hydroxymitragynine was initiated following consideration of these reports.

Similarity to known substances and effects on central nervous system

Mitragynine and 7-hydroxymitragynine are partial agonists at the mu-opioid receptor. Human studies demonstrate the analgesic effects of kratom, while kratom extract, mitragynine and 7-hydroxymitragynine have been shown to be antinociceptive in animal models. The antinociceptive effects are reversed by an opioid antagonist.

Mitragynine also binds to adrenergic receptors, serotonergic and dopamine receptors. Although there is limited information regarding its effects at these receptors, kratom extracts and mitragynine have been reported in animal studies to have a variety of non-opioid-like behavioural effects, including antidepressant and antipsychotic effects.

Reported adverse effects as a result of kratom intoxication have included neuropsychiatric (agitation, confusion, sedation, hallucinations, tremor, seizure, coma), cardiovascular (tachycardia, hypertension), gastrointestinal (abdominal pain, nausea, vomiting) and respiratory (respiratory depression) symptoms. A number of cases of kratom-associated liver toxicity have been documented.

Dependence potential

In animal models, repeated dosing with mitragynine produced dependence, evidenced by naloxone-precipitated withdrawal. The withdrawal syndrome from kratom appears to be less severe than withdrawal from morphine.

In humans, opioid-like withdrawal symptoms have been reported following cessation of kratom use. Limited epidemiological evidence indicates that withdrawal is usually mild. There are a small number of cases of neonatal opioid withdrawal symptoms in neonates born to mothers who used kratom regularly.

Actual abuse and/or evidence of likelihood of abuse

Animal studies with kratom extracts have not shown abuse liability in one animal model. Mitragynine and 7-hydroxymitragynine have effects indicative of abuse liability in some animal models but not in others. Mitragynine is not self-administered by animals, while 7-hydroxymitragynine has been shown to be self-administered, supporting a likely abuse liability.

Kratom can produce serious toxicity in people who use high-doses, but the number of cases is probably low as a proportion of the total number of people who use kratom. Although mitragynine has been analytically confirmed in a number of deaths, almost all involve use of other substances, so the degree to which kratom use has been a contributory factor to fatalities is unclear.

Kratom and mitragynine have been associated with cases of driving under the influence, but their role in driving impairment could not be established in most instances.

Multiple countries across various regions report nonmedical use of kratom. Seizures of kratom and related products have been reported in several countries.

Therapeutic usefulness

People report using kratom to self-medicate a variety of disorders and conditions, including pain, opioid withdrawal, opioid use disorder, anxiety and depression. Kratom is being used as a part of traditional medicine in some countries.

Research is ongoing to determine the basic pharmacology and the potential therapeutic value of kratom, mitragynine and 7-hydroxymitragynine.

Recommendation

Kratom contains multiple alkaloids. The two main known psychoactive alkaloids, mitragynine and 7-hydroxymitragynine, produce at least some effects similar to opioids under international control. Mitragynine, the most abundant of these alkaloids, also has non-opioid actions, the significance of which is unclear. There is mixed evidence on the abuse liability of mitragynine in animal models. Kratom is used for self-medication for a variety of disorders but there is limited evidence of abuse liability in humans. Cessation of regular use of kratom may lead to withdrawal symptoms.

The Committee considered information regarding the traditional use and investigation into possible medical applications of kratom.

The Committee concluded that there is insufficient evidence to recommend a critical review of kratom. With respect to mitragynine and 7-hydroxymitragynine, the Committee, except for one member, also concluded that there is insufficient evidence to recommend a critical review at this time.

Recommendation: The Committee recommended that kratom, mitragynine and 7-hydroxymitragynine be kept under surveillance by the WHO Secretariat.

Phenibut (4-amino-3-phenyl-butyric acid)

Substance identification

Phenibut (IUPAC chemical name: 4-Amino-3-phenylbutanoic acid) is a structural analogue of baclofen and gabapentin. It is produced in various formulations including tablets and powder for oral use, and crystalline form. Phenibut is a registered pharmaceutical in some countries and is also marketed online for a number of uses including as a sleep aid, mood enhancer, treatment for anxiety and a cognitive enhancer.

WHO review history

Phenibut has not been formally reviewed by WHO and is not currently under international control. Phenibut has been under ECDD surveillance since 2017 due to reports from Member States of its abuse and dependence potential. A pre-review was initiated following consideration of these reports.

Similarity to known substances and effects on central nervous system

Phenibut acts primarily as an agonist at the GABA_B receptor, similar to baclofen, and at the $\alpha 2$ - δ subunit of voltage dependent calcium channels, similar to gabapentin.

Animal studies show that phenibut has dose dependent analgesic, antidepressant and anxiolytic effects which are mediated both by its GABA_B agonist effects and actions at voltage dependent calcium channels.

Phenibut intoxication has presented with central nervous system depressive symptoms including decreased level of consciousness, muscle tone, stupor, depressed respiration, temperature dysregulation, hyper- or hypotension and coma. However, in other cases individuals have presented with agitation, hallucinations, seizures, and delirium.

Dependence potential

There are no studies conducted in animals examining the dependence potential of phenibut. People who use phenibut describe escalating dosing suggestive of tolerance, and difficulty in cessation.

There are a limited number of case reports of withdrawal symptoms following abrupt discontinuation of high dose phenibut use. Reported symptoms have included insomnia, psychomotor agitation, delusions, psychosis, disorganized thought patterns, auditory/visual hallucinations, anxiety, depression, fatigue, dizziness, seizures, decreased appetite, nausea and vomiting, palpitations and tachycardia. However, in most cases the use of phenibut was not verified analytically and the clinical picture was complicated by the use of other drugs.

Actual abuse and/or evidence of likelihood of abuse

No controlled animal or human studies have examined the abuse potential of phenibut.

There are reports from different countries of adverse effects due to nonmedical use of phenibut. Medically unsupervised use of phenibut obtained via the internet is often at doses much higher than those used clinically. However, many cases involve multiple drugs and the role of phenibut in these cases remains unclear.

Multiple countries over several regions report seizures of phenibut. However, the extent of non-medical use is unknown.

Therapeutic usefulness

Phenibut is approved in a few countries as a medicine for a range of psychiatric and neurological conditions.

Recommendation

The Committee noted that there has been concern in several countries regarding the nonmedical use of phenibut. While there are reports of adverse effects and of a withdrawal syndrome following cessation of use, the information on these cases is very limited. In addition, there is very little information on the abuse liability of phenibut, on the magnitude of its misuse or abuse and on its similarity to currently internationally controlled substances.

The Committee also noted that phenibut is used therapeutically in a small number of countries.

Recommendation: The Committee recommended that phenibut (IUPAC chemical name: 4-Amino-3-phenylbutanoic acid) should not proceed to critical review but should be kept under surveillance by the WHO Secretariat.
