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

Changes in the scope of control of substances: proposed scheduling recommendations by the World Health Organization on new psychoactive substances and medicines

Note by the Secretariat

Summary

The present document contains recommendations for action to be taken by the Commission on Narcotic Drugs pursuant to the international drug control treaties.

In accordance with article 3 of the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol, the Commission will have before it for consideration a recommendation by the World Health Organization (WHO) to place parafluorobutyrylfentanyl, orthofluorofentanyl, methoxyacetylfentanyl and cyclopropylfentanyl in Schedule I of that Convention.

In accordance with article 2 of the Convention on Psychotropic Substances of 1971, the Commission will have before it for consideration a recommendation by WHO to place ADB-FUBINACA, FUB-AMB (MMB-FUBINACA, AMB-FUBINACA), CUMYL-4CN-BINACA, ADB-CHMINACA (MAB-CHMINACA) and *N*-ethylnorpentylone (ephylone) in Schedule II of that Convention.

* E/CN.7/2019/1.

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I. Consideration of the notification from the World Health Organization concerning scheduling under the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol

1. Pursuant to article 3, paragraphs 1 and 3, of the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol, the Director-General of the World Health Organization (WHO), in correspondence dated 24 January 2019 (received 28 January 2019), notified the Secretary-General of the United Nations that WHO recommended that parafluorobutyrylfentanyl, orthofluorofentanyl, methoxyacetylfentanyl and cyclopropylfentanyl be added to Schedule I of that Convention (see annex for the relevant extract of that notification).

2. In accordance with the provisions of article 3, paragraph 2, of the 1961 Convention, on 1 February 2019, the Secretary-General transmitted to all Governments a note verbale, to which the notification and the information submitted by WHO in support of its recommendations were annexed. On 29 January 2019, the Secretariat informally submitted the notification and the information submitted by WHO in support of those recommendations in advance to all permanent missions to the United Nations in Vienna. The recommendations had been presented by the representative of WHO during the reconvened sixty-first session of the Commission on Narcotic Drugs, held in Vienna from 5 to 7 December 2018.

Action to be taken by the Commission on Narcotic Drugs

3. The notification from the Director-General of WHO is before the Commission on Narcotic Drugs for its consideration, in accordance with the provisions of article 3, paragraph 3 (iii), of the 1961 Convention, which reads as follows:

> If the World Health Organization finds that the substance is liable to similar abuse and productive of similar ill-effects as the drugs in Schedule I or Schedule II or is convertible into a drug, it shall communicate that finding to the Commission which may, in accordance with the recommendation of the World Health Organization, decide that the substance shall be added to Schedule I or Schedule II.

4. With regard to the decision-making process, the attention of the Commission is drawn to rule 58 of the rules of procedure of the functional commissions of the Economic and Social Council, which stipulates that decisions are to be made by a majority of the members present and casting an affirmative or negative vote. Members who abstain from voting are considered as not voting.

5. The Commission should therefore decide:

(a) Whether or not it wishes to include parafluorobutyrylfentanyl in Schedule I of the 1961 Convention;

(b) Whether or not it wishes to include orthofluorofentanyl in Schedule I of the 1961 Convention;

(c) Whether or not it wishes to include methoxyacetylfentanyl in Schedule I of the 1961 Convention;

(d) Whether or not it wishes to include cyclopropylfentanyl in Schedule I of the 1961 Convention.

II. Consideration of a notification from the World Health Organization concerning scheduling under the Convention on Psychotropic Substances of 1971

6. Pursuant to article 2, paragraphs 1 and 4, of the Convention on Psychotropic Substances of 1971, the Director-General of WHO, in correspondence dated 24 January 2018 (received 28 January 2019), notified the Secretary-General that WHO recommended placing ADB-FUBINACA, FUB-AMB (MMB-FUBINACA, AMB-FUBINACA), CUMYL-4CN-BINACA, ADB-CHMINACA (MAB-CHMINACA) and *N*-ethylnorpentylone (ephylone) in Schedule II of that Convention (see annex for the relevant extract of that notification).

7. In accordance with the provisions of article 2, paragraph 2, of the 1971 Convention, on 1 February 2019, the Secretary-General transmitted to all Governments a note verbale, to which the notification and the information submitted by WHO in support of its recommendations were annexed. On 29 January 2019, the Secretariat informally submitted the notification and the information submitted by WHO in support of those recommendations in advance to all permanent missions to the United Nations in Vienna. The recommendations had been presented by the representative of WHO during the reconvened sixty-first session of the Commission on Narcotic Drugs, held in Vienna from 5 to 7 December 2018.

Action to be taken by the Commission on Narcotic Drugs

8. The notification by the Director-General of WHO is before the Commission on Narcotic Drugs for its consideration, in accordance with the provisions of article 2, paragraph 5, of the 1971 Convention, which reads as follows:

> The Commission, taking into account the communication from the World Health Organization, whose assessments shall be determinative as to medical and scientific matters, and bearing in mind the economic, social, legal, administrative and other factors it may consider relevant, may add the substance to Schedule I, II, III or IV. The Commission may seek further information from the World Health Organization or from other appropriate sources.

9. With regard to the decision-making process, the attention of the Commission is drawn to article 17, paragraph 2, of the 1971 Convention, which stipulates that the decisions of the Commission provided for in articles 2 and 3 are to be taken by a two-thirds majority of the members of the Commission. From a practical point of view, this means that, for a decision to be adopted, an affirmative vote of at least 35 members of the Commission is required.

10. The Commission should therefore decide:

(a) Whether it wishes to place ADB-FUBINACA in Schedule II of the 1971 Convention or, if not, what other action, if any, might be required;

(b) Whether it wishes to place FUB-AMB (MMB-FUBINACA, AMB-FUBINACA) in Schedule II of the 1971 Convention or, if not, what other action, if any, might be required;

(c) Whether it wishes to place CUMYL-4CN-BINACA, in Schedule II of the 1971 Convention or, if not, what other action, if any, might be required;

(d) Whether it wishes to place ADB-CHMINACA (MAB-CHMINACA) in Schedule II of the 1971 Convention or, if not, what other action, if any, might be required;

(e) Whether it wishes to place *N*-ethylnorpentylone (ephylone) in Schedule II of the 1971 Convention or, if not, what other action, if any, might be required.

Annex

Extract of the notification from the Director-General of the World Health Organization to the Secretary-General dated 24 January 2019 on new psychoactive substances and medicines: scheduling of substances under the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol, and the Convention on Psychotropic Substances of 1971, including the relevant extract from the report on the forty-first meeting of the Expert Committee on Drug Dependence

With reference to article 3, paragraphs 1 and 3, of the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol, and article 2, paragraphs 1 and 4, of the Convention on Psychotropic Substances of 1971, I am pleased to submit recommendations of the Expert Committee on Drug Dependence at its forty-first meeting regarding new psychoactive substances and two pain-relieving medicines, tramadol and pregabalin, as follows:

New psychoactive substances

To be added to Schedule I of the 1961 Convention:

Parafluorobutyrylfentanyl

Chemical name:
N-(4-fluorophenyl)-*N*-[1-(2-phenylethyl)piperidin-4-yl]butanamide

Orthofluorofentanyl

Chemical name:
N-(2-fluorophenyl)-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide

Methoxyacetylfentanyl

Chemical name:
2-methoxy-*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide

Cyclopropylfentanyl

Chemical name:
N-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]cyclopropanecarboxamide

To be added to Schedule II of the 1971 Convention:

ADB-FUBINACA

Chemical name:
N-[(2*S*)-1-amino-3,3-dimethyl-1-oxobutan-2-yl]-1-[(4-fluorophenyl)methyl]-1*H*-indazole-3-carboxamide

FUB-AMB (MMB-FUBINACA, AMB-FUBINACA)

Chemical name:
methyl (2*S*)-2-({1-[(4-fluorophenyl)methyl]-1*H*-indazole-3-carbonyl}amino)-3-methylbutanoate

CUMYL-4CN-BINACA

Chemical name:
1-(4-cyanobutyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide

ADB-CHMINACA (MAB-CHMINACA)

Chemical name:
N-[(2*S*)-1-amino-3,3-dimethyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide

N-Ethylnorpentylone (ephylone)

Chemical name:
1-(2*H*-1,3-benzodioxol-5-yl)-2-(ethylamino)pentan-1-one

To be kept under surveillance:

Paramethoxybutyrylfentanyl

Chemical name:
N-(4-methoxyphenyl)-*N*-[1-(2-phenylethyl)piperidin-4-yl]butanamide

Medicines

To be kept under surveillance:

Pregabalin

Chemical name:
(3*S*)-3-(aminomethyl)-5-methylhexanoic acid

Tramadol

Chemical name:
(1*R**,2*R**)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexan-1-ol

The assessments and findings on which they are based are set out in detail in the report on the forty-first meeting of the Expert Committee on Drug Dependence.

Extract from the report on the forty-first meeting of the Expert Committee on Drug Dependence

1. Fentanyl analogues

1.1 Parafluorobutyrylfentanyl

Substance identification

Parafluorobutyrylfentanyl (*N*-(4-fluorophenyl)-*N*-[1-(2-phenylethyl)piperidin-4-yl] butanamide) is a synthetic analogue of the opioid analgesic fentanyl. Samples obtained from seizures and from other collections suggest that parafluorobutyrylfentanyl appears in powder, tablet, nasal spray and vaping form.

World Health Organization review history

Parafluorobutyrylfentanyl has not been previously pre-reviewed or critically reviewed by the Expert Committee on Drug Dependence. A direct critical review was proposed based on information brought to the attention of the World Health Organization (WHO) that parafluorobutyrylfentanyl poses a serious risk to public health and has no recognized therapeutic use.

Similarity to known substances and effects on the central nervous system

Parafluorobutyrylfentanyl binds to μ-opioid receptors with high selectivity over κ- and δ-opioid receptors and has been shown to act as a partial agonist at the μ-opioid receptor. In animals, it produces typical opioid effects including analgesia, with a potency between that of morphine and fentanyl. In cases of non-fatal intoxication in humans, parafluorobutyrylfentanyl has produced signs and symptoms such as disorientation, slurred speech, unsteady gait, hypotension and pupil constriction that are consistent with an opioid mechanism of action.

Parafluorobutyrylfentanyl can be readily converted to its isomer *p*-fluoro-isobutyrylfentanyl (*N*-(4-fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide), which is an opioid listed in Schedule I of the 1961 Convention.

Dependence potential

There are no studies on the dependence potential of this substance in humans or laboratory animals. However, based on its mechanism of action, parafluorobutyrylfentanyl would be expected to produce dependence similar to that produced by other opioid drugs.

Actual abuse and/or evidence of likelihood of abuse

There are no controlled studies on the abuse potential of parafluorobutyrylfentanyl and there is very little information on the extent of its abuse. The substance has been detected in biological samples obtained from cases of fatal and non-fatal intoxication. Fatalities have been reported in some countries where the compound has been identified in biological fluids in combination with other drugs, including cases where death has been attributed to the effects of parafluorobutyrylfentanyl.

Therapeutic usefulness

Parafluorobutyrylfentanyl is not known to have any therapeutic uses.

Recommendation

Parafluorobutyrylfentanyl is an opioid receptor agonist that has significant potential for dependence and likelihood of abuse. The limited available evidence indicates that it has typical opioid adverse effects that include the potential for death due to respiratory depression. Parafluorobutyrylfentanyl has caused substantial harm and has no therapeutic usefulness. As it is liable to similar abuse and produces similar ill-effects as many other opioids contained in Schedule I of the 1961 Convention:

Recommendation 1.1: The Committee recommended that parafluorobutyrylfentanyl (*N*-(4-fluorophenyl)-*N*-[1-(2-phenylethyl)piperidin-4-yl]butanamide) be added to Schedule I of the 1961 Convention.

1.2 Paramethoxybutyrylfentanyl

Substance identification

Paramethoxybutyrylfentanyl (*N*-(4-methoxyphenyl)-*N*-[1-(2-phenylethyl)piperidin-4-yl]butanamide) is a synthetic analogue of the opioid analgesic fentanyl. Samples obtained from seizures and from other collections suggest that paramethoxybutyrylfentanyl occurs in powder, tablet and nasal spray forms.

World Health Organization review history

Paramethoxybutyrylfentanyl has not been previously pre-reviewed or critically reviewed by the Expert Committee on Drug Dependence. A critical review was proposed based on information brought to the attention of WHO that paramethoxybutyrylfentanyl poses a serious risk to public health and has no recognized therapeutic use.

Similarity to known substances and effects on the central nervous system

Paramethoxybutyrylfentanyl binds to μ-opioid receptors with high selectivity over κ- and δ-opioid receptors and has been shown to act as a partial agonist at the μ-opioid receptor. In animals, it produces typical opioid effects, including analgesia, and in some tests it has a potency higher than morphine and close to that of fentanyl.

Reported clinical features of intoxication in which paramethoxybutyrylfentanyl is involved included the typical opioid effects of reduced level of consciousness, respiratory depression and pupil constriction. In some cases, treatment with the opioid

antagonist naloxone was shown to reverse the drug-induced respiratory depression. While this is consistent with an opioid mechanism of action, it should be noted that in all such cases at least one other opioid was present.

Dependence potential

There are no studies on the dependence potential of this substance in humans or laboratory animals. However, based on its mechanism of action, paramethoxybutyrylfentanyl would be expected to produce dependence similar to that produced by other opioid drugs.

Abuse potential or evidence of likelihood of abuse

There are no controlled studies on the abuse potential of paramethoxybutyrylfentanyl and very little information on the extent of its abuse. Paramethoxybutyrylfentanyl has been detected in biological samples obtained from a limited number of acute intoxication cases. Reported clinical features are consistent with opioid effects, including respiratory depression. However, in all of the documented cases of severe adverse events associated with use of paramethoxybutyrylfentanyl, other fentanyl derivatives were detected and, hence, the role of paramethoxybutyrylfentanyl is not clear.

Therapeutic applications/usefulness

Paramethoxybutyrylfentanyl is not known to have any therapeutic uses.

Recommendation

The limited available information indicates that paramethoxybutyrylfentanyl is an opioid drug, and an analogue of the opioid analgesic fentanyl. There is evidence of its use in a limited number of countries with few reports of intoxication and no reports of deaths. In the intoxication cases, the role of paramethoxybutyrylfentanyl was not clear, due to the presence of other opioids. It has no therapeutic usefulness. At this time, there is little evidence of the impact of paramethoxybutyrylfentanyl in causing substantial harm that would warrant its placement under international control.

Recommendation 1.2: The Committee recommended that paramethoxybutyrylfentanyl (*N*-(4-methoxyphenyl)-*N*-[1-(2-phenylethyl)piperidin-4-yl]butanamide) be kept under surveillance by the WHO Secretariat.

1.3 Orthofluorofentanyl

Substance identification

Orthofluorofentanyl (*N*-(2-fluorophenyl)-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide) is a synthetic analogue of the opioid analgesic fentanyl. It has two positional isomers (parafluorofentanyl and metafluorofentanyl).

World Health Organization review history

Orthofluorofentanyl has not been previously pre-reviewed or critically reviewed by the Expert Committee on Drug Dependence. A direct critical review was proposed based on information brought to the attention of WHO that orthofluorofentanyl poses a serious risk to public health and has no recognized therapeutic use.

Similarity to known substances and effects on the central nervous system

Receptor binding data show that orthofluorofentanyl binds to μ-opioid receptors with high selectivity over κ- and δ-opioid receptors. There were no preclinical or clinical studies available in the scientific literature. However, the clinical features present in non-fatal intoxication cases include characteristic opioid effects such as loss of consciousness, pupil constriction and respiratory depression. The effects of orthofluorofentanyl are responsive to the administration of the opioid antagonist naloxone, further confirming its opioid agonist mechanism of action.

Dependence potential

There are no studies on the dependence potential of orthofluorofentanyl in humans or laboratory animals. However, based on its mechanism of action, it would be expected to produce dependence similar to that produced by other opioid drugs.

Actual abuse and/or evidence of likelihood of abuse

There are no available preclinical or clinical studies to assess the abuse liability of orthofluorofentanyl. There is evidence of use from several countries, including seizures in Europe and the United States of America. A number of confirmed fatalities associated with the compound have been reported**.** Orthofluorofentanyl is being sold as heroin or an adulterant in heroin. A number of fatalities have been associated with this substance (1 in Europe and 16 in the United States since 2016). As a consequence of orthofluorofentanyl cross-reacting with standard fentanyl immunoassays, it is possible that deaths due to orthofluorofentanyl have been attributed to fentanyl and, hence, the number of recorded orthofluorofentanyl deaths may be an underestimate. Several countries in different parts of the world have placed orthofluorofentanyl under control.

Therapeutic usefulness

Orthofluorofentanyl is not known to have any therapeutic uses.

Recommendation

Orthofluorofentanyl is an opioid receptor agonist that has potential for dependence and likelihood of abuse. The limited available evidence indicates that it has typical opioid adverse effects that include the potential for death due to respiratory depression. Orthofluorofentanyl has caused substantial harm and has no therapeutic usefulness. As it is liable to similar abuse and produces ill-effects similar to those of many other opioids contained in Schedule I of the 1961 Convention:

Recommendation 1.3: The Committee recommended that orthofluorofentanyl (*N*-(2-fluorophenyl)-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide) be added to Schedule I of the 1961 Convention.

1.4 Methoxyacetylfentanyl

Substance identification

Methoxyacetylfentanyl (2-methoxy-*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl] acetamide) is a synthetic analogue of the opioid fentanyl. Samples obtained from seizures and from other collections suggest that methoxyacetylfentanyl has appeared in powders, liquids and tablets.

World Health Organization review history

Methoxyacetylfentanyl has not been previously pre-reviewed or critically reviewed by the Expert Committee on Drug Dependence. A critical review was proposed based on information brought to the attention of WHO that methoxyacetylfentanyl poses a serious risk to public health and has no recognized therapeutic use.

Similarity to known substances and effects on the central nervous system

Methoxyacetylfentanyl binds to μ-opioid receptors with high selectivity over κ- and δ-opioid receptors and has been shown to act as an agonist at the μ-opioid receptor. In animals, it produces analgesia with a potency higher than morphine and close to that of fentanyl. The analgesia was blocked by the opioid antagonist naltrexone, confirming its opioid mechanism of action.

In people using methoxyacetylfentanyl, the most serious acute health risk is respiratory depression, which in overdose can lead to respiratory arrest and death. This is consistent with its opioid mechanism of action.

Dependence potential

There are no studies on the dependence potential of this substance in humans or laboratory animals. However, based on its mechanism of action, methoxyacetylfentanyl would be expected to produce dependence similar to that produced by other opioid drugs.

Actual abuse and/or evidence of likelihood of abuse

In the animal drug discrimination model of subjective drug effects, methoxyacetylfentanyl produced effects similar to those of morphine. It also decreased activity levels and both the discriminative and rate-decreasing effects were blocked by the opioid antagonist naltrexone. Based on its receptor action and these effects in animal models, it would be expected that methoxyacetylfentanyl would be subject to abuse in a manner comparable to that of other opioids.

There is evidence that methoxyacetylfentanyl has been used by injection and by nasal insufflation of powder. A large number of seizures of this substance have been reported in Europe and the United States. A number of deaths have been reported in Europe and the United States in which methoxyacetylfentanyl was detected in post-mortem samples. While other drugs were present in most of these cases, methoxyacetylfentanyl was deemed the cause of death or a major contributor to death in a significant proportion of them. Several countries have controlled methoxyacetylfentanyl in their national legislation.

Therapeutic usefulness

Methoxyacetylfentanyl is not known to have any therapeutic uses.

The Committee considered that methoxyacetylfentanyl is a substance with high abuse liability and dependence potential. It is an opioid agonist that is more potent than morphine and its use has contributed to a large number of deaths in different regions. It has no therapeutic usefulness and it poses a significant risk to public health. The Committee considered that the evidence of its abuse warrants placement under international control.

Recommendation 1.4: The Committee recommended that methoxyacetylfentanyl (2-methoxy-*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide) be added to Schedule I of the 1961 Convention.

1.5 Cyclopropylfentanyl

Substance identification

Cyclopropylfentanyl *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]cyclopropane carboxamide) is a synthetic analogue of the opioid fentanyl. Samples obtained from seizures and from other collections suggest that cyclopropylfentanyl has appeared in powders, liquids and tablets.

World Health Organization review history

Cyclopropylfentanyl has not been previously pre-reviewed or critically reviewed by the Expert Committee on Drug Dependence. A critical review was proposed based on information brought to the attention of WHO that cyclopropylfentanyl poses a serious risk to public health and has no recognized therapeutic use.

Similarity to known substances and effects on the central nervous system

Cyclopropylfentanyl binds selectively to the μ-opioid receptors compared to δ- and κ-opioid receptors. There is no further information on the actions and effects of cyclopropylfentanyl from controlled studies. Based on its role in numerous deaths, as described below, it is reasonable to consider that cyclopropylfentanyl acts as a μ-opioid receptor agonist similar to morphine and fentanyl.

Dependence potential

There are no preclinical or clinical studies published in the scientific literature concerning dependence on cyclopropylfentanyl. However, based on its mechanism of action, cyclopropylfentanyl would be expected to produce dependence similar to other opioid drugs.

Actual abuse and/or evidence of likelihood of abuse

A large number of seizures of cyclopropylfentanyl have been reported from countries in different regions. In some countries, the substance has been among the most common fentanyl analogues detected in post-mortem samples. In almost all of those deaths, cyclopropylfentanyl was determined to either have caused or contributed to death, even in the presence of other substances.

Therapeutic usefulness

Cyclopropylfentanyl is not known to have any therapeutic uses.

Recommendation

The available evidence indicates that cyclopropylfentanyl has opioid actions and effects. It has been extensively trafficked and has been used by several different routes of administration. Its use has been associated with a large number of documented deaths, and for most of these it was the principal cause of death. Cyclopropylfentanyl has no known therapeutic use and has been associated with substantial harm.

Recommendation 1.5: The Committee recommended that cyclopropylfentanyl (*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]cyclopropanecarboxamide) be added to Schedule I of the 1961 Convention.

2. Synthetic cannabinoids

2.1 ADB-FUBINACA

Substance identification

ADB-FUBINACA (*N*-[(2*S*)-1-amino-3,3-dimethyl-1-oxobutan-2-yl]-1-[(4-fluorophenyl) methyl]-1*H*-indazole-3-carboxamide) is encountered as a powder, in solution or sprayed on herbal material that mimics the appearance of cannabis. It is sold as herbal incense or branded products with a variety of different names.

World Health Organization review history

ADB-FUBINACA has not been previously pre-reviewed or critically reviewed by the Expert Committee on Drug Dependence. A critical review was proposed based on information brought to the attention of WHO that ADB-FUBINACA poses a serious risk to public health and has no recognized therapeutic use.

Similarity to known substances/effects on the central nervous system

ADB-FUBINACA is similar to other synthetic cannabinoid receptor agonists that are currently scheduled under the 1971 Convention. It binds to both the CB_1 and CB_2 cannabinoid receptors with full agonist activity as demonstrated by in vitro studies. The efficacy and potency of ADB-FUBINACA is substantially greater when compared to Δ^9-THC. Reported clinical features of intoxication include confusion, agitation, somnolence, hypertension and tachycardia, similar to other synthetic cannabinoid receptor agonists.

Dependence potential

No controlled experimental studies examining the dependence potential of ADB-FUBINACA in humans or animals were available. However, based on its central

nervous system action as a full CB1 agonist, ADB-FUBINACA would be expected to produce dependence in a manner similar to or more pronounced than that of cannabis.

Actual abuse and/or evidence of likelihood of abuse

ADB-FUBINACA is sold and used as a substitute for cannabis. It is invariably smoked or vaped (i.e., using an e-cigarette) but due to the nature of synthetic cannabinoid products (whereby drug components are introduced onto herbal material), users are unaware of which synthetic cannabinoid may be contained in such products. Evidence from case reports in which ADB-FUBINACA has been detected in biological samples has demonstrated that use of this substance has contributed to severe adverse reactions in humans, including death. However, it was also noted that other substances, including other synthetic cannabinoids, were also present in the urine or blood following non-fatal and fatal intoxications and/or in the product used. Evidence of use has been reported in Europe, Asia and the United States. In recognition of its abuse and associated harm, ADB-FUBINACA has been placed under national control in a number of countries in several different regions.

Therapeutic applications/usefulness

There are currently no approved medical or veterinary uses of ADB-FUBINACA.

Recommendation

ADB-FUBINACA is a synthetic cannabinoid receptor agonist that is used by smoking plant material sprayed with the substance or inhaling vapour after heating. Its mode of action suggests the potential for dependence and likelihood of abuse. Its use has been associated with a range of severe adverse effects, including death. These effects are similar to those produced by other synthetic cannabinoids which have a mechanism of action the same as that of ADB-FUBINACA and which are placed in Schedule II of the 1971 Convention. ADB-FUBINACA has no therapeutic usefulness.

Recommendation 2.1: The Committee recommended that ADB-FUBINACA (*N*-[(2*S*)-1-amino-3,3-dimethyl-1-oxobutan-2-yl]-1-[(4-fluorophenyl)methyl]-1*H*-indazole-3-carboxamide) be added to Schedule II of the 1971 Convention.

2.2 FUB-AMB

Substance identification

FUB-AMB (chemical name: methyl (2*S*)-2-({1-[(4-fluorophenyl)methyl]-1*H*-indazole-3-carbonyl}amino)-3-methylbutanoate) is a synthetic cannabinoid that is also referred to as MMB-FUBINACA and AMB-FUBINACA. FUB-AMB is encountered as a powder, in solution or sprayed on herbal material that mimics the appearance of cannabis. It is sold as herbal incense or branded products with a variety of different names.

World Health Organization review history

FUB-AMB has not been previously pre-reviewed or critically reviewed by the Expert Committee on Drug Dependence. A critical review was proposed based on information brought to the attention of WHO that FUB-AMB poses a serious risk to public health and has no recognized therapeutic use.

Similarity to known substances/effects on the central nervous system

FUB-AMB is similar to other synthetic cannabinoid receptor agonists that are currently scheduled under the 1971 Convention. It binds to both the CB_1 and CB_2 cannabinoid receptors with full agonist activity as demonstrated by in vitro studies. The efficacy and potency of FUB-AMB is substantially greater than Δ^9-THC and it shares effects with other synthetic cannabinoids including severe central nervous system depression, resulting in slowed behaviour and speech.

Dependence potential

No controlled experimental studies examining the dependence potential of FUB-AMB in humans or animals were available. However, based on its central nervous system action as a full CB1 agonist, FUB-AMB would be expected to produce dependence in a manner similar to or more pronounced than that of cannabis.

Actual abuse and/or evidence of likelihood of abuse

Consistent with its CB_1 cannabinoid receptor agonist activity, FUB-AMB produces complete dose-dependent substitution for the discriminative stimulus effects of Δ^9-THC in mice by various routes of administration. This suggests that it has abuse potential at least as great as that of Δ^9-THC.

Evidence of the use of FUB-AMB has been reported in Europe, New Zealand and the United States. It is usually smoked or vaped (i.e., using an e-cigarette) but due to the nature of synthetic cannabinoid products (whereby drug components are introduced onto herbal material), users are unaware of which synthetic cannabinoid may be contained within such products.

FUB-AMB use was confirmed in case reports of a mass intoxication in the United States with the predominant symptom being severe central nervous system depression, resulting in slowed behaviour and speech. It was reported that in New Zealand there were at least 20 deaths related to the use of FUB-AMB. It was noted that the amounts of FUB-AMB in confiscated products were 2 to 25 times greater than those reported in the incidents in the United States.

Therapeutic usefulness

There are currently no approved medical or veterinary uses of FUB-AMB.

Recommendation

FUB-AMB is a synthetic cannabinoid receptor agonist that is used by smoking plant material sprayed with the substance or inhaling vapour after heating. Its mode of action suggests the potential for dependence and likelihood of abuse. Its use has been associated with a range of severe adverse effects including a number of deaths. Its mechanism of action and manner of use are similar to those of other synthetic cannabinoids placed in Schedule II of the 1971 Convention. FUB-AMB has no therapeutic usefulness.

Recommendation 2.2: The Committee recommended that FUB-AMB (chemical name: methyl (2*S*)-2-({1-[(4-fluorophenyl)methyl]-1*H*-indazole-3-carbonyl}amino)-3-methylbutanoate) be added to Schedule II of the 1971 Convention.

2.3 ADB-CHMINACA

Substance identification

ADB-CHMINACA (*N*-[(2*S*)-1-amino-3,3-dimethyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide) is a synthetic cannabinoid that is also referred to as MAB-CHMINACA. ADB-CHMINACA is encountered as a powder, in solution or sprayed on herbal material that mimics the appearance of cannabis. It is sold as herbal incense or branded products with a variety of different names.

World Health Organization review history

ADB-CHMINACA has not been previously pre-reviewed or critically reviewed by the Expert Committee on Drug Dependence. A critical review was proposed based on information brought to the attention of WHO that ADB-CHMINACA poses a serious risk to public health and has no recognized therapeutic use

Similarity to known substances/effects on the central nervous system

ADB-CHMINACA is similar to other synthetic cannabinoid receptor agonists that are currently scheduled under the 1971 Convention. It binds to both the CB_1 and CB_2 cannabinoid receptors with full agonist activity as demonstrated by in vitro studies. The efficacy and potency of ADB-CHMINACA is substantially greater than Δ^9-THC and it is among the most potent synthetic cannabinoids studied to date. It shares a profile of central nervous system mediated effects with other synthetic cannabinoids. ADB-CHMINACA demonstrates decreased locomotor activity in mice in a time- and dose-dependent fashion with a rapid onset of action and long-lasting effects.

Signs and symptoms of intoxication arising from use of ADB-CHMINACA have included tachycardia, unresponsiveness, agitation, combativeness, seizures, hyperemesis, slurred speech, delirium and sudden death. These are consistent with the effects of other synthetic cannabinoids.

Dependence potential

No controlled experimental studies examining the dependence potential of ADB-CHMINACA in humans or animals were available. However, based on its central nervous system action as a full CB1 agonist, ADB-CHMINACA would be expected to produce dependence in a manner similar to or more pronounced than that of cannabis.

Actual abuse and/or evidence of likelihood of abuse

Consistent with its CB_1 cannabinoid receptor agonist activity, ADB-CHMINACA fully substituted for Δ^9-THC in drug discrimination tests. This suggests that it has abuse potential at least as great as that of Δ^9-THC.

Evidence of the use of ADB-CHMINACA has been reported in Europe, the United States and Japan, including cases of driving under the influence. It is invariably smoked or vaped (i.e., using an e-cigarette) but due to the nature of synthetic cannabinoid products (whereby drug components are introduced onto herbal material), users are unaware of which synthetic cannabinoid may be contained within such products.

ADB-CHMINACA use was analytically confirmed in case reports of several drug-induced clusters of severe illness and death in the United States. In Europe, 13 deaths with analytically confirmed use of ADB-CHMINACA were reported between 2014 and 2016, and another death occurred in Japan.

Therapeutic usefulness

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

Recommendation

ADB-CHMINACA is a synthetic cannabinoid receptor agonist that is used by smoking plant material sprayed with the substance or inhaling vapour after heating. It has effects that are similar to other synthetic cannabinoid receptor agonists contained in Schedule II of the 1971 Convention. Its mode of action suggests the potential for dependence and likelihood of abuse. Its use has resulted in numerous cases of severe intoxication and death. There is evidence that ADB-CHMINACA has been associated with fatal and non-fatal intoxications in a number of countries. The substance causes substantial harm and has no therapeutic usefulness.

Recommendation 2.3: The Committee recommended that ADB-CHMINACA (chemical name: *N*-[(2*S*)-1-amino-3,3-dimethyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl) -1*H*-indazole-3-carboxamide) be added to Schedule II of the 1971 Convention.

2.4 CUMYL-4CN-BINACA

Substance identification

CUMYL-4CN-BINACA (chemical name: 1-(4-cyanobutyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide) is a synthetic cannabinoid. It is encountered as a powder, in solution or sprayed on herbal material that mimics the appearance of cannabis. It is sold as herbal incense or branded products with a variety of different names.

World Health Organization review history

CUMYL-4CN-BINACA has not been previously pre-reviewed or critically reviewed by the Expert Committee on Drug Dependence. A critical review was proposed based on information brought to the attention of WHO that CUMYL-4CN-BINACA poses a serious risk to public health and has no recognized therapeutic use.

Similarity to known substances/effects on the central nervous system

CUMYL-4CN-BINACA is similar to other synthetic cannabinoid receptor agonists that are currently scheduled under the 1971 Convention. It binds to both the CB_1 and CB_2 cannabinoid receptors with full agonist activity as demonstrated by in vitro studies. The efficacy and potency of CUMYL-4CN-BINACA is substantially greater than Δ^9-THC and it shares a profile of central nervous system mediated effects with other synthetic cannabinoids. Data have shown that it produced hypothermia in mice, in common with other CB_1 cannabinoid receptor agonists.

Dependence potential

No controlled experimental studies examining the dependence potential of CUMYL-4CN-BINACA in humans or animals were available. However, based on its central nervous system action as a full CB1 agonist, CUMYL-4CN-BINACA would be expected to produce dependence in a manner similar to or more pronounced than that of cannabis.

Actual abuse or evidence of likelihood of abuse

Consistent with its CB_1 cannabinoid receptor agonist activity, CUMYL-4CN-BINACA fully substituted for Δ^9-THC in drug discrimination tests. This suggests that it has abuse potential at least as great as that of Δ^9-THC.

Evidence of the use of CUMYL-4CN-BINACA has been currently reported only from Europe but this may be due to underreporting, including through lack of detection in other countries. In Europe, CUMYL-4CN-BINACA has been among the most frequently seized synthetic cannabinoids. It is invariably smoked or vaped (i.e., using an e-cigarette) but due to the nature of synthetic cannabinoid products (whereby drug components are introduced onto herbal material), users are unaware of which synthetic cannabinoid may be contained within such products.

A number of non-fatal intoxications involving CUMYL-4CN-BINACA have been reported. CUMYL-4CN-BINACA has been analytically confirmed as being present in 11 fatalities and 5 non-fatal intoxications in Europe. In 2 deaths, CUMYL-4CN-BINACA was the only drug present.

Therapeutic applications/usefulness

There are currently no approved medical or veterinary uses of CUMYL-4CN-BINACA.

Recommendation

CUMYL-4CN-BINACA is a synthetic cannabinoid receptor agonist that is used by smoking plant material sprayed with the substance or inhaling vapour after heating and is sold under a variety of brand names. It has effects that are similar to other

synthetic cannabinoid receptor agonists placed in Schedule II of the 1971 Convention. Its mode of action suggests the potential for dependence and likelihood of abuse. There is evidence that CUMYL-4CN-BINACA has been associated with fatal and non-fatal intoxications in a number of countries. The substance causes substantial harm and has no therapeutic usefulness.

***Recommendation 2.4*:** The Committee recommended that CUMYL-4CN-BINACA (chemical name: 1-(4-cyanobutyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide) be added to Schedule II of the 1971 Convention.

3. Cathinone

3.1 *N*-Ethylnorpentylone

Substance identification

N-Ethylnorpentylone (chemical name: 1-(2*H*-1,3-benzodioxol-5-yl)-2-(ethylamino) pentan-1-one) is a ring-substituted synthetic cathinone analogue that originally emerged in the 1960s during pharmaceutical drug development efforts. It is also known as ephylone and incorrectly referred to as *N*-ethylpentylone. In its pure form, *N*-ethylnorpentylone exists as a racemic mixture in form of a powder or crystalline solid. However, the substance is usually available as a capsule, powdered tablet, pill or powder often sold as “ecstasy”, or MDMA. *N*-Ethylnorpentylone is also available in its own right and is advertised for sale by Internet retailers.

World Health Organization review history

N-Ethylnorpentylone has not been previously pre-reviewed or critically reviewed by the Expert Committee on Drug Dependence. A critical review was proposed based on information brought to the attention of WHO that *N*-ethylnorpentylone poses a serious risk to public health and has no recognized therapeutic use.

Similarity to known substances/effects on the central nervous system

The information currently available suggests that *N*-ethylnorpentylone is a psychomotor stimulant. *N*-Ethylnorpentylone users exhibit psychomotor stimulant effects including agitation, paranoia, tachycardia and sweating, which are consistent with other substituted cathinone and central nervous system stimulant drugs. Not all reported adverse effects could be causally linked to *N*-ethylnorpentylone alone, but there are indications that the observed effects are consistent with those seen with other psychomotor stimulants, with some instances involving cardiac arrest.

Its molecular mechanism of action is similar to the synthetic cathinones MDPV and α-PVP, which are both listed in Schedule II of the 1971 Convention. In vitro investigations showed that *N*-ethylnorpentylone inhibited the reuptake of dopamine, noradrenaline and, to a lesser extent, serotonin, which is consistent with closely related other substituted cathinones with known abuse liability and with cocaine.

There is no specific information available to indicate that *N*-ethylnorpentylone may be converted into a substance currently controlled under the international drug control conventions.

Dependence potential

No controlled experimental studies examining the dependence potential of *N*-ethylnorpentylone in humans or animals were available. However, based on its action in the central nervous system, it would be expected that *N*-ethylnorpentylone would have the capacity to produce a state of dependence similar to that of other stimulants such as the ones listed in Schedule II of the 1971 Convention.

Actual abuse and/or evidence of likelihood of abuse

In rodent drug discrimination studies, *N*-ethylnorpentylone fully substituted for methamphetamine and cocaine, and it was also shown to increase activity levels, suggesting it has potential for abuse similar to that of other psychomotor stimulants.

N-Ethylnorpentylone has been detected in biological fluids collected in a number of cases involving adverse effects, including deaths. It is frequently used in combination with other drugs. Users may be unaware of the additional risks of harm associated with the consumption of *N*-ethylnorpentylone either alone or in combination with other drugs. Users may also be unaware of the exact dose or compound being ingested.

A number of countries in various regions have reported the use or detection of this compound in either seized materials or biological samples of individuals, including in cases of driving under the influence of drugs. Increased seizures of *N*-ethylnorpentylone were reported by the United States over the last two years. *N*-Ethylnorpentylone has been detected in biological fluids collected from fatal and non-fatal cases of intoxication, and a total of 125 toxicological reports associated with *N*-ethylnorpentylone were documented between 2016 and 2018.

The current available data therefore suggest that *N*-ethylnorpentylone is liable to abuse.

Therapeutic usefulness

N-Ethylnorpentylone is not known to have any therapeutic uses.

Recommendation

N-Ethylnorpentylone is a synthetic cathinone with effects that are similar to other synthetic cathinones listed in Schedule II of the 1971 Convention. Its mode of action and effects are consistent with those of other central nervous system stimulants such as cocaine, indicating that it has significant potential for dependence and likelihood of abuse. There is evidence of use of *N*-ethylnorpentylone in a number of countries in various regions and this use has resulted in fatal and non-fatal intoxications. The substance causes substantial harm and has no therapeutic usefulness. Accordingly:

Recommendation 3.1: The Committee recommended that *N*-ethylnorpentylone (chemical name: 1-(2*H*-1,3-benzodioxol-5-yl)-2-(ethylamino)pentan-1-one) be added to Schedule II of the 1971 Convention.

4. Medicines

4.1 Pregabalin

Substance identification

Chemically, pregabalin is (3*S*)-3-(aminomethyl)-5-methylhexanoic acid.

World Health Organization review history

Pregabalin was pre-reviewed by the Expert Committee on Drug Dependence at its thirty-ninth meeting, in November 2017.

Similarity to known substances/effects on the central nervous system

Pregabalin is an inhibitor of *alpha*-2-*delta* subunit containing voltage-gated calcium channels. Through this mechanism, it decreases the release of neurotransmitters such as glutamate, noradrenaline and substance P. It has been suggested that pregabalin exerts its therapeutic effects by reducing the neuronal activation of hyperexcited neurons while leaving normal activation unaffected. The mechanism or mechanisms by which pregabalin produces euphoric effects or induces physical dependence are unknown.

Despite being a chemical analogue of the neurotransmitter gamma aminobutyric acid (GABA), pregabalin does not influence GABA activity via either GABA receptors or benzodiazepine receptors. However, pregabalin has been found to produce effects that are similar to those produced by controlled substances, such as benzodiazepines, that increase GABA activity.

Dependence potential

Tolerance has been shown to develop to the effects of pregabalin, particularly the euphoric effects. A number of published reports have described physical dependence associated with pregabalin use in humans. The withdrawal symptoms that occur following abrupt discontinuation of pregabalin include insomnia, nausea, headaches, anxiety, sweating and diarrhoea. Current evidence suggests that the incidence and severity of withdrawal symptoms may be dose-related and, hence, those taking doses above the normal therapeutic range are most at risk of withdrawal. At therapeutic doses, withdrawal may be minimized by gradual dose tapering.

Actual abuse and/or evidence of likelihood to produce abuse

While some preclinical research using self-administration and conditioned place preference models has shown reinforcing effects of pregabalin, taken as a whole, the results from such research are contradictory and inconclusive.

In clinical trials, patients have reported euphoria, although tolerance develops rapidly to this effect. Human laboratory research is very limited and only a relatively low dose of pregabalin has been tested in a general population sample; the results indicated low abuse liability. However, a higher dose of pregabalin administered to users of alcohol or sedative/hypnotic drugs was rated similar to diazepam, indicative of abuse liability.

Pregabalin is more likely to be abused by individuals who are using other psychoactive drugs (especially opioids), with significant potential of adverse effects among these subpopulations. The adverse effects of pregabalin include dizziness, blurred vision, impaired coordination, impaired attention, somnolence, confusion and impaired thinking. Other reported harms associated with non-medical use of pregabalin include suicidal ideation and impaired driving. Users of pregabalin in a number of countries have sought treatment for dependence on the drug. While pregabalin has been cited as the main cause of death in over 30 documented overdose fatalities, there are very few cases of fatal intoxications resulting from pregabalin use alone and the vast majority of instances involve other central nervous system depressants such as opioids and benzodiazepines.

There is only limited information regarding the scope and magnitude of the illicit trade in pregabalin, but there is evidence of illicit marketing through online pharmacies.

Pregabalin is under national control in many countries across different regions of the world.

Therapeutic applications/usefulness

Pregabalin is used for the treatment of neuropathic pain, including painful diabetic peripheral neuropathy and postherpetic neuralgia, fibromyalgia, anxiety and the adjunctive treatment of partial seizures. The exact indications for which pregabalin has received approval vary across countries. Pregabalin has also been used for conditions such as substance use disorders, alcohol withdrawal syndrome, restless legs syndrome and migraines.

Recommendation

The Committee noted that there has been increasing concern in many countries regarding the abuse of pregabalin. A number of cases of dependence have been reported and there are increasing reports of adverse effects. While these problems are

concentrated in certain drug-using populations, there is presently limited data on the extent of the problems related to pregabalin abuse in the general population. The Committee also noted that pregabalin has approved therapeutic uses for a range of medical conditions, including some for which there are few therapeutic options. Given the limitations in the available information regarding the abuse of pregabalin:

Recommendation 4.1: The Committee recommended that pregabalin (chemical name: (3*S*)-3-(aminomethyl)-5-methylhexanoic acid) should not be scheduled, but should be kept under surveillance by the WHO Secretariat.

4.2 Tramadol

Substance identification

Tramadol (chemical name: (1*R**,2*R**)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexan-1-ol) is a white, bitter, crystalline and odourless powder soluble in water and ethanol. Tramadol is marketed as hydrochloride salt and is available in a variety of pharmaceutical formulations for oral (tablets, capsules), sublingual (drops), intranasal, rectal (suppositories), intravenous, subcutaneous and intramuscular administration. It is also available in combination with acetaminophen (paracetamol). Preparations of tramadol are available as immediate- and extended-release formulations.

World Health Organization review history

Tramadol has been considered for critical review by the Expert Committee on Drug Dependence five times: in 1992, 2000, 2002, 2006 and 2014. Tramadol was pre-reviewed at its thirty-ninth meeting, in November 2017, and it was recommended that tramadol be subject to a critical review at a subsequent meeting. The Committee requested the WHO Secretariat to collect additional data for the critical review, including information on the extent of problems associated with tramadol misuse in countries. The Committee also asked for information on the medical use of tramadol, including the extent to which low-income countries, and aid and relief agencies, used and possibly relied on tramadol for the provision of analgesia. In response to those requests, the WHO Secretariat collected data from Member States and relief agencies on the extent of medical use of tramadol and its misuse and on the level of control implemented in countries.

Similarity to known substances/effects on the central nervous system

Tramadol is a weak opioid analgesic that produces opioid-like effects, primarily due to its metabolite, O-desmethyltramadol (M1). The analgesic effect of tramadol is also believed to involve its actions on noradrenergic and serotonergic receptor systems. The adverse effects of tramadol are consistent with its dual opioid and non-opioid mechanisms of action and they include dizziness, nausea, constipation and headaches. In overdose, symptoms such as lethargy, nausea, agitation, hostility, aggression, tachycardia, hypertension and other cardiac complications, renal complications, seizures, respiratory depression and coma have been reported. Serotonin syndrome (a group of symptoms associated with high concentrations of the neurotransmitter serotonin that include elevated body temperature, agitation, confusion, enhanced reflexes and tremor and might result in seizures and respiratory arrest) is a potential complication of the use of tramadol in combination with other serotonergic drugs. Tramadol has been detected in a number of deaths. It is often present along with other drugs, including opioids, benzodiazepines and antidepressants, but fatalities have also been reported due to tramadol alone.

Dependence potential

Evidence suggests that the development of physical dependence to tramadol is dose-related, and that the administration of supra-therapeutic doses leads to a similar dependence profile as that of morphine and other opioids such as oxycodone and methadone. There are reports of a considerable number of people with tramadol

dependence seeking help. Withdrawal symptoms include those typical of opioids, such as pain, sweating, diarrhoea and insomnia, as well as symptoms not normally seen with opioids and related to noradrenergic and serotonergic activity, such as hallucinations, paranoia, confusion and sensory abnormalities. Low-dose tramadol use over extended periods is associated with a lower risk of dependence.

Actual abuse and/or evidence of likelihood of abuse

Consistent with its opioid mechanism of action, human brain imaging has shown that tramadol activates brain reward pathways associated with abuse. While reports from people who have been administered tramadol in controlled settings have shown that it is identified as opioid-like, and tramadol has reinforcing effects in experienced opioid users, these effects may be weaker than those produced by opioids such as morphine and may be partially offset by the unpleasant effects of tramadol such as sweating, tremors, agitation, anxiety and insomnia.

Abuse, dependence and overdose from tramadol have emerged as serious public health concerns in countries across several regions. Epidemiological studies in the past have reported a lower tendency for tramadol misuse when compared with other opioids, but more recent information indicates a growing number of people abusing tramadol, particularly in a number of Middle Eastern and African countries. The sources of tramadol include diverted medicines as well as falsified medicines containing high doses of tramadol. Seizures of illicitly trafficked tramadol, particularly in African countries, have risen dramatically in recent years.

The oral route of administration has been the predominant mode of tramadol abuse as it results in a greater opioid effect compared with other routes. It is unlikely that tramadol will be injected to any significant extent. Abuse of tramadol is likely to be influenced by genetic factors; some people will experience a much stronger opioid effect following tramadol administration compared with others. The genotype associated with a stronger opioid effect following tramadol administration occurs at different rates in populations across different parts of the world.

Many countries have placed tramadol under national control.

Therapeutic applications/usefulness

Tramadol is used to treat both acute and chronic pain of moderate to severe intensity. The conditions for which tramadol has been used include osteoarthritis, neuropathic pain, chronic lower back pain, cancer pain and postoperative pain. It has also been used for the treatment of restless legs syndrome and opioid withdrawal management. As is the case with abuse potential, the analgesic efficacy and the nature of adverse effects experienced are strongly influenced by genetic factors. Systematic reviews have reported that the ability of tramadol to control chronic pain such as cancer pain is less than optimal, and its use is associated with a relatively high prevalence of adverse effects.

Tramadol is listed on the national essential medicines lists of many countries across diverse regions, but it is not listed on the WHO Lists of Essential Medicines.

As an opioid analgesic available in generic forms that is not under international control, tramadol is widely used in many countries where access to other opioids for the management of pain is limited. It is also used extensively by international aid organizations in emergency and crisis situations for the same reasons.

Recommendations

The Committee was concerned by the increasing evidence of tramadol abuse in a number of countries in diverse regions, in particular the widespread abuse of tramadol in many low- to middle-income countries. Equally concerning was the clear lack of alternative analgesics for moderate to severe pain for which tramadol is used. The Committee was strongly of the view that the extent of abuse and evidence of public health risks associated with tramadol warranted consideration of scheduling, but the

Committee recommended that tramadol not be scheduled at this time in order that access to the medication not be adversely impacted, especially in countries where tramadol may be the only available opioid analgesic or in crisis situations where there is very limited or no access at all to other opioids.

The Committee also strongly urged WHO and its partners to address, as a high priority, the grossly inadequate access and availability of opioid pain medication in low-income countries. WHO and its partners are also strongly encouraged to update and disseminate WHO pain management guidelines and to support both country-specific capacity-building needs and prevention and treatment initiatives in order to address the tramadol crisis in low-income countries. The Committee recommended that WHO and its partners support countries in strengthening their regulatory capacity and mechanisms for preventing the supply and use of falsified and substandard tramadol.

Recommendation 4.2: The Committee recommended that the WHO Secretariat continue to keep tramadol under surveillance and collect information on the extent of problems associated with tramadol misuse in countries and on its medical use, and that it be considered for review at a subsequent meeting.