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

**Summary of assessments, findings and recommendations
of the 45th World Health Organization's (WHO)
Expert Committee on Drug Dependence (ECDD),
10–13 October 2022***

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45th WHO ECDD summary assessments, findings and recommendations, 10–13 October 2022

Substances to be added to Schedule I of the Single Convention on Narcotic Drugs (1961)

2-Methyl-AP-237

Substance identification

2-Methyl-AP-237 (IUPAC chemical name: 1-[2-Methyl-4-(3-phenyl-2-propen-1-yl)-1-piperazinyl]-1-butanone) is a methyl derivative of the opioid analgesic AP-237 (or bucinnazine).

2-Methyl-AP-237 has been described as a white crystalline powder, a crystalline solid and a white solid.

WHO review history

2-Methyl-AP-237 has been under WHO surveillance but has not been formally reviewed by WHO, and is not currently under international control. Information was brought to the attention of WHO 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 the central nervous system

2-Methyl-AP-237 is an opioid analgesic with a rapid onset of action and a potency and analgesic effects similar to those of fentanyl, which is listed under Schedule I of the Single Convention on Narcotic Drugs, 1961. In animals, it produces acute toxic effects typical of opioids, including respiratory depression. Limited research has been reported on the effects of 2-methyl-AP-237 in humans, although its respiratory depressant effects have been observed, which can be reversed by the opioid antagonist, naloxone.

Dependence potential

No controlled studies of the dependence potential of 2-methyl-AP-237 have been reported in animals or humans. As it is a μ -opioid receptor agonist, it would be expected to produce dependence similar to that induced by other opioids, such as morphine and fentanyl. Online self-reports described tolerance and withdrawal.

Actual abuse and/or evidence of likelihood of abuse

In an animal model predictive of abuse potential, 2-methyl-AP-237 was shown to produce opioid-like effects with a potency between those of morphine and fentanyl. These effects were blocked by the opioid antagonist, naltrexone.

No controlled studies on the abuse potential of 2-methyl-AP-237 in humans have been reported, but, as it is a μ -opioid receptor agonist, it would be expected to produce euphoria and other effects predictive of high abuse liability. Online self-reports support its euphoric and other opioid effects.

Seizures of 2-methyl-AP-237 have been reported in multiple countries in two regions.

A number of deaths in which 2-methyl-AP-237 has been found have been reported, often with multiple substances involved. The deaths occurred in a number of countries and regions.

Therapeutic usefulness

2-Methyl-AP-237 is not known to have any therapeutic use.

Recommendation

2-Methyl-AP-237 (IUPAC chemical name: 1-[2-Methyl-4-(3-phenyl-2-propen-1-yl)-1-piperazinyl]-1-butanone) is a synthetic opioid that is liable to abuse and to have ill effects similar to those of other 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 2-methyl-AP-237 (IUPAC chemical name: 1-[2-Methyl-4-(3-phenyl-2-propen-1-yl)-1-piperazinyl]-1-butanone) be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

Etazene

Substance identification

Etazene (IUPAC chemical name: 2-[(4-ethoxyphenyl)methyl]-*N,N*-diethyl-1*H*-benzimidazole-1-ethanamine), also known as etodesnitazene, is a benzimidazole-derived synthetic opioid. Etazene has been described as a grey crystalline, light-yellow, white or beige powder. It has also been identified in liquid form and in falsified pharmaceutical opioids.

WHO review history

Etazene has not been formally reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO 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 the central nervous system

Etazene binds to the μ -opioid receptor with a potency greater than that of morphine. In studies of analgesia in animals, etazene had full agonist effects, with a potency between those of morphine and fentanyl, which are both controlled under Schedule I of the Single Convention on Narcotic Drugs, 1961. The effects of etazene are reversed by the opioid antagonist, naltrexone.

Dependence potential

No controlled studies of the dependence potential of etazene in animals or in humans have been reported. As it is a potent μ -opioid receptor agonist, it would be expected to produce dependence similar to other opioids, such as morphine and fentanyl. Online self-reports described tolerance with repeated use of etazene.

Actual abuse and/or evidence of likelihood of abuse

In an animal model predictive of abuse potential, etazene had effects similar to those of morphine. No controlled studies have been conducted of the abuse potential of etazene in humans, but, as it is a potent μ -opioid receptor agonist, it would be expected to produce euphoria and other effects predictive of high abuse liability. Online self-reports support its euphoric and other opioid effects.

Seizures of etazene have been reported in multiple countries in two regions.

A number of deaths have occurred in which the presence of etazene was confirmed analytically and in which it was considered to have contributed to death, although other substances were also identified in these cases.

Therapeutic usefulness

Etazene is not known to have any therapeutic use.

Recommendation

Etazene (IUPAC chemical name: 2-[(4-ethoxyphenyl)methyl]-*N,N*-diethyl-1*H*-benzimidazole-1-ethanamine), also known as etodesnitazene, is a synthetic opioid that is liable to abuse and produces ill effects similar to other 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 poses a significant risk to public health.

Recommendation: The Committee recommended that etazene (IUPAC chemical name: 2-[(4-ethoxyphenyl)methyl]-*N,N*-diethyl-1*H*-benzimidazole-1-ethanamine), also known as etodesnitazene, be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

Etonitazepyne

Substance identification

Etonitazepyne (IUPAC chemical name: 2-[(4-ethoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1*H*benzimidazole), also known as *N*-pyrrolidino etonitazene, is a benzimidazole-derived synthetic opioid. Etonitazepyne is found as a yellow powder and crystalline solid and has been identified in falsified pharmaceutical opioid tablets.

WHO review history

Etonitazepyne has not been formally reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO 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 the central nervous system

Studies in animals have demonstrated that etonitazepyne is a potent, full agonist at μ -opioid receptors. In animals, it produces effects similar to those of opioids such as morphine, fentanyl and isotonitazene but with greater potency. There is limited information about the effects of etonitazepyne alone in humans.

Dependence potential

No controlled studies of the dependence potential of etonitazepyne in animals or humans have been reported. As it is a potent μ -opioid receptor agonist, it would be expected to produce dependence similarly to other opioids, such as morphine and fentanyl. Online self-reports describe tolerance and withdrawal after repeated etonitazepyne use.

Actual abuse and/or evidence of likelihood of abuse

In an animal model predictive of abuse potential, etonitazepyne was shown to produce effects that indicated greater potency compared to morphine and fentanyl, and these effects were reversed by the opioid antagonist, naltrexone.

Seizures of etonitazepyne have been reported in multiple countries in two regions. It is reported to be administered by various routes, including snorting, sniffing and oral administration. Etonitazepyne has been identified in falsified medicines, suggesting that its use may sometimes be unintentional.

Etonitazepyne is a relatively new drug on the illicit market, and there is limited information on the prevalence of its use and of its harm, although non-fatal and fatal intoxications have been documented in a number of countries. The number of deaths involving etonitazepyne has increased over a relatively short time but may be underreported because of its recent, rapid appearance.

Therapeutic usefulness

Etonitazepyne is not known to have any therapeutic use.

Recommendation

Etonitazepyne (IUPAC chemical name: 2-[(4-ethoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1*H*benzimidazole), also known as *N*-pyrrolidino etonitazene, is a synthetic opioid that is liable to abuse and to produce ill effects similar to other 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 poses a significant risk to public health.

Recommendation: The Committee recommended that etonitazepyne (IUPAC chemical name: 2-[(4-ethoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1H-benzimidazole), also known as *N*-pyrrolidino etonitazene, be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

Protonitazene

Substance identification

Protonitazene (IUPAC chemical name: *N,N*-Diethyl-5-nitro-2-[(4-propoxyphenyl)methyl]-1*H*-benzimidazole-1-ethanamine), also known as propoxynitazene, is a 5-nitro-2-benzylbenzimidazole synthetic opioid. Protonitazene has been described as a white, yellow or brown powder and as a crystalline solid.

WHO review history

Protonitazene has not been formally reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO 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 the central nervous system

Protonitazene is a chemical analogue of metonitazene and etonitazene, which are controlled under Schedule I of the Single Convention on Narcotic Drugs of 1961. Studies in animals have demonstrated that protonitazene is a full agonist at μ -opioid receptors, with greater potency than morphine and similar potency to fentanyl. Its effects are blocked by the opioid antagonist, naltrexone.

Dependence potential

No controlled studies of the dependence potential of protonitazene in animals or humans have been reported. As it is a potent μ -opioid receptor agonist, it would be expected to produce dependence similar to other opioids such as morphine and fentanyl.

Actual abuse and/or evidence of likelihood of abuse

In animals, protonitazene showed potent opioid effects and abuse potential, similar to those of morphine and fentanyl. Its abuse potential has not been studied in humans; however, online self-reports indicate typical opioid effects, including sedation and euphoria.

Protonitazene is relatively new on the illicit drug market, and there is limited information on the prevalence of its use or of its harm. The only available information is that several fatalities have occurred in which the presence of protonitazene was confirmed, usually with other substances. The number of deaths may be underreported because of limitations in testing, including difficulty in differentiating this substance from isotonitazene.

Protonitazene is reported to be administered through various routes, including intranasally and intravenously. Seizures of protonitazene have been reported in multiple countries in two regions.

Therapeutic usefulness

Protonitazene is not known to have any therapeutic use.

Recommendation

Protonitazene (IUPAC chemical name: *N,N*-Diethyl-5-nitro-2-[(4-propoxyphenyl)methyl]-1*H*-benzimidazole-1-ethanamine), also known as propoxynitazene, is a synthetic opioid that is liable to abuse and to produce ill effects similar to other 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 protonitazene (IUPAC chemical name: *N,N*-Diethyl-5-nitro-2-[(4-propoxyphenyl)methyl]-1*H*-benzimidazole-1-ethanamine), also known as propoxynitazene, 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)

ADB-BUTINACA

Substance identification

ADB-BUTINACA (IUPAC chemical name: *N*-[1-(aminocarbonyl)-2,2-dimethylpropyl]-1-butyl-1*H*-indazole-3-carboxamide) is an indazole-derived synthetic cannabinoid. It is described as a crystalline solid or a beige or yellowish powder and has also been found sprayed onto plant material and paper. It is commonly smoked or vaped, although isolated cases of oral use have also been reported.

WHO review history

ADB-BUTINACA has not been formally reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO 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 the central nervous system

ADB-BUTINACA is a synthetic cannabinoid that binds to CB₁ and CB₂ receptors with high affinity and is a potent full agonist at both receptors. Its effects are similar to those of other potent CB₁ agonists that are currently controlled under Schedule II of the Convention on Psychotropic Substances of 1971.

No controlled studies of the effects of ADB-BUTINACA have been reported. Online self-reports describe euphoria, appetite stimulation, sedation and paranoia after its use. These effects are consistent with the known effects of cannabinoid agonists.

Dependence potential

No controlled studies of the dependence potential of ADB-BUTINACA in animals or humans have been reported. However, its effects at the CB₁ receptor suggest that it would be expected to produce dependence similar to other synthetic cannabinoids.

Actual abuse and/or evidence of likelihood of abuse

In an animal model predictive of abuse potential, ADB-BUTINACA had effects similar to the CB₁ receptor agonist *delta*-9-tetrahydrocannabinol. No studies have been conducted to determine the likelihood of abuse of ADB-BUTINACA in humans; however, CB₁ receptor agonists have known abuse potential.

A number of countries in various regions have reported use of ADB-BUTINACA and harm related to its use, including multiple deaths and presentations of patients to emergency departments with altered consciousness and loss of consciousness. Other substances were usually also involved in these cases, although a number of deaths involved only ADB-BUTINACA.

Therapeutic usefulness

ADB-BUTINACA is not known to have any therapeutic use.

Recommendation

ADB-BUTINACA (*N*-[1-(aminocarbonyl)-2,2-dimethylpropyl]-1-butyl-1*H*-indazole-3-carboxamide) is a potent synthetic cannabinoid receptor agonist with a mechanism of action and effects similar to those of a number of other synthetic cannabinoids that are controlled under Schedule II of the Convention on Psychotropic Substances of 1971. Its mode of action suggests the likelihood of abuse and potential for dependence. Use of

ADB-BUTINACA has been associated with severe adverse effects, including fatal intoxications. ADB-BUTINACA has no known therapeutic use.

Recommendation: The Committee recommended that ADB-BUTINACA (*N*-[1-(aminocarbonyl)-2,2-dimethylpropyl]-1-butyl-1*H*-indazole-3-carboxamide) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

Alpha-PiHP

Substance identification

Alpha-pyrrolidinoisohexanophenone (IUPAC chemical name: 4-Methyl-1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one), also known as *alpha*-PiHP, is a synthetic cathinone. It has been described as an off-white solid, a white powder and a crystalline solid.

WHO review history

Alpha-PiHP has been under WHO surveillance but has not been formally reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO 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 the central nervous system

Alpha-PiHP is an isomer of *alpha*-PHP, which is controlled under Schedule II of the Convention on Psychotropic Substances of 1971. Laboratory studies suggest that *alpha*-PiHP can inhibit the uptake of dopamine and norepinephrine more potently than substances with known abuse potential, including methcathinone, cocaine and methamphetamine. Studies in animals have shown that *alpha*-PiHP is a psychomotor stimulant, with effects comparable to those of cocaine and methamphetamine.

Online self-reports by people who use *alpha*-PiHP describe stimulant effects similar to those of *alpha*-PVP and *alpha*-PHP.

Dependence potential

No controlled studies of the dependence potential of *alpha*-PiHP in animals or humans have been reported. In view of its actions and effects on the central nervous system, it would be expected to produce dependence similarly to other psychostimulants such as methamphetamine.

Actual abuse and/or evidence of likelihood of abuse

Studies in animals predictive of abuse liability indicate that *alpha*-PiHP produces effects similar to those of methamphetamine and cocaine. No controlled studies of the abuse potential of *alpha*-PiHP in humans have been reported.

Seizures of *alpha*-PiHP have been described in multiple countries in three regions.

Alpha-PiHP has been identified in a number of serious adverse events and drug-related deaths. As it is usually detected with other substances, including opioids and benzodiazepines, the role of *alpha*-PiHP is unclear in some instances.

Therapeutic usefulness

Alpha-PiHP is not known to have any therapeutic use.

Recommendation

Alpha-pyrrolidinoisohexanophenone (IUPAC chemical name: 4-Methyl-1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one), also known as *alpha*-PiHP, is a synthetic cathinone with effects similar to those of other synthetic cathinones and other psychostimulants, such as methamphetamine, that are listed under Schedule II of the Convention on Psychotropic Substances of 1971. There is evidence that its abuse is likely to constitute a substantial public health and social problem. It has no known therapeutic use.

Recommendation: The Committee recommended that *alpha*-pyrrolidinoisohexanophenone (IUPAC chemical name: 4-Methyl-1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one), also known as *alpha*-PiHP, be added to Schedule II of the 1971 Convention on Psychotropic Substances.

3-Methylmethcathinone

Substance identification

3-Methylmethcathinone (IUPAC chemical name: 2-(methylamino)-1-(3-methylphenyl)propan-1-one), also known as 3-MMC, is a synthetic cathinone. 3-Methylmethcathinone has been found as a white or off-white powder, a white, yellow or orange solid and a crystalline solid. It has been detected in tablet, capsule and liquid forms.

WHO review history

3-Methylmethcathinone was critically reviewed by the Committee at its 38th meeting, in 2016, when it decided to request a further critical review once more information became available and to consider it at a subsequent meeting. Information was brought to the attention of WHO that this substance is manufactured clandestinely, poses a risk to public health and has no recognized therapeutic use. Information from international agencies suggests that there has been a significant increase in the availability of and harm due to 3-methylmethcathinone in recent years.

Similarity to known substances and effects on the central nervous system

3-Methylmethcathinone is an isomer of 4-methylmethcathinone (mephedrone), which is a synthetic cathinone listed under Schedule II of the Convention on Psychotropic Substances of 1971.

3-Methylmethcathinone has a typical psychostimulant profile, similar to that of 4-methylmethcathinone, including inhibition of the reuptake of dopamine, norepinephrine and serotonin and increased release of dopamine and serotonin.

Clinical features of 3-methylmethcathinone intoxication are consistent with those produced by other stimulants and include tachycardia, hypertension, agitation, aggression, hallucinations, rhabdomyolysis and kidney failure.

Dependence potential

No controlled studies of the dependence potential of 3-methylmethcathinone in animals or humans have been reported. Withdrawal symptoms indicative of physical dependence have been documented in people who use 3-methylmethcathinone. In view of its actions and effects on the central nervous system, 3-methylmethcathinone would be expected to produce dependence similar to other psychostimulants, such as methamphetamine.

Actual abuse and/or evidence of likelihood of abuse

In animal models predictive of rewarding effects, 3-methylmethcathinone produced effects that were similar to those of methamphetamine. 3-Methylmethcathinone also produced behavioural (stimulant) effects similar to methamphetamine. No controlled studies in humans have examined the abuse potential of 3-methylmethcathinone.

3-Methylmethcathinone has been seized in multiple countries in several regions.

Many fatal and non-fatal intoxications involving 3-methylmethcathinone have been reported. Other substances were commonly involved in these cases, although severe intoxication and death have been reported in cases in which 3-methylmethcathinone was the only substance identified.

Therapeutic usefulness

3-Methylmethcathinone is not known to have any therapeutic use.

Recommendation

3-Methylmethcathinone (IUPAC chemical name: 2-(methylamino)-1-(3-methylphenyl)propan-1-one), also known as 3-MMC, is a synthetic cathinone with effects similar to those of other synthetic cathinones and other psychostimulants such as methamphetamine that are listed under Schedule II of the Convention on Psychotropic Substances of 1971. There is evidence that its abuse is likely to constitute a substantial public health and social problem. It has no known therapeutic use.

Recommendation: The Committee recommended that 3-Methylmethcathinone (IUPAC chemical name: 2-(methylamino)-1-(3-methylphenyl)propan-1-one), also known as 3-MMC, be added to Schedule II of the Convention on Psychotropic Substances of 1971.

Substances to be kept under surveillance:

Adinazolam

Substance identification

Adinazolam (IUPAC chemical name: 8-Chloro-*N,N*-dimethyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3- α][1,4]benzodiazepine-1-methanamine) is a triazolobenzodiazepine. Adinazolam appears as a white or yellow powder and is also sold as tablets and capsules, including as falsified pharmaceuticals.

WHO review history

Adinazolam has not been formally reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO 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 the central nervous system

Adinazolam is a short-acting benzodiazepine with moderate affinity for the benzodiazepine receptor. It is a chemical analogue of alprazolam and triazolam.

Consistent with its benzodiazepine receptor action, adinazolam showed anticonvulsant, anxiolytic and antidepressant properties in animals. In humans, adinazolam (and its metabolite *N*-desmethyladinazolam) produced a dose-dependent decrease in psychomotor performance and increased sedation and amnesia. It also had some subjective effects similar to those of benzodiazepines such as diazepam and lorazepam, which are controlled under Schedule IV of the 1971 Convention on Psychotropic Substances.

Dependence potential

No studies have been conducted in animals or humans on the dependence potential of adinazolam. In view of its mechanism of action, however, it would be expected to produce typical benzodiazepine dependence.

Actual abuse and/or evidence of likelihood of abuse

In animals, adinazolam shows behavioural effects consistent with those of drugs with abuse liability. In controlled studies in humans, adinazolam produced sedation, and, in one controlled study, adinazolam produced a self-reported "high" feeling, with a greater estimated street value than placebo.

While seizures of adinazolam have been reported in a few countries in two regions, currently there is insufficient evidence that it is being abused to such an extent as to constitute a public health problem.

Adinazolam was identified in a few drug-related deaths in combination with other psychoactive substances, including opioids and other benzodiazepines; however, there was no evidence that adinazolam played a causative role in these deaths.

Therapeutic usefulness

Adinazolam is not known to have any therapeutic use.

Recommendation

Adinazolam (IUPAC chemical name: 8-Chloro-*N,N*-dimethyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3- α][1,4]benzodiazepine-1-methanamine) has effects similar to those of substances listed under Schedule IV of the Convention on Psychotropic Substances of 1971. There is, however, insufficient evidence that its use is a public health and social problem to justify its placement under international control.

Recommendation: The Committee recommended that adinazolam (IUPAC chemical name: 8-Chloro-*N,N*-dimethyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3- α][1,4]benzodiazepine-1-methanamine) be kept under surveillance by the WHO Secretariat.

Bromazolam

Substance identification

Bromazolam (8-Bromo-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3- α][1,4]benzodiazepine) is a triazolobenzodiazepine. Bromazolam has been described as a white or crystalline solid and has been identified in tablets, capsules, powders, solutions and edible products. Bromazolam has been identified in falsified pharmaceutical benzodiazepine products.

WHO review history

Bromazolam has not been formally reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO 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 the central nervous system

There is currently insufficient information on the pharmacological profile of bromazolam from controlled studies in animals or humans to conclude that it has effects similar to those of benzodiazepines, which are controlled under the 1971 Convention on Psychotropic Substances.

Online self-reports by people who claim to have used bromazolam describe benzodiazepine-like effects, including hypnotic, sedative, muscle relaxant and euphoric effects. There are, however, no clinical reports or analytical confirmation of bromazolam to confirm these effects.

Dependence potential

No controlled studies in animals or humans have been reported on the dependence potential of bromazolam. Online self-reports describe withdrawal symptoms after cessation of chronic use.

Actual abuse and/or evidence of likelihood of abuse

No controlled studies in animals or humans have been reported on the abuse liability of bromazolam. In self-reports online, people have described using the drug for its euphoric and other benzodiazepine-like effects; however, there is no confirmation that that the substance used was bromazolam.

Seizures of bromazolam have been reported in multiple countries in several regions.

Bromazolam has been analytically confirmed in a number of deaths, non-fatal intoxications and instances of driving under the influence of drugs. Because of the presence of other drugs, especially other benzodiazepines, however, the contribution of bromazolam cannot be determined.

Therapeutic usefulness

Bromazolam is not known to have any therapeutic uses and has never been marketed as a medicinal product.

Recommendation

While the chemical structure of bromazolam (8-Bromo-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3- α][1,4]benzodiazepine) is similar to those of other benzodiazepines listed under the Convention on Psychotropic Substances of 1971, its mechanism of action and effects are yet to be confirmed. Although there

is increasing evidence of its use, no studies in animals or humans have been reported on the effects or abuse potential of bromazolam. The limited information on its effects provides insufficient evidence to justify placement of bromazolam under international control.

Recommendation: The Committee recommended that bromazolam (8-Bromo-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine) be kept under surveillance by the WHO Secretariat.

Zopiclone

Substance identification

Zopiclone (IUPAC chemical name: 6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazin-5-yl 4-methylpiperazine-1-carboxylate) is a sedative hypnotic drug of the cyclopyrrolone class. Zopiclone has been reported as a white or slightly yellowish powder. Zopiclone is available as pharmaceutical products in tablet form for oral use. Eszopiclone (the *S*-enantiomer of zopiclone) is marketed as a pharmaceutical product in some countries.

WHO review history

Zopiclone was pre-reviewed by the Committee at its 29th meeting, when it recommended that surveillance be continued but that a critical review was not required. In view of the abuse liability of the drug and the significant number of reports of adverse drug reactions related to zopiclone abuse sent to the WHO international drug monitoring programme, however, zopiclone was pre-reviewed by the Committee at its 33rd meeting, when it recommended a critical review. Zopiclone was critically reviewed at the 34th meeting, in 2006, when the Committee rated its abuse liability as low and its therapeutic usefulness considerable and recommended continued surveillance by WHO. A pre-review was initiated after a proposal was received from an international agency that suggested a significant increase in the reported number of trafficking cases and seizures involving zopiclone.

Similarity to known substances and effects on the central nervous system

Zopiclone binds to the benzodiazepine receptor that forms part of the GABA_A receptor complex. It may bind to different parts of the receptor or cause different changes in the GABA_A receptor complex than benzodiazepines.

In animals, zopiclone has sedative, anxiolytic, anticonvulsant and muscle relaxant properties similar to those of benzodiazepines. In studies in humans, it was less effective than benzodiazepines for treatment of anxiety.

Dependence potential

Studies in animals show evidence of zopiclone tolerance and withdrawal, indicating the development of physical dependence. A number of published reports have described physical dependence associated with zopiclone use in humans. Withdrawal symptoms such as increased anxiety and insomnia have been described in people who cease zopiclone use, usually after prolonged use and dose escalation from clinical use. Tolerance and withdrawal have also been reported in clinical trials. Dependence is documented in databases on adverse events associated with pharmaceutical use.

Actual abuse and/or evidence of likelihood of abuse

Studies in animals suggest that zopiclone may have abuse liability similar to that of benzodiazepines such as midazolam, diazepam, nitrazepam and alprazolam. The effects indicative of abuse liability were blocked by the benzodiazepine antagonist flumazenil, indicating a mechanism of action involving the benzodiazepine receptor.

No controlled studies in humans have been reported on the abuse potential of zopiclone. Published reports describe effects consistent with benzodiazepine-like abuse potential, its use with alcohol and other drugs and escalation to high-dose use. The extent of harm related to the use of zopiclone is, however, unclear.

Zopiclone is widely used therapeutically in many countries and regions, and it is also listed in databases of adverse events associated with pharmaceutical use. Zopiclone is most likely to be misused by individuals to whom it is prescribed for long periods, who are using other psychoactive drugs or in those with psychiatric comorbidities. While seizures of zopiclone have been reported in multiple countries in several regions, the prevalence of non-medical use of zopiclone by the general population is unknown. Furthermore, there is insufficient evidence that significant public health and social problems related to abuse can be directly attributed to sole use of zopiclone.

Therapeutic usefulness

Zopiclone is a widely used medicine primarily indicated for the short-term treatment of insomnia, with marketing authorisations in many countries. It is not listed on the WHO Model List of Essential Medicines.

Recommendation

Zopiclone (IUPAC chemical name: 6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-yl 4-methylpiperazine-1-carboxylate) is a sedative hypnotic drug of the cyclopyrrolone class. The Committee noted that concern has been expressed in several countries regarding non-prescription use of zopiclone. While there have been reports of adverse effects, overdose, withdrawal symptoms and an increased number of seizures of the substance, there is still insufficient evidence that zopiclone is or is likely to be abused to such an extent as to constitute a public health and social problem.

The Committee also noted that zopiclone is widely used therapeutically in many countries.

Recommendation: The Committee recommended that zopiclone (IUPAC chemical name: 6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-yl 4-methylpiperazine-1-carboxylate) not proceed to critical review but be kept under surveillance by the WHO Secretariat.