Journal of
Antivirals & Antiretrovirals

von Hentig, J Antivir Antiretrovir 2016, 8:2
DOI: 10.4172/jaa.1000e131

Editorial Open Access

Potential Drug Interactions Between cART and New Psychoactive Substances

Nils von Hentig*

HIV Center, Medical Department II, Hospital of the J.W. Goethe University, Frankfurt am Main, Germany

Introduction

So-called designer drugs are drugs with so far unknown synthetic chemical structures or structures of known entities that have been changed in order to avoid prosecution. In the past years, a number of these substances emerged on the European (and US) drug market: 164 new psychoactive substances have been reported by the European rapid alert system of the EMCDDA (European Monitoring Center for Drugs and Drug Addiction) between 2005 and 2014. Synthetic cannabinoids and synthetic phenylethylamine/ cathinones are responsible for about two thirds of all new substances but also a number of substances of rather rare occurrence were seized. Often, the molecular structure of common narcotics is changed, so that law prosecution doesn´t take effect, but drug effects remain or are even increased. These drugs are marketed as legal highs, research chemicals, herbal mixtures, air refreshers, bath salt or even plant fertilizer without showing the ingredients or chemical structures. The manufacturers give the impression that these drugs are safe and nonhazardous.

In contrast to that, these drugs can have harmful side effects such as circulatory collapse, syncope, paralysis, psychosis or even death [1].

Besides the already well-known metamphetamines and mephedrone, in particular six new substances have gained in importance during the past 10 years. Most of these have not been subject to law enforcement until at least 2014 (Table 1).

The new "Legal-Highs"

Whereas ketamine, GHB or metamphetamine are probably well known by the majority of HIV- therapists, it may be worthwhile focusing on drugs that have reached the "market" during the past two years: MT-45, 4,4´-DMAR, MDPV, Methoxetamin, 25I-NBOMe und AH-7921 [1,2].

MT-45

MT-45 (alias IC-6) is typically applied orally or via nasal insufflation, the gas of the heated free base can be inhaled, the water-soluble hydrochloride-salt can be injected i.v. One single dose amounts between 15-30 mg (nasal) and 25-75 mg (oral). Users often take more than one dose consecutively. Effects occur 15 (nasal) to 60 (oral) minutes after intake and last about 2 hours. The effect corresponds to other opioids and estimates a magnitude of ~0.8 in correlation to morphine. MT-45 causes no euphoria but sedation and a potent analgesic effect is stated by consumers.

Substanz (engl.)	Jahr	Name
1-cyclohexyl-4-(1, 2-diphenylethyl) piperazine	2014	MT-45
4-methyl-5-(4-methylphenyl)-4, 5-dihydrooxazol-2-amine (4, 4′-dimethylaminorex, 4, 4′-DMAR)	2014	4,4´-DMAR
1-(1, 3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one	2014	MDPV
2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone	2014	Methoxetamin
2-(4-iodo-2, 5-dimethoxyphenyl)-N-(2-methoxybenzyl) ethanamine	2014	25I-NBOMe
3, 4-dichloro-N-{[1-(dimethylamino)cyclohexyl]methyl} benzamide	2014	AH-7921
N,α-dimethylbenzeneethanamine (alt: 4-methylamphetamine)	2014	Methamphetamin
4-methylmethcathinon	2011	Mephedron

Table 1: New psychoactive substances, of which the first six are not underlying law enforcement until at least 2014.

There are no data existing about the pharmacokinetics of MT-45 and so far, no metabolites of the degradation in human organisms have been identified. The racemic formulation of MT-45 has the same opioid effects as the single (S)- and (R)-enantiomeres, whereat the (S)-enantiomer is several times more potent than morphine. MT-45 works as an agonist of the κ- and δ-opioid-receptors with much higher affinity than morphine itself. The acute adverse effects are obvious and are especially constipation and respiratory depression. The acute toxicity of MT-45 is much higher in correlation to morphine, especially after intravenous injection [3,4].

4,4´-DMAR

Regularly, 4,4´-DMAR (street name is chemically incorrect "Aminorex") has been detected as addition to ecstasy tablets or as blend of cocaine sold in the street. The application route is usually nasal or oral and a typical dose amounts to 10-60 mg, single cases reported of the intake of up to 200 mg [5].

There are no data existing about the pharmacokinetics of 4,4´-DMAR and so far, no metabolites of the degradation in human organisms have been identified.

Up to date, the pharmacology has only been evaluated in *in vitro* studies and could show that 4,4´-DMAR even in very low concentrations in the CNS increases the release of dopamine (DA, EC50 8.6), norepinephrine (NE, EC50 26.9 nM) und serotonin (5-HT, EC50 18.5 nM) [6].

Although studies in humans are lacking, 4,4`-DMAR most probably interacts pharmacodynamically with SSRI, MDMA or cocaine. Especially, it indicates the danger of developing a serotonin-syndrome. High doses and/or the concomitant application with other catecholamine-releasing drugs in the CNS lead to psychotic symptoms, agitation and potentially hazardous cardiovascular events via norepinephrine-release in the periphery. Consumers report about euphoria, mental and physical stimulation, empathic effects or

***Corresponding author:** Nils von Hentig, HIV Center, Johann Wolfgang Goethe University, Theodor-Stern-Kai 7, 60590 Frankfurt am Main, Germany, Tel: 069-6301-7680; E-mail: Hentig@em.uni-frankfurt.de

Received March 25, 2016; **Accepted** March 26, 2016; **Published** March 30, 2016

Citation: von Hentig N (2016) Potential Drug Interactions Between cART and New Psychoactive Substances. J Antivir Antiretrovir 8: LXIV-LXVIII. doi:10.4172/jaa.1000e131

Copyright: © 2016 von Hentig N. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

changes of visual perception. In 2014, 31 fatal casualties were registered throughout Europe, especially caused by hyperthermia, convulsions, respiratory problems and cardiac arrest [6-9].

MDPV

MDPV (street names Flakka, Flex, Cloud Nine, Monkey Dust, MTV, Magic, Super Coke, Peevee) is one of more than 50 cathinones, which have been reported by the EMCDDA in the past years; other examples are mephedrone (4-MMC) and methylone (bk-MDMA). MDPV is marketed typically as bath salt, which can be solved in water and injected i.v. or subcutaneously. There also exist tablet- and capsule-formulations and sometimes rectal application or nasal insufflation. Common doses are 5-11 mg (insufflation), 8-15 mg (oral) and 6-12 mg (rectal). The wanted effects occur about 30 minutes after intake and last 2 to 7 hours.

MDPV inhibits selectively the catecholamine uptake (via dopamine transporter, DAT, or norepinephrine transporter, NET), while serotonin uptake is less affected [10]. In animal models, the effects of MDPV lasted much longer than those of cocaine [11,12].

Phase-1 metabolism, which was found in animal and *in vitro* studies include demthylation, followed by methylation, aromatic side chain-hydroxylation and oxidation of the pyrrolidine to its corresponding lactam and the opening of the cycle to a carboxyl acid [13-16]. No data exist about the biological activity of these metabolites.

When seized, MDPV was found often blended with lidocaine, procaine, piracetam, trimethoprim or diltiazem as well as cocaine, ketamine, methamphetamine, TFMPP, BZP, mephedrone, methylone, 4-MEC, MDPBP, alpha-PVP and synthetic cannabinoids. Results of various *in vitro* and *in vivo* animal studies show an effect on behavior comparable to cocaine or methamphetamine.

The pharmacological key mechanism is the inhibition of catecholamine transporters as mentioned above, whereas MDPV is 10-50 times more potent in this regard than cocaine. MDPV e.g. increased the dopamine concentration in CNS structures of rats significantly, leading to hyperthermia and hypertonia.

The hepatic metabolism of MDPV involves the cytochrome oxidases (CYP) 2C19, 2D6 and 1A2 [16], which has importance regarding genetic polymorphisms in the expression of the cytochromes in humans as well as potential DDIs (Table 2).

The typical effects are comparable to those of cocaine, amphetamines and mephedrone and are shown in Table 2 [17]. There also have been reports about malignant hyperthermia, rhabdomyolysis, renal failure and stroke [18-21]. 108 fatal casualties have been reported in the EU until 2014 in relation to the use of MDPV [22].

Methoxetamin

Regarding its structure, methoxetamine is comparable to ketamine [23-25]. Usually methoxetamine is applicated via nasal insufflation, orally taken but can also be solved in water and injected i.m. or i.v.

An *in vitro* study could show that methoxetamine like ketamine is affine to the NMDA-(*N*-methyl-D-aspartate)-receptor [26], but other than ketamine also to the serotonin transporter [27].

Substances	Uptake	Pk/Metabolism	Pharmakodynamics	Effects	Toxicology	Interactions (PD)	Interactions (PK)
MT-45	nasal, oral, inhalation, i.v.	unknown	κ- and δ-opioid-agonist	euphoria, dissociation	respiratory depression, obstipation	unknown	unknwon
4,4´-DMAR („Aminorex“)	Nasal, oral, i.v.	unknown	dopamine-, serotonin und epinephrin-release	euphoria, stimulation, altered visual perception	agitation, hyperthermia, psychosis, convulsions, cardiac arrest	possible with efavirenz* SSRI, MDMA, cocaine	unknown
MDPV	Nasal, oral, rektal, s.c., i.v.	CYP 2C19 CYP 2D6 CYP 1A2	dopamien- and epinephrin-reuptake-inhibiton	Euphoria, stimulation, altered visual and auditive perception	e.g. tachykardia, convulsions, respiratory problems, depression, confusion, agitation, anxiety, auditive and visuelle hallucinations, paranoid psychosis	nelfinavir, fluoxetine, carbamazepine, moclobemide, tramadol, haloperidol, diltiazem, citalopram, caffeine, diazepam, cannabis, olanzapine, warfarine	buproprione, paroxetine, fluoxetine, quinidine, duloxetine, sertralin, terbinafine [1] possible with ritonavir
Methoxetamine	Nasal, oral, rektal, i.m., i.v.	demethylation oxidation glucuronidation CYP 2B6 CYP3A4	NMDA-receptor-agonist SERT-inhibiton	euphoria, empathy, intense sensoric effects, dissociation, derealisation, increased social intercourse, hallucinations,introspection and antidepressive effects	Vomiting, diarrhea, bradycardial arrhythmia, loss of conscience, sweating, sight disorders, headache, tremor, disorientation, depression, fear, katatonia, confusion, agiation, aggression, hallucinations, paranoia, psychosis	diazepam, alcohol	raltegravir, dolutegravir ritonavir, cobicistat, atazanavir, efavirenz
25I-NBOMe	Nasal, (oral), sublingual, inhalativ, rectal, i.m., i.v.	CYP1A2, CYP3A4, CYP2C9 CYP2C19	5HT2A-agonist (main effect) 5HT-agonist SERT-inhibiton	auditive and visual hallucinations	Serotoninergic syndrome tachcardia, hyperthermia, hypertonia, convulsions, muscular rigidity, agitation, aggression, burst of violence	SSRI, and other serotoninergic substances	possible with cART **
AH-7921	Oral, i.v.	N-demethylation (CYP??)	μ-opioid -receptor-agonist minor affinity to κ-opioid –receptor	analgesic effects	Respiratory depression, obstipation, vomiting, nausea	hypnotics, anxiolytics, tricyklic antidepressants sedating antihistamnics	unknown

Table 2: Overview of effects, pharmacology and potential DDIs of the new designer drugs.

It seems by descriptions of users, that effects are comparable to those of ketamine, a dissociative analgesic drug and are euphoria, increased empathy, intense sensory effects, dissociation from the physical body, derealisation, feelings of security, increased social interaction, hallucinations, introspection and short-time antidepressive effects. [28], Methoxetamin is taken in single doses of 10-200 mg, although a single dose should not extend 50 mg. The effects occur about 30-90 minutes after nasal insufflation, 90 minutes after oral intake and 5 minutes after i.v. injection and last about 1-7 hours.

Two studies evaluated the pharmacokinetics of methoxetamine and found a number of phase-I and phase-II metabolites, which evolved from demethylation, oxidation and glucuronidation [27,29].

The toxic profile of methoxetamine resembles largely to ketamine. Methoxetamine was seized either alone or in blends together with other stimulants like caffeine, lidocaine or phenacetine.

Up to 2014 about 120 non-fatal intoxications and 20 fatal casualties have been registered throughout the EU. Toxic effects are shown in Table 2. An acute intoxication often shows up with agitation, tachycardia and hypertensive crisis, which is similar to ketamine, but also unlike ketamin with ataxia and nystagmus [30].

So far, no data exist about potential pharmacokinetic DDIs with other drugs, but pharmacodynamic interactions can occur with other CNS-effective substances such as alcohol, in this case aggravating depressive and respiratory depression effects. Since the concomitant intake of diazepam and other benzodiazepines reduces the plasma clearance of ketamine, it may be suggested that this could also be possible with methoxetamine.

Regarding the cART, higher doses of methoxetamine may interfere with integrase inhibitors dolutegravir/raltegravir, which is also glucuronidated via UGT, but this has not been proven yet and may only be concluded from so far known metabolic pathways of these drugs.

One publication from 2015 shows also a role of CYP 2B6 and 3A4 regarding the hepatic metabolism of methoxetamine, leading to potential DDIs with ritonavir and/or cobicistat. However, this is unclear and potential effects of generated metabolites remain unknown [27].

25I-NBOMe

25I-NBOMe (street name: 2C-I-NBOMEe, 25I-N-Bomb) had been produced in the early 2000s. Typically, 25I-NBOMe is seized as paper-trips, i.e. absorbent paper, saturated with 25I-NBOMe for a sublingual application. The typical dose ranges from 500 to 800 µg and its effects occur after 15-120 min and last about 6-10 hours.

A number of pharmacological in-vitro and animal studies have evaluated the PK and PD of 25I-NBOMe. It was proven in cell-assays that 25I-NBOMe is a full 5-HT2A-receptor-agonist with a high receptor-affinity even at very low nanomolar concentrations. The addition of a N-(2-methoxybenzyl) group increased markedly the receptor binding capacity in comparison to e.g. 2C-I.

Reports of users suggest that 25I-NBOMe has foremost hallucinogenic effects. The results of animal studies, which used the head, twitch behavioural response (HTR) e.g. in mice as marker for hallucinogenic effects of a 5-HT2A-receptor activation, confirmed these statements.

25I-NBOMe produced a distinct and lasting effect in the HTR, which could be reversed by the 5HT2A-receptorantagonist volinanserin. However, 25I-NBOMe was about 10-fold more potent than 2C-I in these test arrangements. Furthermore, affinity to other receptors in the CNs, e.g. Weitere 5-HT1A/2B/2C, 5-HT6, dopamine D3 and D4, α2C adrenoreceptor and serotonin transporter (SERT), was found. 25I-NBOMe is mainly metabolized by O-demethylation, O,O-bis-demethylation, hydroxylation, and combinations of these reactions as well as subsequent glucuronidation and sulfatation (phase II). Altogether, 68 metabolites have been identified. A screening of cytochromoxidases showed that also CYP 1A2, CYP 3A4, CYP 2C9/2C19 are involved in metabolism [31]. The last involved CYP2C9/2C19 lead to O-demethylation, and the emerging metabolite N-(2-Hydroxybenzyl) is also a strong 5HT receptor-agonist. Further metabolites have not been identified [32].

Effects include those of other psychoactive substances (e.g. LSD, psilocybin or 2C-B (two, 5-dimethoxy-4-bromo-phenethylamine)), but clinical case reports have also shown serotoninerge intoxication such as agitation and confusion. Some users described severe psychic behavioural deviations with the use of 25I-NBOMe: These include intense auditive and visual hallucinations, severe agitation, aggression and unpredictable outbreaks of violence, which -in some cases-led to trauma or death (effects and side effects are shown in Table 2).

Interactions with other medication o drugs are difficult to predict, but pharmacodynamically it is most probable that additive toxicities occur when concomitantly taken with other serotoninerge substances, e.g. SSRI, which increase serotonin concentrations in the CNS. Symptoms of a serotoninerge syndrome are tachycardia, hyperthermia, hypertonia, muscle rigidity and convulsions. Possible pharmacokinetic interactions are listed in Table 2.

Information of users and from seizures proved that 25I-NBOMe is sold as "legal" substitute for LSD or is sometimes directly marketed as LSD on the illegal market [32].

AH-7921

AH-7921 (street name "Doxylam") structurally is an atypical synthetic morphine opioid analgesic, which has already been found in the mid 70 ies of the last century. Chemically it is a derivate of hylaminocyclohexan [33]. As a synonym for AH-7921 is "doxylam" it is sometimes mixed up with doxylamin, an internationally available generic of an antihistaminic drug with also hypnotic and sedating effects. For this reason, doxylam could be taken as doxylamin with a high danger of overdosing, since both drugs have a distinct dosing range.

Various studies in animals and *in vitro* evaluations described the pharmacodynamic characteristics, e.g. sedation and analgesia of AH-7921: AH-7921 is a morphine-like analgesic, with a main effect as µ-opioid (MOP)-receptor agonist and a lower affinity to the κ-opioid (KOP)-receptor. Antagonists are e.g. naloxone, which is atypical opioid-antagonist used in clinical settings. A number of animal studies proved a high analgesic potency of AH-7921, being several-fold that of codeine and comparable to that of morphine. It has also been found that analgesic doses were close to toxic doses, so that it has a very narrow therapeutic window. The side effects profile is comparable to that of morphine, but it´s respiratory depressive potency is 1.6-fold higher.

Data of post-mortem investigations in humans showed the formation of two *N*-desmethyl metabolites, which are products of a sequential *N*-demethylation of the *N*,*N*-dimethylamino groups of the original compound. So far, there is also no information about a biological activity of these metabolites existing.

The lethal dose (LD50) of AH-7921 in mice is 10 mg/kg when intravenously injected [34]. Further side-effects-studies in animals could define a steep linear dose-effects relation with a high risk for respiratory depression, comparable to that of morphine. Commonly taken doses range between 40 and 150 mg, often enhanced by a subsequent intake of further doses in order to extend the effects up to 6-12 hours. The potential for developing addiction is more or less that of classic morphine [35]. Until 2014, 15 deaths related to the intake of the drug have been reported in the EU.

As the pk of AH-7921 has not been fully evaluated, no data about interactions with other drugs or medical compounds are available [36]. However, sedating effects are most probably comparable to morphine [37]. Meanwhile AH-7921 has been prosecuted in some countries worldwide, e.g. the UK (January 2015), Brasil (May 2015) or China (October 2015).

Outlook

Finally, this overview underlines the lack of knowledge about the pharmacology of the new, so-called *legal highs,* synthetic drugs, which in many cases are not prosecuted but sold legally e.g. via the internet. Systematic studies of pharmacokinetic interactions with cART or other medical products are lacking, so that therapists can only warn patients about an incalculable risk of taking these drugs together with ARVs. Therapists must understand that, if severe adverse events or failing cART are reported in this context, documentation and evaluation of these cases can add to the knowledge of the public. In this context, it is crucial that patients are willing to report the consumption of and experience with legal highs in a confiding relationship to their therapists. Therapists have to ask about a possible consumption of these drugs and should update regularly their knowledge about these drugs in order to be able to assess possible correlations to a failure of cART or DDIs.

The ignorance about the fast growing use of legal highs is a crucial threat to an effective prevention and therapy of HIV all over Europe.

As discussed above, exact medical and pharmacological information can be accessed via the internet websites of the EMCDDA [38] and other internet based sources, specialized on this issue.

References

1. Mit Prävention die Gesundheit im Blick behalten (2015) Drogen- und Suchtbericht 2015 der Bundesregierung.
2. EMCDDA (2014) EMCDDA-Europol 2014 Annual report on the implementation of Council Decision 2005/387/JHA. EMCDDA Annual Report 2014, Brussels, EU.
3. EMCDDA (2015) Risk Assessment Report of a new psychactive substance. 1-cyclohexyl-4-(, 2-diphenylethyl) piperazine. Risk Assessment Report, EMCDDA, EU.
4. Rosenbaum CD, Carreiro SP, Babu KM (2012) Here today, gone tomorrow... and back again? A review of herbal marijuana alternatives (K, Spice), synthetic cathinones (bath salts), kratom, Salvia divinorum, methoxetamine, and piperazines. J Med Toxicol 8: 15-32.
5. Karch SB, Mari F, Bartolini V, Bertol E (2012) Aminorex poisoning in cocaine abusers. Int J Cardiol 158: 344-346.
6. Hofmaier T, Luf A, Seddik A, Stockner T, Holy M, et al. (2014) Aminorex, a metabolite of the cocaine adulterant levamisole, exerts amphetamine like actions at monoamine transporters. Neurochem Int 73: 32-41.
7. Glanville J, Dargan PI, Wood DM (2015) 4-methyl-5-(4-methylphenyl)-4,5-dihydrooxazol-2-amine (4,4'-DMAR, 4,4'-dimethylaminorex): availability, prevalence of use, desired effects and acute toxicity. Hum Psychopharmacol 30: 193-198.
8. Karch SB, Defraia B, Messerini L, Mari F, Vaiano F, et al. (2014) Aminorex associated with possible idiopathic pulmonary hypertension in a cocaine user. Forensic Sci Int 240: 7-10.
9. Hess C, Ritke N, Sydow K, Mehling LM, Ruehs H, et al. (2014) Determination of levamisole, aminorex, and pemoline in plasma by means of liquid chromatography-mass spectrometry and application to a pharmacokinetic study of levamisole. Drug Test Anal 6: 1049-1054.
10. Cameron K, Kolanos R, Vekariya R, De Felice L, Glennon RA (2013) Mephedrone and methylenedioxypyrovalerone (MDPV), major constituents of "bath salts," produce opposite effects at the human dopamine transporter. Psychopharmacology (Berl) 227: 493-499.
11. Fantegrossi WE, Gannon BM, Zimmerman SM, Rice KC (2013) In vivo effects of abused 'bath salt' constituent 3,4-methylenedioxypyrovalerone (MDPV) in mice: drug discrimination, thermoregulation, and locomotor activity. Neuropsychopharmacology 38: 563-573.
12. Baumann MH, Partilla JS, Lehner KR, Thorndike EB, Hoffman AF, et al. (2013) Powerful cocaine-like actions of 3,4-methylenedioxypyrovalerone (MDPV), a principal constituent of psychoactive 'bath salts' products. Neuropsychopharmacology 38: 552-562.
13. Coppola M, Mondola R (2012) 3,4-methylenedioxypyrovalerone (MDPV): chemistry, pharmacology and toxicology of a new designer drug of abuse marketed online. Toxicol Lett 208: 12-15.
14. Anizan S, Concheiro M, Lehner KR, Bukhari MO, Suzuki M, et al. (2016) Linear pharmacokinetics of 3,4-methylenedioxypyrovalerone (MDPV) and its metabolites in the rat: relationship to pharmacodynamic effects. Addict Biol 21: 339-347.
15. Marusich JA, Antonazzo KR, Wiley JL, Blough BE, Partilla JS, et al. (2014) Pharmacology of novel synthetic stimulants structurally related to the "bath salts" constituent 3,4-methylenedioxypyrovalerone (MDPV). Neuropharmacology 87: 206-213.
16. Negreira N, Erratico C, Kosjek T, van Nuijs AL, Heath E, et al. (2015) In vitro Phase I and Phase II metabolism of alpha-pyrrolidinovalerophenone (alpha-PVP), methylenedioxypyrovalerone (MDPV) and methedrone by human liver microsomes and human liver cytosol. Anal Bioanal Chem 407: 5803-5816.
17. Beck O, Franzen L, Backberg M, Signell P, Helander A (2015) Intoxications involving MDPV in Sweden during 2010-2014: Results from the STRIDA project. Clin Toxicol (Phila) 53: 865-873.
18. Mugele J, Nañagas KA, Tormoehlen LM (2012) Serotonin syndrome associated with MDPV use: a case report. Ann Emerg Med 60: 100-102.
19. Murray BL, Murphy CM, Beuhler MC (2012) Death following recreational use of designer drug "bath salts" containing 3,4-Methylenedioxypyrovalerone (MDPV). J Med Toxicol 8: 69-75.
20. Thornton SL, Gerona RR, Tomaszewski CA (2012) Psychosis from a bath salt product containing flephedrone and MDPV with serum, urine, and product quantification. J Med Toxicol 8: 310-313.
21. Watterson LR, Kufahl PR, Nemirovsky NE, Sewalia K, Grabenauer M, et al. (2014) Potent rewarding and reinforcing effects of the synthetic cathinone 3,4-methylenedioxypyrovalerone (MDPV). Addict Biol 19: 165-174.
22. EMCDDA (2014) Report on the risk assessment of 1-(, 3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl) pentan-1-one in the framework of the Council Decision on new psychoactive substances. Risk Assessment Report, EMCDDA, EU 2014.
23. Corazza O, Schifano F, Simonato P, Fergus S, Assi S, et al. (2012) Phenomenon of new drugs on the Internet: the case of ketamine derivative methoxetamine. Hum Psychopharmacol 27: 145-149.
24. Craig CL, Loeffler GH (2014) The ketamine analog methoxetamine: a new designer drug to threaten military readiness. Mil Med 179: 1149-1157.
25. Hofer KE, Grager B, Müller DM, Rauber-Luthy C, Kupferschmidt H, et al. (2012) Ketamine-like effects after recreational use of methoxetamine. Ann Emerg Med 60: 97-99.
26. Roth BL, Gibbons S, Arunotayanun W, Huang XP, Setola V, et al. (2013) The ketamine analogue methoxetamine and 3- and 4-methoxy analogues of phencyclidine are high affinity and selective ligands for the glutamate NMDA receptor. PLoS One 8: e59334.
27. Meyer MR, Bach M, Welter J, Bovens M, Turcant A, et al. (2013) Ketamine-derived designer drug methoxetamine: metabolism including isoenzyme

kinetics and toxicological detectability using GC-MS and LC-(HR-)MSn. Anal Bioanal Chem 405: 6307-6321.

28. Kjellgren A, Jonsson K (2013) Methoxetamine (MXE)-a phenomenological study of experiences induced by a "legal high" from the internet. J Psychoactive Drugs 45: 276-286.

29. Menzies EL, Hudson SC, Dargan PI, Parkin MC, Wood DM, et al. (2014) Characterizing metabolites and potential metabolic pathways for the novel psychoactive substance methoxetamine. Drug Test Anal 6: 506-515.

30. EMCDDA (2014) Report on the risk assessment of methoxetamine in the framework of the Council Decision on new psychoactive substances Risk Assessment Report, EMCDDA, EU 2014.

31. Caspar AT, Helfer AG, Michely JA, Auwarter V, Brandt SD, et al. (2015) Studies on the metabolism and toxicological detection of the new psychoactive designer drug 2-(4-iodo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine (25I-NBOMe) in human and rat urine using GC-MS, LC-MS(n), and LC-HR-MS/MS. Anal Bioanal Chem 407: 6697-6719.

32. EMCDDA (2014) Report on the risk assessment of 2-(4-iodo-, 5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine in the framework of the Council Decision on new psychoactive substances. Risk Assessment Report, EMCDDA, EU 2014.

33. Coppola M, Mondola R (2015) AH-7921: a new synthetic opioid of abuse. Drug Alcohol Rev 34: 109-110.

34. Structure activity studies of two classes of beta-amino-amides: the search for kappa-selective opioids. In: Harris LS, Frenking G, Berzetei-Gurske I, Polgar W, eds. Problems of drug dependence. NIDA Research Monograph 90. 1988, Rockville, MA: U.S. Department of Health and Human Service: 144-151.

35. Drugs. ACotMo. RE: ACMD's recommendation on the synthetic opiate AH-7921.

36. Wohlfarth A, Scheidweiler KB, Pang S, Zhu M, Castaneto M, et al. (2015) Metabolic characterization of AH-79, a synthetic opioid designer drug: in vitro metabolic stability assessment and metabolite identification, evaluation of in silico prediction, and in vivo confirmation. Drug Test Anal.

37. EMCDDA (2014) Report on the risk assessment of 3, 4-dichloro-N {[1(dimethylamino)cyclohexyl]methyl}benzamide in the framework of the Council Decision on new psychoactive substances Risk Assessment Report, EMCDDA, EU.

38. EMCDDA (2015) Drugs-in-focus. Responding-to-new-psychoactive-substances.