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# Structure and Laboratory Diagnostics of Non-Medical Consumption of Modern Synthetic Drugs

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**ABSTRACT** The emergence of new synthetic narcotic drugs is noted all over the world. The situation causes significant difficulties for toxicologists, resuscitators, narcologists, and clinical laboratory diagnostics doctors due to the lack of available data on the clinical picture of poisoning by these compounds and laboratory diagnostic methods. In most cases, the clinical picture of drug intoxication or poisoning with new synthetic substances differs from the symptoms caused by previously known drugs, such as cocaine or opiates. Therefore, chemical toxicological research is one of the important aspects for establishing the fact of intoxication or poisoning.

**Keywords:** drug intoxication, synthetic cannabinoids, fentanyl derivatives, cathinones, chemical and toxicological studies

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## INTRODUCTION

According to the European Union Early Warning System, 101 new uncontrolled psychoactive substances were first detected in 2014 [1], and 541 new psychoactive substances were registered between 2009 and 2014 according to UN data from 95 countries [2].

As a rule, synthetic narcotic drugs, including designer drugs, are analogues or derivatives of controlled (prohibited) substances that reproduce an effect similar to the classical ones. At the same time, only a small amount of data has been accumulated on the dangers of new drugs due to the short period of their stay on the market and the constant appearance of other drugs of this kind.

Most of the new psychoactive substances reported in 2014 were synthetic cannabinoids (39%) and synthetic cathinones (15%) [2].

Synthetic cannabimimetics (cannabinoids**)** is a large group of compounds. Since 2010, this group has repeatedly occupied a leading position in the number of new connections registered through the European Union Early Warning System [1]. Despite the fact that some governments have introduced restrictive measures (including Russia), the spread of synthetic cannabimimetics has not stopped, and there is a steady demand for them [3]. The pharmacological effect of synthetic cannabimimetics, similar to the action of tetrahydrocannabinols (marijuana, hash, anasha), is associated with their activity against human cannabinoid receptors [4].

It should also be noted that recently, cases of detection of halogenated synthetic cannabimimetics have begun to appear. The introduction of halogens, especially fluorine, into the aliphatic chain of known synthetic cannabinoids is a common approach to the synthesis of new active drugs not listed in the banned compounds to increase their effectiveness.

Research work in the field of drug development has shown that halogenation of synthetic cannabinoids of naphthoylindoles and benzoylindoles into the lateral chain may lead to an increase in their affinity for binding to CB 1 and CB2 receptors [5–7].

The results show that replacing one fluorine atom on the pentyl end chain increases the binding ability to the CB1 receptor. For example, AM-2201 has approximately 10 times greater affinity than its non-fluorinated analogue JWH-018, and AM-694 is approximately 1,709 times stronger bound than its non-fluorinated analogue AM-679. Moreover, AM-698, an iodine-substituted analogue of AM-679, has 10 times less ability to bind to the CB1 receptor.

Synthetic cathinones are one of the two main groups of psychoactive drugs, leading (along with synthetic cannabinoids) both in the number of new compounds and in volumes seized by regulatory authorities in Europe.

Despite the large number of synthetic cathinones (the European Monitoring Center for Drugs and Drug Addiction *(EMCDDA)* over 110 new compounds formally registered over the indicated period), their popularity among consumers is extremely different. This value can be indirectly estimated through the frequency of detection of the components of the group of synthetic cathinones in biological samples taken during chemical-toxicological surveys on the state of intoxication. According to our observations, one of the most frequently detected compounds in the Russian Federation is *PVP* (α-*PVP* — α-pyrrolidinovalerophenone; 1-phenyl-2- (pyrrolidin-1-yl) pentan-1-one).

For the first time, some properties of *PVP* were described back in 1963 [8], but its presence in European markets has been noted since 2012 [9]. *PVP* is a central nervous system stimulant which is often distributed as bath salts. Moreover, its psychoactive effect is associated with an increase in the extracellular level of monoamines in the brain caused by inhibition of the reuptake of dopamine and norepinephrine.

The main methods of administration are oral, intravenous and intranasal; dosages are approximately 1–25 mg. More than 20 cases of acute poisoning in Europe (2012–2015) that are fatal and associated with the use of *PVP* are known [9, 10]. *PVP* turnover is controlled in 16 countries of the European Union and is prohibited in the Russian Federation [9, 11].

**The purpose of the study** is to analyze the structure and select the best methods of chemical and toxicological diagnosis of non-medical consumption of new synthetic drugs (for example, the Leningrad region).

## MATERIAL AND RESEARCH METHODS

A comparative analysis of the results of chemical and toxicological studies of biological samples delivered to the chemical and toxicological laboratory of SBHI Leningrad Regional Narcological Dispensary (CTL SBHI LRND) during a medical examination for intoxication or determination of toxic substances and acute poisoning of patients admitted to district hospitals of Leningrad region.

Studies on narcotic drugs and psychotropic substances were carried out in accordance with the order of the Ministry of Health and SD dated 01/27/2006 No. 40 and the order of the Ministry of Health of Russia of 12/18/2015 No. 933n by doctors of the chemical-toxicological laboratory SBHI LRND in 2 stages:

1) preliminary research methods using immunochromatographic test systems;

2) confirmatory research methods produced using:

- 6890 *V* gas chromatograph connected to a 5977 single-quadrupole mass spectrometer (*Agilent Technologies*, USA);
- *Nexera XR* modular liquid chromatograph with *LCMS*-8040 tandem mass spectrometer *(Shimadzu)*.

## RESEARCH RESULTS AND DISCUSSION

A distinctive feature of modern drug traffic in Russia, as well as throughout the world, is the expansion of their assortment, as new synthetic drugs appear. As a result of this, the number of biological samples sent to the chemical-toxicological laboratory for preliminary and confirmatory chemical-toxicological studies is increasing annually. In 2014, 2,432 biological objects were delivered to the CTL SBHI LRND, in 2015 – 7,984, and in 2018 – 12,936. The increase in the number of biological samples received for the study, and consequently the number of studies is also associated with entry into the force of certain orders, namely, the order of the Ministry of Health of Russia dated December 18, 2015 No. 933n "On the procedure for conducting a medical examination for intoxication (alcohol, drug or other toxic)", order of the MH of the Russian Federation dated 06.10.2014 No. 581n "O the procedure for conducting preventive medical examinations teaching their number in educational organizations and professional educational organizations, as well as educational institutions of higher education for the early detection of illegal use of narcotic drugs and psychotropic substances", Order of the MH of the Russian Federation dated December 22 , 2016 No. 988n "On the procedure for issuing a certificate of absence of employees who in accordance with their labor duties must have access to narcotic drugs, psychotropic substances listed in list 1 and table I of list IV of the list of narcotic drugs, psychotropic substances and their precursors to be controlled in the Russian Federation, precursors or cultivated drug-containing plants, drug addiction, substance abuse, chronic alcoholism", Order of the MH of the Russian Federation dated June 30, 2016 No. 441n "On the procedure for conducting a medical examination for medical contraindications to gun ownership and chemical-toxicological studies of the presence of narcotic drugs, psychotropic substances and their metabolites in the human body." This significantly increases the load on CTL.

The structure of synthetic cannabimimetics found in the Leningrad region, according to the results of the study of biological samples, is presented in the table.

*Table*

**Synthetic cannabimimetics found in the Leningrad Region (data provided by CTL SBHI LRND)**

| Synthetic cannabimimetics | 2014 | 2015 | 2016 | 2017 | 2018 | Total |
|---|---|---|---|---|---|---|
| 5F-ADB-PINACA | | 6 | 45 | 31 | 27 | 109 |
| 5F-AB-PINACA | 7 | 5 | 3 | 13 | | 28 |
| ADB-FUBINACA | 6 | 24 | 1 | | | 31 |
| ADB-CHMICA | | | | 14 | | 14 |
| AB-CHMINACA | | 42 | 39 | 13 | 1 | 95 |
| AB-PINACA | 2 | | | | | 2 |
| CBL-2201 | 8 | 11 | 1 | | | 20 |
| PB-22F | 4 | | | | | 4 |
| 5F-ADB ICA | | | | | 5 | 5 |

As can be seen from the data presented in the table, the synthetic cannabimimetic 5 *F-ADB-PINACA*, which belongs to the group of alkylindazole-3-carboxamides, derivatives of amide of valine and which is subject to the decree No. 788 dated 09.09.2013 of the Government of the Russian Federation as N-(1-carbamoyl-2-methylpropyl)-1-pentyl-1H-indazole-3-carboxamide and its derivatives, is the leader in the largest number of abuses over the past 3 years by the frequency of occurrence in samples [11].

The largest number of cases (over 80) of the identification of metabolites of synthetic cannabimimetics was in the period 2015–2017. It should be noted that some synthetic cannabimimetics were simultaneously detected in some examined in laboratory diagnostics. This is usually a combination of *AB-CHMINACA* and *ADB-FPINACA*, *CBL*- 2201 and *ADB-FUBINACA*.

The use of standard research methods, in accordance with the order of the Ministry of Health of Russia dated 12/18/2015 No. 933n as well, based on the use of preliminary research methods that exclude visual assessment, did not allow to detect any drugs in the urine of 299 patients where subsequently metabolites of synthetic cannabimimetics were identified, and in 9 examined persons, amphetamine and / or tetrahydrocannabinol acid were additionally detected.

In 2015, *PVP* was detected in only one case, and in 71 samples in 2018. At the same time, preliminary research methods (test systems for cathinones) did not show sufficient sensitivity and information content, namely, a large number of false-negative research results were observed. Mephedrone (4-methylmethcathinone) is a narcotic drug, also belonging to the group of synthetic cathinones, was determined only in isolated cases.

A feature of most synthetic drugs is their fast and almost complete metabolism, passing at least two phases (phase I and phase II), which explains the lack of starting compounds in the urine and their rapid removal from the bloodstream [4]. Phase I involves dealkylation and/or hydroxylation (as mono- and polyhydroxylation), resulting in the formation hydrophilic compounds, which are further removed from the body via the urinary system. As a result of phase II, the metabolites of phase I and/or native compounds are bound to glucuronic acid, which leads to the formation of hydrophilic glucuronides and their excretion from the body using the urinary system. Therefore, a urine test for narcotic drugs and other toxic substances is more informative than a blood test, since it allows you to more likely determine not only native compounds, but also their metabolites. In addition, the concentration of most toxic compounds in the urine significantly exceeds their concentration in the blood, which makes it possible to determine these compounds even several days after use.

The determination of the majority of metabolites and/or markers of narcotic drugs, especially synthetic cannabimimetics and cathinones, in biological objects (blood, urine) with the aim of diagnosing drug intoxication is possible only using several methods and methods of sample preparation. For the identification of phase I metabolites, it is necessary to carry out hydrolysis, which significantly increases the duration of the analysis, and subsequent analysis by gas and liquid chromatography with mass spectrometric detection. However, the determination of phase II metabolites (glucuronides) due to the significant molecular weight and low thermal stability is possible only when using liquid chromatography-

mass spectrometers (LC-MS/MS). Therefore, we use 2 confirming methods for identification of modern synthetic drugs: a method of gas and liquid chromatography and mass spectrometry, which greatly improves the accuracy of the results.

## CONCLUSION

The results of the study indicate that there are constantly new synthetic drugs in the Leningrad region, which amount is increasing every year.

For the detection of synthetic drugs in the urine, namely synthetic cannabimimetics and cathinones, the preliminary research methods are uninformative due to the significant number of false-negative results. Therefore, in cases of suspected intoxication or poisoning with synthetic narcotic drugs, it is advisable to send urine to a chemical and toxicological laboratory to conduct confirmatory methods. At the same time, during chemical-toxicological studies, it is necessary to use 2 confirmatory methods – GCMS and LC-MS/MS:

- gas chromatography method with mass selective detection, which allows to determine the phase I metabolites;
- a method of liquid chromatography with mass selective detection, capable of determining the metabolites of both phase I and phase II.

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