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# НОВЫЕ ПСИХОАКТИВНЫЕ ВЕЩЕСТВА: ВЗГЛЯД ПСИХИАТРА

Аннотация: появление новых психоактивных веществ («дизайнерских наркотиков»), включающих синтетические каннабиноиды, производные катинонов, фенэтиламинов, новых психостимуляторов, синтетических опиоидов, производных триптаминов, фенциклидина, пиперазинов, агонистов GABA (A/B) рецепторов, стало серьезной проблемой для потребителей, и врачей. Потребителей данных веществ привлекает, прежде всего, степень выраженности психоактивных эффектов, а также «юридическая чистота», декларируемая нелегальными производителями, что указывает на значительные трудности в лабораторной идентификации новых психоактивных веществ. При употреблении дизайнерские наркотики оказывают влияние на большинство нейротрансмиттеров/рецепторов: дофамин, каннабиноидные рецепторы первого типа (CB1), рецепторы ГАМК (A/B), 5-HT2A рецепторы, глутамат, и k-опиоидные рецепторы (KOR), что приводит к развитию полиморфных психотических расстройств.

**Ключевые слова**: «дизайнерские» наркотики, новые психоактивные вещества, лабораторная диагностика, наркотическая зависимость, фенэтиламины, синтетические каннабимиметики, фенциклидины, синтетические катиноны, синтетические триптамины, психотические нарушения.

### NEW PSYCHOACTIVE SUBSTANCES: PSYCHIATRIST'S VIEW

**Abstract**: appearing not long ago, new psychoactive substances (designer drugs), including synthetic cannabinoids, derivatives of cathinone, phenethylamines, new stimulants, synthetic opioids, tryptamine derivatives, phencyclidine, piperazine, the GABA (A/B) receptors agonists, have become a serious problem for consumers

and for physicians. Consumers of these substances are attracted primarily by the intensity of psychoactive effects, and the «legal high» declared by the black manufacturers, which indicates that significant difficulties in a laboratory identification of new surfactants. Designer drugs, when ingested, can be influenced on many neurotransmitter pathways/receptors: dopamine, cannabinoid (CB1), GABA (A/B), 5-HT2A, glutamate, and k-opioid receptors (KOR), the imbalance of which leads to the development of polymorphic psychotic disorders.

*Keywords*: designer drugs, new psychoactive substances, laboratory diagnostics, drug addiction, phenethylamines, synthetic cannabimimetic, phencyclidine, synthetic cathinone, synthetic tryptamines, psychosis.

## Introduction.

Concurrent with a decrease in consumption of the «classical» drugs controlled worldwide, the market of new surfactants grows annually [1]. The penetration level of the «new» drugs into the environment of the drug-addicted is rather high. Nowadays, the distribution of designer drugs is revealed in 94 countries worldwide [2]. The average age of the designer drugs consumers are 19–24 years. The Internet and web technologies play one of the leading roles in the distribution of new drugs [3]. Consumers of designer drugs are attracted, first by the psychoactive effects rendered by the latter and because they are hardly identified by laboratory-which creates some legal problems in many countries, including Russia [4]. The magnitude of designer drugs spread represents a serious problem, both for the physicians occupied with diagnostics and treatment of addictive disorders, and for the security agencies staff [4; 8; 9] whose forces are directed to fight against illicit drug trafficking [3; 6; 7]. Particularly, in the last 3–4 years, there grows a level of psychotic disorders both, acute and chronic, bound to the use of new (designer) drugs [5]. Basing on the international medical networks Medline/PubMed, Medscape, Scopus, Cochrane Library, and our own clinical observation data, we used the following search query combinations as «new psychoactive substances», «designer drugs», «screening of the psychoactive

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substances», «psychoses in designer drugs use», «designer drugs addiction». The following direction of the search was the newly synthesized chemical substances being a part of designer drugs that have the ability to cause one or another mental disorder after its consumption. In case of any lack of information on the chemicals in the reviewed literature, the search was performed by using search queries, Google, Yandex, Yahoo, Bing, as well as through the specialized Internet forums and web sites.

## Synthetic cannabimetics

Synthetic cannabimetics are the narcotic substances consisting of the vegetable basis (various herbs; the presence of marijuana is not excluded) processed by the mix of synthetic cannabinoids made in vitro. Ways to use: peroral, liquid for smoking, substrate for injections. The reference package of a «spice» dose can consist of several types of synthetic cannabinoids. The psychoactive effects caused by its consumption can be various on structure, intensity degree, and duration. There are cases described when drugs of one consignment caused various effects directly bound to a concentration of synthetic cannabimetics. Nowadays, there exist several hundreds of synthetic cannabimetic modifications on the black market [8; 9; 89]. Synthetic cannabinoids can be divided into 5 groups depending on their chemical structure: 1) Dibenzopyrans (HU-210); 2) Cyclohexylphenols (CP 47,497 and its homologues); 3) Naphthoylindoles (JWH-018, JWH-073, JWH-398); 4) Phenylacetylides (JWH-250); 5) Oleamids. Designer cannabinoids have a very high level of an affinity to cannabinoid receptors of a human body that causes the more pronounced psychotropic effect than natural TGC [22; 23; 89]. So, today it is known that the classical tetrahydrocannabinol (THC) – when ingested affects as a partial agonist on receptors like CB1, while artificially synthesized JWH-018, when ingested, acts as a complete and potential agonist. By their structure, synthetic cannabimetics are liposoluble, and nonpolar, consist of 22–26 atoms of carbon which explains their high volatility when smoking. Unlike the nabilone which is a synthetic analog of the THC, and, the approved by US Food and Drug Administration (FDA), to treat nausea and vomiting caused by chemotherapy, the synthetic cannabinoids contained in spices do not dis-

cover similar effects. Besides, some synthetic cannabinoids can cause the pharmacological effects which are the padding factor of alarm for clinical physicians such as the N-methyl-D-aspartat (NMDA) receptors antagonism [25], and the ability to exert the inhibiting impact [26; 89] on monoamine oxidase (MAO). Almost all synthetic cannabinoids are indole-derivatives that can promote the dysfunction of 5-HT2A receptors finally leading to development of a hallucinative disorder in the mental state [27–30; 89]. The new generation of synthetic cannabinoids is often exposed to fluorination process in the black chemical labs that leads to the fastest penetration of a terminating substance through a hematoencephalic barrier [32; 33]. Symptoms of acute intoxication by synthetic cannabinoids include motor exaltation, severe anxiety to a degree of a raptus, visual hallucinations (clinical broken consciousness), and auditory hallucinations of imperative character, pronounced tachycardia, BP rise, an acute hyperglycemia, dispone, vomiting, and epileptiform attacks. Among other significant somatic disorders in the clinic of acute intoxication by synthetic cannabinoids, it is possible to note the transient disturbance in brain blood circulation, development of encephalopathy, an acute myocardial infarction, development of an acute renal failure [37–40]. Death as a result of suicide after the ingestion of synthetic cannabinoids, or the combined use of synthetic cannabinoids and other psychoactive substance [41– 51,89] is confirmed by a number of analytical researches. A prolonged synthetic cannabinoids abuse can cause a tolerance growth, and development of addiction [35; 52], and under deprivation of drug, a heavy and lingering abstinence syndrome [53–56]. The chronic use of marijuana leads to development of psychotic disorders, in correlation with a dose of narcotic substance, which is repeatedly described in literature [57]. Similarly, the use of synthetic cannabinoids is often bound to development of acute transitional psychotic disorders with a polymorphic clinical picture, and also promotes an aggravation of the pre-existing chronic mental disorders. Prospective follow-up monitoring shows the retention by some patients of psychotic symptoms despite the received psycho-pharmacotherapy. Similar states are called by some researchers «Spiceophrenia» [6]. A separate category can be represented by the patients https://interactive-plus.ru

with maniacal states and those having a developing phase of the pre-existing bipolar disorder against the background of synthetic cannabinoids abuse [58; 59]. From our own observations out of 28 patients with the clinic of acute psychosis after the «spic-es» ingestion, in nine cases (32,14% – content of CP-47,497 was detected in a laboratory study) – the clinic of an acute verbal hallucinosis was noted; in 11 cases (39,29% content of JWH-018 was detected in laboratory tests) – the clinic of a paranoid syndrome (hallucinate option); in five cases (17,86% laboratory tests typed the content of AM-2201) the leading disorders were affective derangements (a maniac delusional syndrome); and in three cases the clinic of the broken consciousness as not developed oneiric syndrome took place (10,71% -content of JWH-250 detected in a laboratory study).

### Synthetic cathinones

Synthetic cathinones were first raised in 2008 when the international group of researchers by means of web cartography, analyzing thematic forums, and the range of online stores, revealed the numerous mentions of these substances [4]. Structurally synthetic cathinones beta-ketophenylethylamine similar amphetaare to mines/catecholamine, with minor changes in structure owing to which chemical properties, the rendered effects, a pharmacokinetics, and a pharmacodynamics change. The popularity of synthetic cathinones among consumers is caused by the absence of «pure cocaine» on the black market, its cost, and also legal problems bound to the use and purchase of cocaine. The important role in abundance of synthetic cathinone, was played by the limitative measures entered in many countries concerning 3,4-methylene-dioxi-Metamphetaminum (MDMA, «ecstasy») [3,86,87]. As a rule, synthetic cathinones are used either orally, or in the form of injections. Smoking did not get a wide spread occurrence for the reason that narcotic substance quickly decays at high temperature. For a mefedron (falls into synthetic cathinone), the elimination half-life makes about an hour that increases the risk of overdose [60,86,87]. Any of synthetic cathinones effects on serotonin production, dopamine, and noradrenalin. All synthetic cathinones have a sympathomimetic activity that finally results

in amphetamine-like effects in a body [8; 9; 86; 87]. The psychoactive effects rendered by synthetic cathinones on the body include: strengthening of an attention, transitional, acute paranoiac reactions, euphoria, development of delirious states, hallucinative disorders (verbal are more often), agitation, motor exaltation. It is possible to refer to somatic displays of intoxication the various disorders of cardiac activity, expansion of pupils, pains in epigastric area, a hyperemia of integuments, a hyperhidrosis, a cold fit [8; 9; 61; 86; 87]. Affective disorders and psychotic derangement of paranoiac structure are more often present in consumers whose narcotization experience is over one year [61–64; 86; 87]. Also, there are described cases of a malignant hyperthermia, rhabdomyolysis, a phenomenon of a renal failure, and epileptiform attacks as somatic complications which have persons durably using mefedron. Lethal outcomes among the users of synthetic cathinones are generally described among those consuming mefedron [47; 61; 62; 86; 87], metilon and butilon [65; 86; 87]. Most part of synthetic cathinone consumers manifests the growth of tolerance, development of mental dependence, an abstinence syndrome [66; 86]. The conducted researches, using positron emission tomography, of the chronic metcathinone consumers being in abstinence, show a decrease in the density of a striatum which influences the development of dopamine, and in the long term, can cause heavy neurologic and mental disorders [67; 86]. According to our observations, out of 12 people hospitalized in a state of acute intoxication after the use of synthetic cathinones (the laboratory diagnostics has identified a pyrovalerone), the structure of psychotic disorders was distributed as follows: two patients had an acute verbal hallucinosis (16,67%), in 4 cases – a depressive and paranoid syndrome (33,33%), three cases- the clinics of a paranoid syndrome with an acute course (25%), and three patients (25%) manifested a manic-delusional syndrome [88].

Designer phenethylamines (MDMA-like drugs)

MDMA («Ecstasy») – is one of the most known drugs of a phenethylamine origin. The newly synthesized substances, for a circumvention of the legal bans, include several 2C molecules, i.e. are, in fact, a derivative of the «classical» MDMA: https://interactive-plus.ru

2,5-dimetoksi-4-bromophenetilamin (2-CB, «Nexus») [68], 2,5-dimetoxi-4yodophenetilamin (2C-I) [69], and 2,5-dime-toxi-4-etilphenetilamin (2C-E) [70]. The majority of substances 2C have an affinity to 5-HT2A-receptories, and some of this group are capable to inhibition of dopamine and noradrenalin, and can provide the inverse capture of a serotonin from a fissure presynaptica [3]. Because of the chemical properties, this group of substances is widely used among consumers as an ecstasy substitute. MDMA-like drugs cause empathogen-similar effects which make them very popular among teenagers and youth: the increased mood, sense of inflow of forces and energy, sense of improvement of ability to communication. Along with this, due to a toxic influence on the serotonergic system, and sympathomimetic effects, as somatic disorders can be met: tachycardia, BP rise, metabolic acidosis, epileptiform disorders, rabdomyolis, mydriasis, vomiting, diarrhea, and thrombocytopenia. The development of an acute renal failure in a combination to a malignant hyperthermia is a frequent consequence of the narcotic substance overdose [3,7,71,72]. 3Cbromo-dragonfly («B-Fly») – one of the heaviest drugs of this group. After its use, the psychoactive effects can be observed within 3 days. Some consumers of this drug having used it for many years were noted by the various hallucinatory disorders. Along with the mood elevation in the period of acute intoxication, paranoiac structure experiences, delirious disorders, severe anxiety, flashbacks are noted [73]. 25C-NBOMe («N-bomb», «Pandora») – one of the most popular compounds among the designer phenetilamines [74]. On its basis, several similar medicines are already created that allows speaking about the NBOM-like substances. Drugs of this subgroup cause a serious concern among physicians of different countries [8,9]. In underground online stores, it is positioned as a legal analog of lysergic acid. It is usually eaten inside or sublingually. «N-bomb» is a partial 5-HT2A receptors agonist. In acute intoxication, it is capable to cause motor exaltation, auditory and visual hallucinations, orientation disturbance, severe anxiety, unmotivated aggression and cruelty [74]. Practically all consumers of «B-Fly», «N-bomb», a paramethoxyamphetamine (PMA, «Dr. Death»), 4 methylthioamphetamines (4-MTA, «flat liners») and 6-(2 aminofuryl) coumarone (6-APB, «Benzofuryl») – had toxic reactions, criminal violations in intoxication, different trauma [47; 73; 74].

## Designer opioids

These compounds are similar to Morphinum by its clinical and pharmacological effects: the ability to cause an analgetic effect, sedation, euphoria, a respiratory depression. AH-7921 («doxylam») by its psychoactive effects is the closest to Morphine [78]. First synthesized 45 years ago, it is now accessible in the majority of black online stores in a powder form to inhalation through a nose, or per oral application. In literature, several fatal cases which came right after the use of this substance [62] are described. The following substance which is rather often presented on the black websites, and illegal online stores is MT-45. This drug was synthesized in the early seventies of the last century, as a potential analog of the known anesthetic medicine «Lefetamine» [79]. By its structure it is a mu/delta/sigma agonist to opioid receptors [80]. Now it is the designer opioid, very popular among consumers, which is often applied in a combination with synthetic cathinone («Wow») or in the isolated option [82]. According to consumers self-reports about MT-45, it strongly oppresses respiration, influences hearing (up to a deafness development) [81]. A slight increase in a dose can cause a lethal outcome [82]. Among other narcotic substances of this group it is necessary to call Nortilidine-being the NMDA receptors antagonist, and an inhibitor of the inverse capture of dopamine, by pharmacological effects is not inferior to Morphine [82], because of high activity in respect of mu-opioid agonists of W15 and W18 [83]. The last on the list of designer opioids are the analogs of methadone: 4 fluoride butyrfentanyl «4FBF») and SK-26 («methiodone»).

## Designer tryptamines

For the first time a synthetic tryptamine appeared on the black drug market in the mid-nineties of the last century [78]. Within the last 5–7 years, they have been forced out by the gaining popularity synthetic cathinone «salts», phenethylamines, and designer Piperazines [82; 79]. Despite this circumstance, the newly synthesized tryptamine such as N-diallyl-5-methoxy-tryptamine, 5-MeO-DALT; alpha metyltryp-

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tamine, AMT; 5 - methoxy-alpha-methyltryptamine, 5-MeO-AMT; N, N-diallyl-4hydroxytryptamine, 4-HO-DALT; 5- methoxycinnamyl-tryptamine, 5-MeO-DIPT; 5methoxy-N, N-dime-tiltmeter, 5-MeO-DMT; N, N- diethyltryptamine, DET; 5-(2 aminopropyl) indole, 5-IT-continue to appear in the results of laboratory tests for narcotic substances [2; 82; 69; 71]. An overwhelming majority of exogenetic tryptamine are substances with psychotropic, more often hallucinate effect [72–76]. The high content of tryptamine is noted in Delosperma family plants, (dimethyltryptamine, DMT; 5-MeO-DMT). Besides, the increased concentration of tryptamine is found in a hallucinogenic fungi (psilocin; 4-OH-DMT), and in tissues of some representatives of an amphibious class (amphibians) (bufotenine). Bufotenine and DMT of an endogenic origin are found in the normally functioning human bodies; today the biological functions of these endogenic tryptamines are not studied enough [77-79]. The main clinical effects of tryptamines are primarily associated with the 5-HT2A brain receptors agonism, and an inhibition of a serotonin transporting [80-83]. This psychopharmacological profile involves the ability of tryptamine to cause visual hallucinations with the clinic of stupefaction, various perception disorders (illusion, pareydolics), psychosensorial frustration (body scheme disorder), and depersonalization disorders of varying severity, polar affective fluctuations, panic attacks, anxiety, and psychomotor exaltation [68; 78]. Among the significant somatic disorders in the acute period of intoxication by tryptamines, it is possible to note cardiac rhythm and conduction disorders, and a malignant hyperthermia [61]. In a habitat, bufotenine originates from the Bufo genus of toads (skin), fly agarics, plants of the Anadenanthera peregrine/Piptoderma peregrina class [59]. The psychoactive effect of bufotenine is bound to its fermentation in the body to 5-MeO-DMT. Consumers use bufotenine by means of smoking the crystals received by exsiccation of the secret derived from the toad skin. The peroral use, and intravenous reception of the drug occurs in some self-reports. Designer tryptamines are accessible on the black drug market in the form of tablets, and liquids for smoking [76]. 5-MeO-AMT and 5-MeO-DMT are structurally similar to an amphetamine which explains sympathomimetic effects of these drugs. 5-IT – a positional isomer of amitriptyline and substituted phenylethylamines which has become available on the black market since 2012, produces a strong hallucinogenic and psychoactive effect [68; 69].

## Phencyclidine-like designer drugs.

«Dissociative drugs» are very popular among the consumers, at the same time having reputation of substances to which both medical and legal problems [58–60] are bound. Ketamine hydrochloride («Ketamine») is widely applied for the medical purposes throughout the world. This medicine gained a wide distribution in veterinary practice during various surgical interventions. The ability of the medicine to cause hallucinative disorders, are bound to a function of the central agonizm related to 5-HT2A receptors, the NMDA receptors antagonism, and a high affinity to the mu/delta / sigma-opiod receptors. During its non- medical intake, ketamine is usually used in the form of inhalation of a powder, smoking, or rectal administration, in the wide range of dosages - from 25 to 300 mg. The psychotropic effects produced on the body includes: a thinking rate disturbance, sense of «bifurcation ", depersonalization frustration, a body scheme disturbance, stupefaction to a degree of an affective, and derealization, and depersonalization [84; 85]. During a long-lasting intake of ketamine there can appear a tolerance growth, formation of a mental addiction, formation of «chronic flashbacks», schizophrenic symptoms range state development, chronic disorders of perception, illusory disorders, which are preserved, even after its application quits. In a third of Ketamine consumers with the recreational purpose, the various problems of urological character are noted: a neurogenic bladder, a dysuria, pains in suprapubic area, a hematuria, a decrease in bladder capacity, a hydronephrosis, and the change of a histological picture of tissues of bladder. Among other somatic problems connected immediately with the Ketamine intake it is possible to note the various GL problems [85]. The use of high doses of the medicine during its application can cause the development of a cardiovascular and respiratory failure. Paresthesias, hypomyotonia, various perception disturbances owing to the use, can be the cause of injuries, burns, falling [47; 50]. Metoxylamine (MXE, «Special M») is the https://interactive-plus.ru 10

designer analog of Ketamine [49] which has appeared rather recently on the black market. It is used orally, by a powder inhalation, by a parenteral administration, a sublingual intake is possible. The range of doses various from 5 to 100 mg [9; 80; 77; 66]. «MXE» has the NMDA receptors antagonism, and also affects as an inhibitor of dopamine and serotonin transportation. A majority of «MXE» consumers in their self-reports point to the prolonged psychotropic effects after its use. This drug is positioned by the underground producers as an absolutely safe analog of Ketamine. However, the closer studying and observation of the patients taking «Special M» causes serious concern in medical specialists [85]. There are described cases of the heavy cerebellar disorders development, epileptiform disorders, in a state of acute intoxication. Several fatal cases after the «MXE» intake [68] are described. Difenidin («DND»), and metoxphenidin («MXP», «Mexican peso»), are new Lefetamine- derivative designer drugs. Affect as the NMDA receptors antagonist, and as inhibitors of serotonin transportation, dopamine agonists, and opioid agonists [84]. These narcotic substances are taken orally, by a powder inhalation of, by intravenous introduction – in dosages from 50 to 150 mg. The duration of their action varies from 8 to 12 hours [85]. When high doses of «DND» and «MXP» over 180 mg are ingested, there may develop a serotonin syndrome [80,83,76]. Dextromethorphan («DXM»)-OTC medicine for cough treatment used in a number of countries of Europe and America. Avery weak mu-opioid receptors agonist, acting as the NMDA receptors antagonist, and, can be a serotonin transport suppressor. Many authors point to a possibility of the tolerance growth, and formation of the phenomena of the mental and physical addiction as a result of its recreational application. As a result of the long-lasting abuse of Dextromethorphan, in the period of its deprivation there may develop various alienations in the state: subpsychotic affective fluctuations, anxiety disturbance, dysphoric reactions, resistant insomnia, flashbacks [8,9]. An abrupt cessation causes also a number of somatic withdrawal symptoms: vomiting, diarrhea, pains in various muscle groups, a profuse diaphoresis. The use of high doses of Dextromethorphan for the non-medical purposes can cause the development of a serotonin syndrome.

## Resume

The number of new psychoactive substances appearing on the black market grows from year to year. Psychiatrists and narcology experts are seriously challenged by a difficult laboratory identification of these substances. The use of new psychoactive substance causes an imbalance of neurotransmitters that leads to the development of psychopathological disorders. The emergence of psychotic disorders is most often bound to: 1) strengthening of dopamine; 2) activation of cannabinoid CB1-receptors; 3) activation of 5-HT2A receptors; 4) the fissile antagonism related to NMDA receptors; 5) activation of k-opioid receptors. Children, teenagers, persons suffering from different mental disorders are the most vulnerable to the new threats of designer drugs distribution. This part of the population, by means of web technologies, can fall a victim of black sellers of illegal online stores where new surfactants are represented as completely safe for health. A particular knowledge concerning new surfactants can be gained at specialized Internet forums which, despite blocking, continue working. It should be clear that the knowledge about new psychoactive substance mechanism of action, gained from the Internet, without independent check, and independent clinical trials, cannot claim reliability. Consumers of the psychoactive substances more often seek medical care only in medical emergencies, though concealing the fact of surfactant intake; at the same time the padding complexity for physicians is created by the negative laboratory tests on the commonly used surfactants, with the available clinical manifestations. This circumstance creates difficulties in the choice of the therapy tactics when the state of one or another psychopathological disorder is developing. In view of the new SAS pharmacology and toxicology uncertainty, benzodiazepines can be the medicines of choice in this situation. In case of poor effect of the benzodiazepines use, neuroleptics can be applied as the padding medicines.

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