Approach to Classifying "Design" Drugs and New Potentially Dangerous Chemical Substances, With a Brief Review of the Problem

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ABSTRACT

The urgency of this study has become vivid in the light of the growing problem of prevalence and use of new synthetic drug types. Lately there has been a tendency of expanding the range of psychologically active substances (PAS) used by addicts with the purpose of their illegal taking. The aim of this research is an attempt of systematizing and classifying "design" drugs according to their chemical structure, neurochemical mechanisms of action and clinical manifestations. As a result, we have found that they can be divided into ten big groups. This classification will allow to better arrange new clinical phenomenology in modern addictology. This paper would be useful for psychiatrists, experts in narcology, as well as for personnel of institutions and agencies engaged in anti-drug activity.

Introduction

Urgency of the problem

Recently, the sphere of illegal turnover of narcotic substances has shown an apparent trend of producing the so-called "design drugs" (DN): new potentially dangerous psychologically active substances (NPDPAS) obtained by means of chemical synthesis, possessing a high narcotic effect and manufactured with the

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purpose of bypassing the existing legislation on control of drug trafficking (Asadullin, Akhmetova & Uritsky, 2015). Presently the classification of the latest synthetic substances is complicated and has a lot of allowance. Mainly, these are only separate representatives of certain psychologically active substances that have been subjected to classification (Shevyrin & Morzherin, 2015). A number of researchers classify and describe narcotic drugs based on similarity with some natural analogs of these substances that produce a similar effect. This natural substance is considered the progenitor of a certain group of drugs (Shevyrin & Morzherin, 2015; Golovko, 2015).

Aim of the research

The purpose of this research is an attempt to create a classification of modern synthetic drugs that would be user-friendly for psychiatrists specializing in narcology. The following tasks were set: 1) Analysis of the existing literature on natural and synthetic narcotic substances; 2) Systemization of the data obtained; 3) Stratification of modern synthetic drugs into groups based on their structural and functional peculiarities.

Results and Discussion

For clustering we used the following criteria: 1) chemical structure; 2) neurochemical effect; 3) clinical effect. The research conducted allowed to divide all the "designer" drugs into ten large groups: 1)derivatives of phenylethylamie; 2) Synthetic cathinones; 3) Synthetic cannabinoids (or cannabimimetics); 4) Synthetic opioids; 5) Synthetic derivatives of cocaine; 6) Derivatives of lysergic acid; 7) Synthetic derivatives of tryptamine; 8) Derivatives of phencyclidine (Blockers of NDMA receptors); 9) Derivatives of piperazine; 10) GABA agonists of A/B receptors and their derivatives.

1) Derivatives of phenylethylamine. The following substances refer to these: methamphetamine   (pervitin,   meterin,   "ice"), 3,4methylendioximethamphetamine   (MDMA,   «ecstasy»),   4-methylioamphetamine and many others. 2C-designer drugs of phenylethylamine are also known. The first agent of 2C series was synthesized in 1974 by A.F. Shulgin. The substance is called 2C-B – 2,5-dimetoxi-4-bromphenethylamine ("Nexus"). The main mechanism of action is agonistic interaction mostly with 5-HT2A-receptors. The clinical picture changes with the increase of toxic doses: from stimulatory effects when using small doses to lethal outcome when using large doses. The representatives of the next generation are derivatives of 2C-compounds with substitution of hydrogen in the aminogroup by 2-methoxybenzyl radical, such as 25I-NBOMe, 25B-NBOMe 25C-NBOMe and others. The following substances of this group are represented by coupling of indole or benzofuran and phenylethylamine: 5 and 6-(2-aminopropyl) benzofurans (5-APB, 6-APB), as well as hydrogenated derivatives and additionally substituted on the amino group, such as 5-MAPDB. Substances of the following generation of this composition are defined as derivatives of 2C composition and benzodihydrofuran - 2-C-B-FLY, 2C and benzodifuran - Bromo-DragonFLY, 2C and benzohexahydrodipyran - 2CB-ButterFLY. Derived 2-aminoindans should also be referred to this group. The main representatives are 5,6-methylendioxi-2-aminoindan (MDAI), 5,6- methylendioxi -H-methyl-2-aminoindan (MDMAI), 5-iodo-2- aminoindan (5-IAI), 5-methyl, 6-metoxi-2-

aminoindan (MMAI) (Akhmetova et al., 2016; Golovko, 2015; Poklis, 2015; Lowe, 2015).

2) Synthetic cathinones. Natural cathinone (norethedrine) is an alkaloid first isolated from khat (Catha edulis). One of the first synthetic cathinones, methcathinone, was synthesized in 1928. Synthetic cathinones can be divided into two large groups: derivatives with cyclization of the amino group into the pyrrolidinone ring - methylendioxypyovalerone (MDPV), alpha-PVP, alpha-PVT, MHPH, etc. and ß-ketones with a free amino group – methylone, ethylone, mephedrone etc. Their common principle of action is based on inhibiting reuptake and stimulating excretion of norepinephrine, serotonin and dopamine in the nerve endings. The clinical picture of acute poisoning is characterized by pronounced delirium, paranoiline condition, anxiety. The main toxic manifestations are nausea, severe headache (Akhmetova et al., 2016; Golovko, 2015; Abbott and Smith, 2015).

3) In the last few years there has been a sharp rise in synthetic cannabinoids (SC) withdrawal and their detection in biological media of examined patients. They first entered the Russian drug market as legal smoking blends (“spice”) being delivered in the form of dried herbs pre-processed by chemical substance with psychotropic effects. In 2009 it was it was established that the active ingredient mixtures are synthetic analogs of a substance of plant origin – tetrahydrocannabinol (Δ9-THC) isolated from cannabis by Raphael Mechoulam in 1960s. The progenitor of SC is the substance HU-210, created in Jerusalem university (HU – Hebrew University) in 1988 under the leadership of professor R.Mechoulam. Research groups under the guidance of professors J.W.Huffman and Aleksandros Makriyannis also contributed to SC synthesis. They synthesized such products as JWH-018; JWH-081; JWH-250; AM-2202; AM-2201. SC represent by themselves substances possessing the ability to affect cannabinoid receptors– CB1 и CB2. The stimulating effect of CB1 receptors in the central nervous system results in pronounced psychotropic effects. Stimulation of CB2 receptors in the cells of the immune system causes immunomodulating effects with anti-inflammatory action (Akhmetova et al., 2016; Bokhan, 2015; Mendelevich, 2014).

All the synthetic cannabinoids may be divided into the following six subgroups presented below (Shevyrin & Morzherin, 2015; Chavant, 2015; Golovko, 2015):

1.Classical cannabinoids: Derived dibenzopyran, tetrahydrocannabiol, other chemical compounds presented in cannabis, and structurally related synthetic analogs such as HU-210.

2. Non-classical cannabinoids: Derived cyclohexylphenol or 3-arylcyclohexanol, such as CP 47497 and CP 55940.

3. Hybrid cannabinoids: Combined structural features of classical and non-classical cannabinoids, such as AM-4030.

4. Aminoalkylindoles, which can be further divided into the following groups: a) naphthoylindoles (such as JWH-015, JWH-018, JWH-073, JWH-081, JWH-122, JWH-200, JWH-210, JWH-398); b) phenylacetyl indoles (such as JWH-250, JWH-251); c) benzoyl indoles (such as pravadoline, AM-694, RSC-4); d)naphtylmethylindoles (such as JWH-184); e) cyclopropoyl indoles (such as UR-

144, XLR-11); f) adamantoilindoles (such as AB-001, AM-1248); g) indole carboxamides (such as APICA, STS-135).

5. Eicosanoids: Such endocannabinoids as anandamide (AEA), and their synthetic analogs, such as methanandamide (AM-356).

6. Others: Those comprise other structural types like diaryl pyrazoles (such as Rimonabant®), naphtoyl pyrroles (such as JWH-307), naphtylmethyl indenes (such as JWH-176) and indazolecarboxamides (such as APINACA).

Synthetic cannabibimetics of the latest generation:

a) Indazolecarboxamides: AB-PINACA, AB-FUBINACA, AB-CHMINACA, ADB-FUBINACA, ADB-PINACA, APINACA.

b) Indolyl carboxamides: APICA (ADM-018), STS-135 (ADM-2201), CBM-2201, ADBICA, ADBICA-F.

c) Indolyl ketones: UR-144, XLR-11, RCS-4, AM-2201, AM-1220, AM-1248.

4) Synthetic opioids. In 1874 diacetylmorphine (diamorphine), more known as heroine, was synthesized by an English chemist Alder Wright. By methylation of morphine they obtain codeine. Codeine containing medications are the base for producing desomorphine. New "design"-opioids have been emerging in the market in the last few years: μ-opioid agonists AH 7921– 3,4-dichloro-N-{[1-(dimethylamino)cyclohexine]methyl}benzamide, derivatives of piperidine W15 and W18, 4-fluorobutyl phentanyl («4FBF»), methylphenylpropionoxipiperidine («MPPP») and piperazine MT-45 (1-cyclohexyl-4-(1,2-diphenylethyl) piperazine), as well as the analog of methadone IC-26. Synthetic opioids produce the following effects: analgesia, sedation, euphoria. They also produce a depressing effect on the respiratory center. The narcotic effect is connected with changes in opioid receptors, disintegration of "opioid receptors-secondary mediator systems" bonds, malfunction of the dopaminergic neurotransmitter system (Ismailova, 2013; Vorce, 2014; Helander, Beackberg & Beck, 2014).

5) Synthetic derivatives of cocaine. These include phenyltropane group. RTI series is distinguished, such as RTI-111, RTI-112, RTI-126 etc. Another group comprises the derivatives of tropacocaine, a minor alkaloid of cocci («Erythroxylum coca»), such as PFBT (fluorotropokokain). Under inhalation use it produces euphoric state, excessive talkativeness, insomnia, asthenia. Substances within this group act as inhibitors of reuptake of serotonin, dopamine and norepinephrine (Abbott & Smith, 2015).

6) Derivatives of lysergic acid. Seeds of morning glory and Hawaiian rose, as well as the parasitic fungus ergot, contain amides of lysergic acid. The simplest of them, ergine, was the original source of synthesis of LSD (N,N-diethylamide of lysergic acid). Synthetic LSD was first synthesized by Hofmann and Stoll in 1938 in the laboratory of a Swiss firm named Sandoz. The chemical analog of LSD is ALD-52 (N-acetyl-LSD) which forms LSD during the hydrolysis (Chavant, 2015).

7) New synthetic derivatives of tryptamine. According to their chemical structure tryptamines (TA) refer to indolalkylamines among which N-substituted tryptamines such as N,N-diethitryptamine (DET), N,N-diallyl-5-metoxitryptamine (5-MeO-DALT), N,N- diallyl -4-hydroxitryptamine (4-HO-DALT), N,N-dimethyl-5-metoxitryptamine (5-MeO-DMT), and α-alkyltryptamines, such as α –methyltryptamine (AMT), 5-metoxi-α–

methyltryptamine (5-MeO-AMT), 5-metoxi- diisopropyltryptamine (5-MeO-DIPT) are distinguished. In forming the narcotic effect excitation of the 5-HT2A and 5 - HT1A-histamine receptors is of significance. The clinical picture consists in visual hallucinations, accompanied by the phenomena of derealization and depersonalization (Arunotayanun, Dalley & Huang, 2013).

8) Derivatives of phencyclidine. Blockers of NMDA receptors are represented by the PCP and its derivatives - ketamine, methoxiamine (MXE, "SpecialM"), a group of diarylethylenes which includes definedin (ДНА), metoxiphenyl (MXP). Phencyclidine was synthesized in 1956 and was used as general anesthetic in surgery. Starting from mid-70s of the last century the series of "design"-phencyclidines has been used for abuse (PCM, PCH, PCE, TCP, TCM, 3 or 4-Meo-PCP etc.). As an alternative to phencyclidine ketamine was synthesized by K. Stevens in 1962. The effects of synthetic ketamines are connected with central 5-HT2A agonism, antagonism of NMDA receptor, and high affinity for μ-/ δ- /σ -opioid receptors. Symptom of withdrawal is accompanied by dyspeptic symptoms, myalgia, increasing anxiety, insomnia (Graeff, 1997).

9) Derivatives of piperazine. In 1973 two teams of researchers, Bye et al. (1973) and Campbell et al. (1973), showed that benzylpiperazine (BZP) produces pharmacological effects that are very similar to amphetamine. Benzylpiperazine, 3-Trifluoromethylphenylpiperazine (TFMPP), meta-chlorophenylpiperazine (mCPP), 4-flluorophenylpiperazine (p-FPP) are frequently used in combination with МДМА, "extasy", as related components or are passed off as "extasy" (Chavant, 2015; Golovko, 2015).

10) Agonists of GABA A/B receptors and their derivatives. Alongside with the activation of GABA A/B receptors, the effect of these compounds is stipulated by the increase in the level of dopamine in the central nervous system. Gamma-hydroxybutyric acid (GHB) was developed as anesthetic of about 50 years ago. Currently, synthesised gamma-butyrolactone (GBL) and 1,4-butandiol are used. High doses promote sleepiness, lethargy. Confusion, delirium, hallucinations, convulsions may also arise (Nenastieva et al., 2015).

Gabapentines - pregabalin, gabapentin. The mechanism of their action is based on the ability to bind to the alpha-2-Delta subunit of calcium channels in neurons (calcium channels of N- and P/O type) due to which the absorption of calcium into neurons decreases. As a result, there occurs a reduction or cessation of the release of neurotransmitters, including glutamate and norepinephrine. Gabapentin is used in the treatment of epilepsy, anxiety disorders and neuropathic pain. Because of the release of information about pregabalin abuse, at the end of 2015, in Russia this drug was included in the group of subject-quantitative account. Professor E.M. Krupitsky (2016) notes that the use of pregabalin because of the development of dependence should be distinguished from self-intake of it without medical prescription under medical treatment of withdrawal syndrome of opiates.

Conclusion

For a detailed analysis of new synthetic drugs, and possible forecasting of future threats, there is a need in a user-friendly taxonomy and classification of such substances, an example of which is proposed in this article. It will allow us to respond more quickly to the emergence of new narcotic drugs and new

potentially dangerous psychoactive substances, and to identify possible ways of dealing with them.

Recommendations

This paper would be useful for any officials of narcological patient care institutions, narcological psychiatrists, experts in narcology and preventology, as well as for personnel of institutions and agencies engaged in anti-narcotics activity.

Disclosure statement

No potential conflict of interest was reported by the authors.

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