Synthetic Cathinones and Cannabinoids Are New Psychoactive Substances (Review)

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New psychoactive substances, or designer drugs, are currently a large group of substances, primarily of synthetic origin, which are designed and come on a shadow market in circumvention of the current law. The popularity of these substances among young people is due to the off-the-shelf availability, low cost, and expected safety compared to traditional drugs. As practice shows, a resulting intoxication is life-threatening.

Currently, the ordered data on these substances classes, as well as clinical manifestations of poisoning related to their consumption is practically non-existent due to certain difficulties in their diagnosis. The review considers the main groups of new psychoactive substances (synthetic cathinones and cannabinoids, derivatives of piperazine, aminoindans) circulating in a shadow market. We have distinguished the basic mechanisms of their effect on human body and described the main manifestations of their consumption.

When writing the review we used the data of specialized poison control medical centers, as well as the information obtained from users.

Key words: new psychoactive substances; synthetic cathinones; bath salts; mephedrone; synthetic cannabinoids; spice.

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history data of drug-addicts. Therefore, the obtained information has low scientific value. The description of symptoms arising from taking a certain substance is impeded, since a substance is scarcely ever detected or the intoxication is due to the consumption of several substances.

To analyze the current situation, assess pharmacological and clinical effects of the most common NPS classes, we have chosen and studied the publications with the data on pharmacology, epidemiology, clinical manifestations of NPS effects, as well as the reports of monitoring centers of European and American countries.

**New psychoactive substances usage in Europe and USA**

Now it is hard to say when these substances have gained popularity and become widespread, but they were first mentioned in USA in 2006, in Europe they have been first reported about since 2008, in Russia — since 2009 [8].

In Germany drug trafficking is under government control, and governed by Medicines Act (Arzneimittelgesetz, AMG) and Drug Act (Betäubungsmittelgesetz, BtMG). To dodge the law, NPS are presented as chemical substances for researches, herb repertory or aromatic bath salts, and marked "for external application only". It will take a long time to detect and report about a new substance, which includes its characteristics, control measures at the European level, and, finally, the implementation of elaborated instructions by common European national legislative authorities. Thus, a great number of NPS fall outside the scope of BtMG law.

Before 2009 UK Poisons Information Service did not record telephone calls related to synthetic cathinones. However, over the period from 2009 to 2010 the number of inquiries for synthetic cathinones and their derivatives equaled to those for cocaine and MDMA (3,4-methylenedioxymethamphetamine) [9]. Web-based Google application, which monitors the search criteria and volume, demonstrates no inquiries for mephedrone before 2008. The situation drastically changed in 2009, when in Great Britain the inquiries for mephedrone set records and reached a peak. Most synthetic cathinones became popular due to their legal status.

A great deal of evidence on using NPS has been collected in MoSyD study (Monitoring System for Drug Trends, Frankfurt on the Main, Germany) [10]. In 2012 the abundance of NPS usage was found in 7% of population aged 15–18. Moreover, 16% respondents declared that they knew others who used NPS. More information has emerged about NPS usage in clubs and among young people at risk. Hermanns-Clausen et al. [11] analyzed the data on 50 patients who were admitted to the emergency department, and were reported to Freiburg Toxicological Centre due to the suspected intoxication by synthetic cathinones from September 2008 to April 2011. In addition, there are reports in Germany including the descriptions of cases with those driving under the effect of synthetic cathinones [12], and case histories of patients with abstinence symptoms and drug abuse after taking the spice under the trademark "spice gold" [13].

As in the situation with many "classical" drugs, it is very difficult to evaluate the prevalence of synthetic cathinones. Most of the information was obtained from reports run during the treatment of drug abusers. Online enquiry of night club visitors in Great Britain showed that 41% respondents used mephedrone and 10% — methylone. One third used mephedrone last month, and 14% respondents reported about its weekly consumption [14]. Another enquiry, in which UK secondary school students and college students took part, demonstrates 20% of them to have used mephedrone at least once, and 4% students reported about daily consumption, all respondents being under 21 [15].

The authors of the Finnish study [16] analyzed the blood of drivers suspected in driving while intoxicated, and found that 286 of 3,000 tests contained MDPV (methyleneoxyprovalerone) (8.6%). 208 of these drivers were tested using such tests as walking on a flat surface, a speech test, and then detained and referred to medical testing. The blood count in most users appeared to have several substances including benzodiazepines, amphetamines, tetrahydrocannabinol and ethanol.

In USA, the data on NPS prevalence and usage are extremely limited. American Association of Poison Control Centers reported about 303 phone calls related to bath salts in 2010, and 2,371 phone calls were recorded in May 2011.

A detail study of NPS prevalence among adolescents enables to conclude that the number of users is greater than those mentioned in statistical reports. The reasons can be the following: the lack or unavailability of information; imperfection of tests for drug detection; rare confirmation by laboratory testing in patients with clinical presentation of unclear etiology and/or uncommon intoxication compared to consumption.

Mephedrone users report about two main ways of purchasing: internet and local dealers. Purchase in retail dealers has become more preferable due to the prohibitions in legislation of many countries, e.g. Great Britain [14, 17]. Currently, the cost of 1 g of mephedrone in Great Britain is about 16£ (25$), it is 10£ more than that before the prohibition [17]. In USA 1 g of the substance costs 20–35$ [18].

Synthetic cathinones can be bought in three main forms: powders, pills, capsules. In 95% cases, when they were withdrawn by Scotland Yard officers, synthetic cathinones were in a form of powder.

**Synthetic cathinones**

Synthetic cathinones are the derivatives of bk-amphetamine (β-keto-α-methyl-phenylalkilamin), which
is chemically similar to methamphetamine "cristal meth" and 3,4-methylenedioxymethamphetamine ecstasy [19] (Figure 1).

Cathinone is isolated from natural raw material: Catha edulis growing in Yemen, local citizens chew it to experience a psycho-stimulating effect [20]. Cathinone extracted from the leaves of this plant acts unless the leaves are flaccid, that is why it can be chewed for several days only.

Cathinone like amphetamine causes sympathomimetic effects including tachycardia and arterial hypertension, and has a psychotropic effect causing euphoria and enhancing anxiety. Regular chewing of the leaves is related to a high risk of myocardial infarction, dilated cardiomyopathy and duodenal ulcer [21].

Cathinone derivatives were used as antidepressants in the Soviet Union in 1930s [22, 23]. Methamphetamine was given to German soldiers during World War II under the trademark Pervitin to struggle with fatigue. Such pharmaceutical as pyrovalerone was studied in France and USA; in 1970 it was used as a stimulator in patients with chronic fatigue. The studies carried out showed its stimulating effect on CNS and revealed motor hyperactivity in volunteers [24].

Synthetic cathinones, especially mephedrone, are currently sold as aromatic bath salts. They can be in the form of crystals of white, beige or brown color [25]. More frequently they are synthesized and packed in China and/or India, and held for sale in Europe and Russian Federation [26]. According to the online survey of British clubmen in 2009, 43% respondents said they used mephedrone at least once [27]. In USA the number of cases of mephedrone intoxication has increased from 2009 to 2011, and started decreasing in 2012 [28, 29].

The prevalence of synthetic cathinones in USA among the senior pupils in 2012 was 1.3% [30], in schools of Germany the indices are the same: 2% [10].

Synthetic cathinones are serotonin, dopamine and non-adrenalin reuptake inhibitors. Selectivity changes from one substance to another [31]. The substances can be divided into three groups [32]:

- cocaine-like type — MDMA of mixed type (mephedrone, methylone, ethylone, butylone, and naphrynone); nonspecific inhibition of reuptake monoamines (dopamine) is approximately five times as high than that of serotonin. All substances except naphrynone, promote serotonin release. Mephedrone contributes to dopamine release;
- methamphetamine-like type (cathinone, flephedrone, and methcathinone): these substances selectively inhibit dopamine and norepinephrine reuptake and stimulate dopamine release;
- pyrovalerone-like type (pyrovalerone, MDPV): selectively inhibit catecholamine reuptake, do not promote the release of monoamines.

Flephedrone, mephedrone and methcathinone are 5HT2A receptors agonists. Blood-brain barrier is highly-permeable for mephedrone and MDPV [31]. These substances are metabolized under isoenzymes of P-450 cytochrome and produced by the kidneys or biliary system [6].

Synthetic cathinones are usually taken in two ways: intranasally — by insufflating the powder through nose and by swallowing [9, 33]. “Bombing” is the way of swallowing, when powder is wrapped in tissue paper and swallowed [34]. Conveniendy, 1 g of the substance can be divided into 5–8 doses [35]. It has been known from the interviews of drug addicts undergoing treatment that the range of doses is wide, they varying from several mg to over 1 g [9, 14, 33, 36]. Consumers cannot know an accurate concentration of an active substance contained in powder, it depending on a manufacturer [33, 35].

Currently, the following descriptions are available: rectal administration, gum rubbing, inhalation, and intramuscular or intravenous administration [34, 27]. Mephedrone users say that a psychotropic effect comes 10–20 min after intranasal administration, with expected duration of about 1–2 h, after swallowing — in 15–45 min with duration of 2–4 h. Those who prefer intravenous administration, report about a desired effect reaching its maximum within 10–15 min and with 30-minute duration [27].

The effects reported by users. Desired effects according to users of synthetic cathinones include: energy increase, sympathy and sociability, increased libido [14, 37]. Approximately 20% users stated the side effects of mephedrone [15, 33]: diaphoresis, palpitation, nausea and vomiting, headache, muscular twitching, vertigo and short memory loss (Table 1).

When comparing cocaine and mephedrone effects, 60–75% responds mentioned the longer effect of mephedrone; 50% considered mephedrone to have “the best” effect, while other 50% gave their preference to cocaine. The half of respondents stated the use of cocaine to be as dangerous as that of mephedrone. However, 25% respondents said mephedrone to be less dangerous, and 25% declared its complete safety [27, 39].

Several groups of substances are popular among the consumers of synthetic cathinones. More that...
Clinical effects related to the use of synthetic cathinones, according to the users` reports [14, 27, 35, 37, 38]

<table>
<thead>
<tr>
<th>Manifestations in impaired functioning of systems and target organs</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular system</td>
<td>Palpitation, breathlessness, chest pain</td>
</tr>
<tr>
<td>ENT</td>
<td>Xerostomia, nasal bleeding, rhinolalia, nasal “burn”, pain in oropharynx, tinnitus</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Stomachache, anorexia, nausea, vomiting</td>
</tr>
<tr>
<td>Genitourinary system</td>
<td>Anorgasmsia, erectile dysfunction, increased libido</td>
</tr>
<tr>
<td>Musculoskeletal manifestations</td>
<td>Arthralgia, numbness, tingling, muscular rigidity and muscle spasm</td>
</tr>
<tr>
<td>Neurological system</td>
<td>Aggressiveness, teeth grinding, vertigo, headache, memory loss</td>
</tr>
<tr>
<td>Ophthalmological manifestations</td>
<td>Visual deterioration, pupillary dilation (mydriasis)</td>
</tr>
<tr>
<td>Pulmonary manifestations</td>
<td>Shallow breathing</td>
</tr>
<tr>
<td>Psychological manifestations</td>
<td>Anger, anxiety, auditory and visual hallucinations, depression, dysphoria, sympathy, euphoria, weariness, formication (tactile hallucinations), short-period bursts of energy, enhanced and reduced attention concentration, talkativeness, panic, paranoia, restlessness</td>
</tr>
<tr>
<td>Others</td>
<td>Fever, “mephedrone” smell, diaphoresis, nightmares, skin rash</td>
</tr>
</tbody>
</table>

80% respondents reported about combined usage of cathinones with alcohol, smoking, MDMA, cannabis, cocaine [14]. All patients admitted to the intensive care unit with the diagnosis of mephedrone overdose used several drugs [36]. Screening assay of drug urinalysis [18] revealed 16 cases of 17 to show drugs of other groups. Frequently, the postmortem toxicological evaluation also shows the presence of drugs of different groups [40–42].

Those who use synthetic cathinones report about euphoria, increased motor activity, talkativeness, the origin of movement need, and the need to do something, mood improvement, reduced aggression, clear consciousness, sexual activity increase and increased music appreciation [27, 43]. The doses within the range of 5–20 mg are usually taken by mouth or intranasally, though rectal and intravenous administration is also possible [43].

The drugs of this group cause strong addiction with a constant desire to increase a dose: 80% users said that they purchased more mephedrone than they had initially intended [44]. There is the information about drug users who injected more than 10 single doses one by one [45]. Users concern most of all about their body odor, the smell appearing when using mephedrone [46]. The rare complications include: syncope, ST segment alterations, and myocarditis [47]. Psychotic changes after using “bath salts” include the following: paranoia with auditory and visual hallucinations [48], which can persist up to 4 weeks [48, 49]. In most cases, intoxications proceeding with psychotic signs is the consequence of MDPV usage [29].

Side effects of using synthetic cathinones according to the records of specialized medical facilities. Cardiovascular, psychiatric and neurological symptoms and signs are the most common side effects of synthetic cathinones.

The most typical syndrome is excitement, which develops from moderate to severe psychosis requiring medical sedation. The retrospective data of British National Poisons Information Service shows that 28% cases of supposed intoxication caused by synthetic cathinones were accompanied by excitement and aggression [9]. In a clinical series of 72 patients admitted to London intensive care unit with suspected synthetic cathinone intoxication, 39% patients were in a state of excitement. Laboratory findings confirmed mephedrone use in nine of these patients [37]. In a retrospective review of Scottish intensive care unit data, excitement was also qualified as the most common sign [50]. The researches carried out in USA give evidence of excitement in 66% intoxication cases caused by synthetic cathinones [18].

The complications associated with cardiovascular system rank second after excitement and, according to various sources, account for 25–30%. The difficulties in receiving reliable information are due to the fact that a substance causing intoxication is not always detected, or intoxication is caused by a combination intake of several substances [40–42].

Table 2 demonstrates the most common symptoms and syndromes accompanying synthetic cathinones inone intoxication mentioned in the reports of specialized medical centers. Hyponatremia is a common complication resulting from MDMA intake. Hyponatremia is considered to be the consequence of overhydration caused by drug-induced secretion of vasopressin [51].

The role of synthetic cathinones in the changed balance between sodium and water in body is still unclear. In literature there are the descriptions of three cases of hyponatremia resulted from the intoxication of synthetic cathinones. Mephedrone was revealed in all three cases, while MDMA was not found.

A 14-year-old girl after taking alcohol with white color powder was admitted in critical condition, Glasgow coma scale score being 11. The tests showed hyponatremia:
118 mmol/L, with concurrent increased intracranial pressure. NMR revealed subcortex changes of the white matter. Neurological signs were arrested against the background sodium balance normalization. Moderate dysphasia and anterograde amnesia were persisting. Complete normalization was recorded two months later [56].

Two other cases were fatal. A 29-year-old man was admitted to the intensive care unit being in coma. Tests showed hyponatremia: 125 mmol/L. Computed tomography revealed cerebral edema. He died after brain death after removing from life support [52].

An 18-year-old woman after taking cannabis and mephedrone underwent cardiac arrest. She was resuscitated. Tests revealed hyponatremia: 120 mmol/L. Computed tomography revealed cerebral edema. She died 36 h after admission [57].

Postmortem reports

**Mephedrone.** The first fatal case of mephedrone intoxication accompanied by hyponatremia was described in Sweden [57]. Then reports of other fatal cases related to mephedrone intoxication followed. All those cases were studied and analyses were performed to reveal the role of mephedrone in the death cause. There were described four lethal cases associated with mephedrone usage that showed one of them to be reliably caused by mephedrone.

A 19-year-old man had convulsions several hours after taking mephedrone, MDMA and alcohol. When found, “his eye were rolling, and he was choking with cough”. While being taken to hospital, he had heart arrest, and resuscitation had no effect, the patient passed away. The postmortem toxicological analysis showed alcohol, 3-fluoromethylphenylpiperazine and mephedrone in blood [41].

The second case was a 49-year-old woman, who felt acute retrosternal pain after mephedrone inhalation, alcohol drinking and cannabis smoking. The cause of death was mephedrone intoxication with accompanying factors, such as cardiac fibrosis and coronary artery atherosclerosis [41].

Moreover, mephedrone as a contributing factor was mentioned in two other cases: the death of a patient with multidrug overdosage, and a fatal crush [41].

Mephedrone caused the death of a man with delirium, who broke a pane of glass and cut his hands. The death was caused by mephedrone intoxication with excessive bleeding, however, the toxicological test revealed several substances except mephedrone: cocaine and its metabolites, MDMA [42].

In United Kingdom, from September 2009 to October 2011, there were recorded 128 fatal cases associated with mephedrone usage: of 62 cases that could be estimated, 26 deaths were caused by an acute toxic effect, and 18 suicides were committed against the background of a long-term intake of mephedrone [58]. MDPV, butylone and mephedrone played a key role in fatal cases in 2011 and 2012 [32].

**Methedrone.** Two fatal cases associated with methedrone use were recorded in Sweden. One of them had hyperthermia up to 42°C. The autopsy in both cases revealed pulmonary tissue edema [59].

**Butylone.** There are reports about two deaths related to butylone intoxication. The first sufferer succumbed to injuries falling from height. The postmortem toxicological evaluation revealed butylone in blood. Another case: a woman died of taking butylone in combination with other substances. The autopsy discovered cerebral edema, pulmonary edema and multiple hemorrhages: in the lungs, liver, spleen and kidneys, as well as myocardial necrosis being found [60].

Currently, medical literature has no descriptions of fatal cases resulted from the intoxication of MDPV and other representatives of synthetic cathinones.

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**Table 2**

Clinical effects related to the use of synthetic cathinones, according to medical centers (including intensive care units) and poison control centers [9, 18, 37, 50, 52–55]

<table>
<thead>
<tr>
<th>Manifestations in impaired functioning of systems and target organs</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular system</td>
<td>Chest pain, arterial hypertension, tachycardia, myocarditis</td>
</tr>
<tr>
<td>ENT</td>
<td>Nasal bleeding</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Stomachache, renal dysfunction, nausea, vomiting, renal failure</td>
</tr>
<tr>
<td>Musculoskeletal manifestations</td>
<td>High creatinine kinase, peripheral vasoconstriction, rhabdomyolysis</td>
</tr>
<tr>
<td>Neurological system</td>
<td>Excitement, aggression, mental status change, vertigo, drowsiness, dystonia, headache, hyperreflexia, myoclonia, paraesthesiae</td>
</tr>
<tr>
<td>Ophthalmological manifestations</td>
<td>Visual deterioration, mydriasis</td>
</tr>
<tr>
<td>Pulmonary manifestations</td>
<td>Shallow breathing, tachypnoea</td>
</tr>
<tr>
<td>Psychological manifestations</td>
<td>Agitation, hallucinations, paranoia, psychosis</td>
</tr>
<tr>
<td>Renal manifestations</td>
<td>Renal dysfunction, acute renal failure</td>
</tr>
<tr>
<td>Others</td>
<td>Diaphoresis, fever, hyponatremia, skin rash</td>
</tr>
</tbody>
</table>
Synthetic cannabinoids

The first experience on preparing substances having an effect on cannabinoid receptors can be referred to 1960s [61, 62]. First cyclohexylphenols (CP series) were first synthesized in the 70–80s by a pharmaceutical company Pfizer (USA) [63, 64]. Later, since the start of the 90s till the present time, a large part of cannabinoids has been synthesized under the guidance of American chemists John W. Huffman and A. Makriyannis, therefore these substances got the corresponding abbreviations: JWH and AM [65]. Synthesis of new substances (agonists, antagonists and inverse agonists) pursued several aims:

1) antagonists of the first subtype (CB1) cannabinoid receptors were considered as potential means for substance abuse (nicotine, opiate, cocaine, alcohol, cannabis, etc.) therapy, as well as for obesity treatment [66–68];

2) to obtain high-affinity ligands for cannabinoid CB2 receptors, since the agonists of corresponding receptors are presented by promising in the terms of the therapy of neurodegenerative, immune oncological and other diseases [69, 70];

3) to study endocannabinoid neurotransmitter systems [65, 71].

The first spice appeared in Europe in 2005. Its advertisement claimed that a psychotropic effect was due to its natural plant components [72]. Its true active substance was found in 2009 by Auwärter et al. in Freiburg University (Germany), it appeared to be a synthetic agonist of cannabinoid receptors (CB) [73].

CB-agonists are classified according to their chemical structure [74] (Figure 2):

- classical cannabinoids, such as Δ⁹-tetrahydrocannabinol (THC) isolated from natural marihuana (Cannabis sativa), antiemetic agent (nabilone) and HU (Hebrew University) cannabinoids, which have close affinity to THC;
- nonclassical cannabinoids, such as cyclohexophenol; aminoalkylindoles — JWH series, synthesized by a chemist J.W. Huffman, contain many CB ligands;
- eicosanoids, such as endocannabinoid anandamide.

Synthetic cannabinoids are sold under the mask of herb repertory, and presented as the substances of plant origin. However, the fact is that intact plant material is oversprayed by synthetic material, which comprises the most spice. The composition indicated on a pack with the herb frequently has nothing in common with the content. One gram of spice averages from 77.5 to 202 mg of synthetic cannabinoid, the variability from one pack to another being high [75, 76]. Thus, a consumer does not know what substance he uses and what the dose is. In addition, β2-mimetic clenbuterol is often a part of the composition. It is responsible for sympathomimetic manifestations of spice intoxication, such as tachycardia, hypokalemia. Moreover, a large amount of tocopherol (vitamin E) can be found in the composition, and the function of tocopherol is the active substance masking [74].

The study of cannabinoid system showed several hundreds of agonists, which exhibit

**Figure 2.** Classification of agonists of cannabinoid receptors according to their chemical structure [74]. Classical cannabinoids: (a) Δ⁹-tetrahydrocannabinol (THC), isolated from natural marihuana (Cannabis sativa); (b) nabilone, antiemetic agent, and HU (Hebrew University) cannabinoids, which have close affinity to THC; (c) nonclassical cannabinoids, such as cyclohexophenol; aminoalkylindoles: (d) JWH series, synthesized by a chemist J.W. Huffman; (e) eicosanoids, such as endocannabinoid anandamide.
various affinity degrees to CB1 and CB2 receptors [4]. Endocannabinoid system participates in the regulation of physiological processes, such as thermal exchange, and controls the arterial smooth muscular tone [77, 78]. CB1 type receptors are located primarily in the nervous system, while CB2 receptors are in the spleen, tonsils, and immune cells, as well as on neurons of special kinds [74]. Synthetic cannabinoids are powerful agonists of CB1 receptors, and JWH-018 affinity to CB1 receptors is 5 times higher than in THC, and in AM-695 it is 500 times higher [78, 79].

The users say that spice has more psychotropic effect than marihuana [80]. Synthetic cannabinoids produce THC-like effect, with the change of mood, perception, sleep and wake, body temperature and cardiovascular system functioning [11]. Their side effects are more various and marked than those in THC. The most common ones are tachycardia, arterial hypertension, hyperglycemia, hypokalemia, hallucinations and excitement (Table 3).

Chest pain, myocardial ischemia and psychosis are rare in occurrence [13, 83]. Since spice can contain different substances at different time, therefore, side-effects will be different as well. In USA, for instance, fluorinated synthetic cannabinoid XLR-11 has obtained a wide circulation, its usage being related to the cases of acute renal failure in young men at the end of 2012 [72].

Synthetic cannabinoids are able to cause addiction [13, 83]. Currently, there is little substantiated data on fatal cases resulted from the use of synthetic cannabinoids: one case of fatal coronal ischemia is known, as well as one suicide due to the depression following systematic substance usage [4].

Other new psychoactive substances

**Piperazine derivatives.** Piperazine is a medicinal agent, which is structurally related to various classes of preparations including antidepressants (e.g., trazodone), atypical antipsychotics (e.g., olanzapine), and antihistamines (e.g., cetirizine). Psychotropic derivatives of piperazine, such as 1-benzyl piperazine (BZP) and trifluoromethylphenylpiperazine (TFMPP), became narcotic drugs as early as in 2000 [84]. More frequently, they are oral, or taken in combination with other substances. Piperazine derivatives stimulate the release of dopamine, noradrenaline and serotonin, and inhibit reuptake [85].

Psychotropic substances BZP and TFMPP were studied in controlled researches. Intoxication manifestations are typical for stimulants. The study of effects in combination of alcohol was ceased due to high arterial hypertension, tachycardia, psychomotor agitation, restlessness, hallucinations, vomiting, insomnia and migraine [86]. The manifestations depend on substance concentration in plasma: 0–0.5 mg/L concentration is accompanied by panic, vomiting

### Table 3
Adverse effects of synthetic cathinones (intoxication after effects and signs)

<table>
<thead>
<tr>
<th>Functional impairments</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular:</strong></td>
<td></td>
</tr>
<tr>
<td>tachycardia</td>
<td>37–76</td>
</tr>
<tr>
<td>arterial hypertension</td>
<td>10–34</td>
</tr>
<tr>
<td>cardiogram alterations</td>
<td>2–14</td>
</tr>
<tr>
<td>chest pain</td>
<td>7–10</td>
</tr>
<tr>
<td>hypotonia</td>
<td>2–7</td>
</tr>
<tr>
<td>syncope</td>
<td>3–4</td>
</tr>
<tr>
<td>bradycardia</td>
<td>2–3</td>
</tr>
<tr>
<td>cardiac ischemia</td>
<td></td>
</tr>
<tr>
<td><strong>Neurological:</strong></td>
<td></td>
</tr>
<tr>
<td>vertigo</td>
<td>9–24</td>
</tr>
<tr>
<td>loss of consciousness</td>
<td>2–17</td>
</tr>
<tr>
<td>drowsiness</td>
<td>17–19</td>
</tr>
<tr>
<td>sense shock</td>
<td>2–10</td>
</tr>
<tr>
<td>seizures</td>
<td>3–4</td>
</tr>
<tr>
<td>headaches</td>
<td>3</td>
</tr>
<tr>
<td>ataxia</td>
<td>2</td>
</tr>
<tr>
<td>shivering</td>
<td>4</td>
</tr>
<tr>
<td>irritation</td>
<td>Nd</td>
</tr>
<tr>
<td><strong>Psychiatric:</strong></td>
<td></td>
</tr>
<tr>
<td>excitement</td>
<td>19–41</td>
</tr>
<tr>
<td>hallucinations</td>
<td>11–38</td>
</tr>
<tr>
<td>anxiety/agitation</td>
<td>21</td>
</tr>
<tr>
<td>confusion</td>
<td>9–14</td>
</tr>
<tr>
<td>anterograde amnesia</td>
<td>7</td>
</tr>
<tr>
<td>psychosis</td>
<td>3</td>
</tr>
<tr>
<td>aggressive behavior</td>
<td>3</td>
</tr>
<tr>
<td>delusion</td>
<td>Nd</td>
</tr>
<tr>
<td><strong>Metabolic:</strong></td>
<td></td>
</tr>
<tr>
<td>hyperglycemia</td>
<td>31</td>
</tr>
<tr>
<td>hypokalemia</td>
<td>28</td>
</tr>
<tr>
<td>other electrolytic changes</td>
<td>2</td>
</tr>
<tr>
<td><strong>Gastrointestinal:</strong></td>
<td></td>
</tr>
<tr>
<td>nausea/vomiting</td>
<td>9–28</td>
</tr>
<tr>
<td>renal failure</td>
<td>Nd</td>
</tr>
<tr>
<td><strong>Pulmonary:</strong></td>
<td></td>
</tr>
<tr>
<td>breathlessness</td>
<td>5</td>
</tr>
<tr>
<td>hyperventilation</td>
<td>2–4</td>
</tr>
<tr>
<td><strong>Muscular:</strong></td>
<td></td>
</tr>
<tr>
<td>increased creatine kinase</td>
<td>14</td>
</tr>
<tr>
<td>myalgia</td>
<td>7</td>
</tr>
<tr>
<td><strong>Dermal:</strong></td>
<td></td>
</tr>
<tr>
<td>xerostomia</td>
<td>14</td>
</tr>
<tr>
<td>diaphoresis</td>
<td>4</td>
</tr>
<tr>
<td>pallor</td>
<td>1</td>
</tr>
<tr>
<td>photosensitivity</td>
<td>Nd</td>
</tr>
<tr>
<td><strong>Ophthalmological:</strong></td>
<td></td>
</tr>
<tr>
<td>mydriasis</td>
<td>3–38</td>
</tr>
<tr>
<td>conjunctival hyperemia</td>
<td>14</td>
</tr>
<tr>
<td><strong>Others:</strong></td>
<td></td>
</tr>
<tr>
<td>fever</td>
<td>2</td>
</tr>
<tr>
<td>hyperthermia</td>
<td>Nd</td>
</tr>
</tbody>
</table>

He r e: Nd — no data.
and palpitation, the concentration over 0.5 mg/L is accompanied by excitement and confusion. Attacks can be caused lower concentrations as well: 0.05 mg/L, and if the values are over 2.15 mg/L attacks occur regularly [87].

**Aminoindans.** Psychoactive substances of this group — MDAI (5,6-methylenedioxy-2-aminoindan), 5-IAI (5-iodo-2-aminoindan) and MMAI (5-methoxy-6-methyl-2-aminoindan) — have the so called entactogenic effect (i.e. they enhance the perception of self-emotions), and therefore, they are sold as “legal” MDMA substitutes [88]. These preparations are weak inhibitors of monoamine reuptake, and except this they stimulate nonvesicular serotonin release. 5-IAI and MDAI have spread more widely after mephedrone was banned. Their expected effects are moderate euphoria, distortion of space and time perception, intensive color perception, and the thought that an addict understands better the emotions of other people. An effect starts 10 min after intake, and lasts for an hour, and then gradually becomes exhausted.

Side effects include cardiovascular and nervous disorders. Scientific literature offers not enough data on potential toxicity of 2-aminoindan derivatives. In the experimental study [88] the dose 40 times as high than the dose causing behavioral changes had no toxic effects (including neurotoxic). And still, it does not mean that the substances are safe: the users were found to have hyperemia, serotonin syndrome, acute necrosis of skeletal muscles, and there were fatal cases [88–90].

**Brome Dragonfly.** This substance, 1-(8-bromobenzo[1,2-b;4,5-b']difuran-4-yl)-2-aminopropane, is a substituted phenethylamine with a hallucination effect, similar to LSD [91]. It is a power agonist of 5-HT1, 5-HT2A and α1 receptors. The effect starts 6 h after intake in the form of visual and auditory hallucinations, a sense of well-being and solidarity, and can last for three days [91].

Due to the fact that the number of active substance varies from one lot to another, it may be a problem of overdosage [92]. Brome Dragonfly is very toxic, and can cause acidosis, pulmonary edema, a long-lasting angiospasm leading to gangrene and multiple organ failure [91, 93]. There are reports about fatal cases. The case is known to have vascular spasm, which occurred after taking Brome Dragonfly; despite the therapy, the necrosis of toes developed [91, 93].

**Conclusion**

Today anyone taking NPS can choose a type of a desired narcotic effect, and the necessary narcotic is ordered at single-click ease. Many of these substances have already been included in Narcotic Drugs List and are illegal both in Europe and Russia. However, those who sell narcotic drugs, manage to find new ways to avoid the law and deliver their lethal products to consumers. The most unprotected group is young people, who think the use of NPS is safe and legal. This is precisely why this problem requires a new systemized approach, and adopting new prohibiting or limiting laws.

Federal Law dated February 3, 2015 No.7 “Concerning the Introduction of Amendments to Certain Legislative Acts of the Russian Federation” entered into force in the Russian Federation [94]. This law prescribes to make amendments in Federal Law dated January 8, 1998 No.3 “Concerning Narcotics and Psychotropic Substances” [95], we would like to mention the most significant of the amendments in the present review.

Article 1 of No.3 Law was amended by the paragraphs specifying:

“New potentially dangerous psychoactive substances — substances of synthetic or natural origin, included in the Register of new potentially hazardous psychoactive substances, which are illegal in the Russian Federation;

the trafficking of new potentially hazardous psychoactive substances — production, manufacturing, processing, storage, transporting, transmission, purchase, usage, importation into the Russian Federation, exportation from the Russian Federation, as well as the marketing of new potentially hazardous psychoactive substances (their sale, donation, exchange or their alienation to other people by any ways)”. 

Article 6.9 is amended by article 2, which introduces such concept as Register:

“The Register of potentially hazardous psychoactive substances, the trafficking of which is prohibited in the Russian Federation includes the substances causing in human the state of drug intoxication or other toxic intoxication dangerous to his life and health, as well as those, which have neither Sanitary and Epidemiological Requirements nor the measures of control over their trafficking specified by the appropriate authorities of the Russian Federation”.

Moreover, article 2 presents the procedure to have the substances entered the Register. In turn, Register and Federal decisions on the control over the trafficking of narcotic drugs and psychotropic substances should be published in Internet.

On the other hand, there are still a number of problems requiring further explanations, namely: the determination of new psychoactive substances as the target of crime, their signs and a procedure of assigning them to the substances under control. Moreover, based on the law, there should be developed the methodological guidelines for assigning NPS to Register and then to the list.

Collaterally, from our point of view, it is necessary to carry out a strong information campaign to promote a healthy lifestyle among young people starting with children of primary school age. If we preserve a young generation, we will preserve our future.
References


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incense or cannabinoid designer drugs?  


