

Designer drugs in psychiatric practice – A review of the literature and the recent situation in Hungary

ERIKA SZILY AND ISTVAN BITTER

Semmelweis University, Department of Psychiatry and Psychotherapy, Budapest, Hungary

In recent years service providers experienced a new phenomenon in the drug markets of Hungary: the dramatically increasing sale and use of designer drugs. In psychiatric practice, the first sign of this new trend was the increasing number of hospitalized patients with acute psychosis using a new type of designer drug: MDPV (3,4-Methylenedioxypropylamphetamine). The range of designer drugs available is wider than ever before. They are inexpensive and many times are known to be legal, undetectable, safe or natural to the consumers. In fact, the compounds and their biological effects are many times unknown to the consumers and to the physicians as well, while a recently emerging body of data suggests that the somatic and mental consequences of their consumption are frequent, severe, and sometimes even life-threatening. The aims of this paper are to summarize the most important general information about some widely used designer drugs (synthetic cathinones and cannabinoids); to draw attention to present and upcoming trends of substance abuse patterns; and to highlight the importance and consequences of these trends in every day clinical practice, considering the most important and challenging somatic and psychiatric consequences of designer drug abuse.

(Neuropsychopharmacol Hung 2013; 15(4): 223-231)

Keywords: designer drugs, MDPV, cannabinoids, psychiatric clinical practice

DESIGNER DRUGS

Over the past decade the designer drug industry and sub-culture has exploded, leading to public health and legal problems worldwide.

Designer drugs are produced in laboratories, created to be similar, but not identical to illicit drugs in structure and/or psychoactive effect. Their psychoactive effects, depending on their “parent drug” can range from cannabis-like effects through psychomotor stimulation to hallucinogenic or psychedelic effects. The range of substances available is wider than ever before, thanks to the internet being a global marketplace, and to the problems of legal regulations. They are sold inexpensively as “legal highs” or are deceptively labeled as “bath salt”, “plant food”, “incense”, “spice” and many others. The compounds (and the biological effects) of these chemicals are many times unknown even to the consumers, and they can’t be detected on standard urine drug tests. All these features can explain the worldwide trend of the rapidly increasing use of these substances. On the other hand, their chemical properties, ways of action, adverse

effects, and the potential somatic or psychiatric risks of their abuse are essentially unknown for users and health care professionals as well.

Currently used designer drugs can be classified by their psychoactive properties, by their chemical structure or by their biological targets. The most frequently used drugs can be divided into four major groups (Madras, 2012):

1. Stimulants: synthetic cathinones and amphetamines [eg. mephedrone, MDPV, pyrovalerone, pentylone, pentedrone, APVP (alpha-pyrrolidinovalerophenone), methylone, naphyrone, 4-MEC (4-methylethcathinone), 5-IT (5-(2-aminopropyl)indole), fluoroamphetamine, and many, many others];
2. Cannabinoids (CB): synthetic CB1 agonists (e.g. JWH-018,073; CP-47,497; Am-694; HU-210, and hundreds of other molecules);
3. Hallucinogens: phenethylamines, benzylphenethylamines (e.g. 2C-Bfly, Br-fly, Br-dragonfly);
4. Synthetic opioids: MPPP (1-Methyl-4-phenyl-4-propionoxypiperidine), dextropropion, dezomorphin (crocodile).

We will discuss below the synthetic cathinone group in details and the synthetic cannabinoid group briefly.

HISTORY

Synthesizing cathinone and cannabinoid molecules is not only a phenomenon of recent decades, and the beginnings of designer activity are often related to medical purposes (for summary, see Prosser and Nelson, 2012; Madras, 2012 for example).

Synthetic cathinones: Cathinone is a natural compound found in the leaves of the *Catha edulis* (Khat) plant. Chewing the leaves of this plant for stimulant effects has been popular for centuries in certain Middle Eastern countries, particularly Yemen. The first synthetic cathinone derivatives (methcathinone, mephedrone) appeared in the late 1920s, many of them were synthesized originally for medical purposes. Methcathinone, first synthesized in 1928 was used as an antidepressant in Russia. Pyrovalerone (developed in the 1960s) was used as a drug to treat lethargy, chronic fatigue, and obesity but was withdrawn due to abuse and dependency in patients. Currently, bupropion is the only cathinone derivative that carries a medical indication (Prosser and Nelson, 2012). It's difficult to pinpoint exactly when cathinones started to gain worldwide popularity among drug users. The first widely used synthetic cathinone was mephedrone around 2007, causing an international alert by producing serious intoxications and deaths in various countries (Hadlock et al., 2011). After this compound had been scheduled in many countries, another synthetic cathinone, 3,4-methylenedioxypyrovalerone (MDPV) got popular among drug users, causing seriously negative health consequences again (Coppola and Mondola, 2012a). Currently, MDPV is banned in most European countries, but the emergence of new representatives of this group is continuous.

Synthetic cannabinoids: Herbal incense products as legal alternatives to marijuana started appearing on the internet around 2004 and their use soon became widespread. These products, not being "herbal" or "natural" at all, contain one or more representatives of the several hundred different types of synthetic cannabinoids produced in laboratories. Most of them were developed in the 1980s and the 1990s in the context of pharmaceutical research projects, and originally were not intended for recreational/illicit usage, naturally. They are divided into four main groups. Their most common group, the JWH series (e.g., JWH-018, JWH-073, JWH-210) was

created by John W. Huffman at Clemson University. The AM series (e.g. AM-694) was designed by Alexandros Makriyannis. HU group (e.g. HU-210) was designed at Hebrew University, and CP group (e.g. CP 47,497) was created by Pfizer laboratories (e.g. Madras, 2012).

There are hardly any data available on the epidemiology of synthetic cannabinoid use. Concerning that THC is the most frequently used illicit drug, especially among younger consumers, possibly the use of its hardly detectable, "legal" and "safe" alternatives (which are abundantly available via the internet), is also frequent. According to data of Vandrey et al. (2012), about 11% of US high school seniors admitted using Spice. Abuse of Spice and alcohol was observed in 10 out of 11 adolescents (15–19 years old) evaluated at the South Miami Hospital Addiction Treatment Center in Miami – Dade County, Florida (Castellanos et al., 2011). Jerry et al. (2012) cite 2010 data of the US Drug Enforcement Administration indicating that 30% to 35% of specimens submitted by juvenile probation departments were positive for synthetic cannabinoids.

RECENT SITUATION – HUNGARIAN DATA

Mephedrone appeared on the Hungarian drug market in 2010. After it had been added to the schedule of illicit substances in 2011, it was followed by the spreading of other synthetic cathinones (first of all MDPV, called "MP4" on the street), and the increasing use of herbal blends treated with synthetic cannabinoids (National Drug Focal Point annual report, 2012). After MDPV, other members of the cathinone group and numerous synthetic cannabinoids had been scheduled at the beginning of 2012, the use of these compounds decreased rapidly. Nowadays, according to data of Hungarian National Focal Point and BSZKI (National Drug Focal Point annual report 2012; BSZKI 2011. II. Letter), the emergence of new, partly unscheduled representatives of both groups is continuous. In everyday psychiatric practice physicians regularly see patients with drug-induced psychosis: patients often report the use of MDPV-like new drugs, called "Crystal", "Pentacrystal" or "Benzone", the active compound of them most likely being pentylone, pentedrone, benzedrone, or any other, older or newer, potentially unknown amphetamine or cathinone derivative, or their combinations.

Parallel to the appearance and spreading of new designer drugs, the use of well-known, "classical" illicit drugs, like heroin, decreased. At the same time,

problem drug use and negative health consequences got more widespread.

In 2012 the Hungarian National Focal Point carried out a survey on the new phenomena among the clients of NSPs (needle and syringe programme), outpatient and inpatient treatment units, drug therapy institutes and low threshold programs in Hungary. The majority of the treatment units reported an increased use of new psychoactive substances, first of all synthetic cathinones in 2011 (National Drug Focal Point annual report 2012).

Tarján's data on NSP clients (National Drug Focal Point annual report 2012) show that the proportion of intravenous drug users (IDUs) injecting heroin dropped significantly: the proportion of clients using primarily heroin was 56% in 2009, 47% in 2010, and 24% in 2011. The use of amphetamine (around 40%) and cocaine (below 1%) remained constant over these years. "Other drug" usage was reported in 4% (2009), 8% (2010) and 34% (2011). In 2011, among the clients using "other drugs" (N=760) 40% injected primarily MDPV. In order of prevalence, MDPV was followed by illegally used methadone (26%), mephedrone (17%) and 4-MEC (7.5%). Below the age of 25 the most commonly injected primary drugs were MDPV (42.5%) and mephedrone (30.5%) among "other drug" users.

The trend is also supported by data of Dudás et al. (National Drug Focal Point annual report 2012), who investigated the drug usage customs of patients of voluntary sexually transmitted disease (STD) screening programs (N=186). These data shows again, that while the proportion of primary opioid use dropped significantly (60% in 2010, 27% in 2011), the proportion of "other drug" use increased dramatically (7.7% in 2010, 39.8% in 2011).

According to data, in the "post-mephedrone era" MDPV was the most widely used drug among clients, though several other similar drugs were available on the market. Decreasing number of opiate users was reported, too. Many of the clients injected MDPV, and service providers found that, MDPV-injecting clients rapidly increased the number of drug injecting occasions per day as compared to the clients injecting heroin. Intended and unintended polydrug use was more frequent among clients, the latter mainly due to lack of knowledge of the active agent. Another important feature is that designer drug use seems to cause physical and mental problems in a relatively short time. Many clients reported massive weight loss and deterioration of global somatic condition. After a few months use many of them developed a

psychotic state characterized by paranoid delusions and/or hallucinations. These features can partly explain the facts that designer drug users get in contact with the treatment system relatively soon, and the number of psychiatric hospitalizations is relatively high among them (National Drug Focal Point annual report 2012). According to personal information from dr. Gábor Zacher, their visits in toxicology units are remarkably common, and their symptoms can be severe, requiring intensive care unit treatment.

SYNTHETIC CATHINONES

Pharmacology

Synthetic cathinones are phenylalkylamine derivatives. Due to a ketone group attached at the beta position on the amino alkyl chain attached to the phenyl ring they are often termed as beta-keto-amphetamines (Zaitsev et al., 2011). Similar to phenylethylamine molecules (like MDMA), most of them possess both amphetamine- and LSD-like properties. The amphetamine-like sympathomimetic activity is significant in every representative of the cathinone group, essentially. Other qualities, like LSD-like activity, duration and extent of psychoactive effects, or solubility (so injectability and blood brain barrier penetrancy) vary largely on functional group structure. Usually, with some exceptions, they are less potent than their corresponding phenylethylamine analogues due to their decreased penetration of the blood brain barrier, which is a consequence of their increased polarity (caused by the beta-ketone group) (Coppola and Mondola, 2012a). MDPV is an interesting exception to this rule: due to the pyrrolidine ring and a tertiary amino group in its structure it is more lipophilic than other cathinone molecules, more easily penetrates biological membranes (BBB included), thus it is an especially potent member of the group (Coppola and Mondola, 2012a).

Understanding of the mechanism of action of synthetic cathinones is limited. However, based on similarities in structure to amphetamines or MDMA, similar mechanisms are expected. User reports seem to support this assumption: according to them these agents have both stimulant effects (resembling those of amphetamines) and psychedelic effects (comparable to use of MDMA or LSD) (Newcomb, 2009).

To date, there are few published data on the pharmacodynamics of the currently popular synthetic cathinones. Amphetamines and derivatives seem to exert their effects by increasing synaptic concentra-

tions of biogenic amines, such as dopamine, norepinephrine, and serotonin. These increases occur via two main mechanisms. These molecules inhibit monoamine uptake transporters, causing decreased clearance of the neurotransmitters from the synaptic cleft. In addition, they increase the neurotransmitter release from intracellular vesicles via changes in vesicular pH as well as inhibition of the vesicular monoamine transport (VMAT2) receptor (Cozzi et al., 1999). Furthermore, some of the synthetic cathinones, e.g. MDPV may have a direct 5-HT_{2a} agonist effect (Coppola and Mondola, 2012b).

Psychoactive effects

Similarly to amphetamines or MDMA again, due to their effects on the monoamine systems, synthetic cathinones produce a relatively short (several hours long) “high” after ingestion, insufflation, rectal or i.v. use. The required dose, the duration and strength of the symptoms varies between the different compounds, depending on their chemical structure and properties. The “high” is characterized by alertness, euphoria, intense stimulation, enhanced psychomotor speed, mild sexual arousal, empathy, sociability, increased intensity of sensory experiences, and perceptual distortions at high doses (Madras, 2012), increased blood pressure and heart rate. After the several hours of “high”, a “come-down” period is experienced by many users: feelings of anxiety, agitation, dysphoria, depersonalization and severe craving (Farkas et al., 2013).

Apart from their “desired” effects listed above, synthetic cathinones have numerous negative somatic and mental adverse effects, which will be discussed below.

There is little consistent information on the addictive potential of these drugs. Based on their structures, mechanisms of action and the reports of their users, it is likely that most will have addictive potentials. In surveys of mephedrone users, half of them considered it to be addictive, or reported continuous use for more than 48 hours, and more than 30% of them fulfilled three or more criteria for abuse/addiction, according to DSM-IV (Winstock et al., 2011). Watterson et al. (2012) found that MDPV activates brain reward circuitry and has potent rewarding and reinforcing effects in rat. Psychological and/or physical withdrawal symptoms (irritability, panic attacks, hypersomnia, muscle or skeletal pains, intense craving) are also reported (Kalapos, 2011; Benzie et al., 2011).

Somatic complications

There are numerous papers in international and some in Hungarian literature concerning the somatic adverse effects of cathinone derivatives, mainly that of mephedrone and MDPV. Many of the symptoms detailed in these articles are related to their sympathomimetic toxicity (Jerry et al., 2012). Though the “high” caused by these compounds lasts only for a few hours, the adverse effects caused by them can last for even 24 hours or more. This finding can be explained by the presence of toxic metabolites of these drugs. Consequences of long-term use should also be considered. Adverse effects mainly include cardiovascular, neurological (and psychopathological) symptoms, but respiratory, gastrointestinal and some other side effects are also known, sometimes causing fatalities. (For summary, see e.g. Durham, 2011; Penders and Gestring, 2011; Jerry et al., 2012; Madras, 2012; Coppola and Mondola 2012a,b; Kalapos, 2011; Prosser and Nelson, 2012.)

1. Cardiovascular side effects: hypertension, tachycardia, arrhythmias, Q-T prolongation, chest pain, heart attacks, collapse of cardiovascular system, peripheral vasoconstriction;
2. Neurological side effects: seizures, cerebral edema, stroke, mydriasis, dizziness, memory loss, tremors, motor automatisms, parkinsonism, headache, hyperreflexia, paraesthesia, hyperkinesia;
3. Respiratory side effects: nasal irritation, nose bleed, breathing difficulties;
4. Gastrointestinal side effects: nausea, vomiting, anorexia, abdominal pain, sore throat;
5. Other side effects: serotonin syndrome, muscle rigidity, rhabdomyolysis, kidney failure, thermoregulatory changes, hyponatraemia, sweating, chills, bloodshot eyes, skin rash. Long-term i.v. use is associated with weight loss, cachexia, immune system alterations and infections e.g. thrombophlebitis, abscesses or septicemia.

There are several reports on cases of mortality related to consumption of cathinone derivatives. With mephedrone, there are at least 60 suspected deaths in the UK, and some fatalities occurred with MDPV as well. As an example, Murray et al. (2012) report a case of a 40-year-old male using MDPV, who was hospitalized because of severe agitation, got a cardiac arrest, was resuscitated, but then developed hyperthermia, rhabdomyolysis, acidosis, anoxic brain injury, and died. In other two cases, fatal outcome was a consequence of hyponatraemia and cerebral edema (Wood et al., 2012; Gustavsson and Escher, 2009). There are

reports on fatalities in connection with methylene and/or butylone consumption: e. g. Warrick et al. (2012) report the case of a 24-year-old patient who suffered serotonin syndrome, multi organ failure and died after using methylene and butylone.

At this time, limited information is available to guide treatment for patients with somatic complications of acute synthetic cathinone intoxication; supportive treatment and BZD therapy is needed and helpful in most cases (Prosser and Nelson, 2012). Co-abuse with other drugs may be the source of further complications and pharmacological interactions.

Psychiatric complications

There are reports in the literature not only on the somatic, but on the psychological complications linked to synthetic cathinone consumption. These adverse effects range from mild, but frequently seen symptoms to serious pathologies, like intoxication delirium or drug-induced psychotic states.

According to data, most frequently seen (in 20-60% of the cases, varying between studies) psychopathological symptoms are agitation, anger, irritability, restlessness, insomnia, concentration and memory disturbances, transient paranoid thoughts, hallucinations and anxiety (Prosser and Nelson, 2012; Jerry et al., 2012; Kalapos, 2011). Transient depressive mood alterations, suicidal ideas were also reported (Coppola and Mondola, 2012b). These symptoms can be the cause of or may be registered during medical treatment, sometimes leading to auto- or heteroaggressive behavior. Their fast and adequate treatment is certainly inevitable, though no treatment evidences or guides exist to date. Short-time administration of benzodiazepines seems to be effective and probably safe in reducing agitation, violent behavior, seizures and sympathetic hyperactivity (Coppola and Mondola, 2012b). Typical and atypical antipsychotics may be helpful in certain cases, but interactions must be considered, especially in terms of QT-prolongation.

In some cases (Fullajtár and Ferencz, 2012; Penders and Gestring, 2011) delirium-like syndromes are reported following synthetic cathinone usage. These episodes are characterized by severe alterations in consciousness, orientation and attention, hallucinations and thought disturbances. Somatic complications, drug interactions and maybe underlying medical conditions can play a role in the emergence of the symptoms. There are practically no data available in the literature on the typical onset, duration and treatment of these cases, and clinical experiences are rare, too.

Recently, in everyday psychiatric practice, the growing number of drug-induced psychotic states means a wanting challenge to service providers. Aside from the transient psychotic symptoms during acute intoxication or delirium, the short- or long-term consumption of cathinone derivatives can lead to psychotic episodes in mentally otherwise healthy consumers, and probably can exacerbate symptoms of patients living with psychotic disorders.

Benzie et al. (2011) report a series of 35 cases treated in emergency unit after using 'Bath Salts'. Four of them were treated because of psychosis-like symptoms, most of them having psychiatric co-morbidities as well. Kim et al. (2010) report about a young man consuming 'Ivory Wave' and having delusions and hallucinations and involuntary movements of extremities. His symptoms lasted for two weeks, and he was treated with benzodiazepines. Thornton et al. (2012) report the case of a 23-year-old male with a prior psychiatric history, who got severely psychotic upon using MDPV and flephedrone. His symptoms resolved during treatment with droperidol and lorazepam. Kolli et al. (2013) describe the case of a 19-year-old female without any psychiatric history, developing catatonic symptoms (psychomotor agitation altering with negativistic state) after using mephedrone. She was treated with haloperidol and lorazepam, her symptoms completely remitted in 72 hours. Antonowitz et al. (2011) report two cases of paranoid psychosis related to MDPV consumption. Both patients, none of them having psychiatric history, got severely psychotic after four-days of MDPV use, having delusions, hallucinations and disorganized behavior. One of them took regularly buprenorphine/naloxone, too. One of them was observed without any medication, the other received risperidone, and both patients' symptoms remitted in four days. Penders et al. (2013) discuss the case of a patient having persistent psychotic symptoms despite discontinuing MDPV use, and the efficacy of electroconvulsive therapy.

Kalapos (2011) reviews the symptoms of 15 patients treated in an outpatient addictology unit. According to self reports, patients consumed MDPV, but toxicology analysis was not available. 8 of the 15 patients had psychotic symptoms (delusional thoughts and/or hallucinations). Combined risperidone and clonazepam treatment seemed beneficial to these patients, though not all of them remained abstinent.

Farkas et al. (2013) report a case series of five inpatients, who were admitted acutely to a psychiatric department due to developing psychotic symptoms related to self reported MDPV abuse. None of the

patients had a history of schizophrenia or other psychotic disorders. All patients' symptoms remitted after few days' treatment with low-dose antipsychotics (risperidone, olanzapin, haloperidol, zuclopenthixol) and BZDs.

These data show that drug-induced psychotic states are not uncommon among synthetic cathinone users. It remains unclear whether these episodes are "simple" drug-induced, or exacerbations or first episodes of otherwise existing mental disorders. At the time of the writing of this manuscript to our knowledge no follow-up studies were available in literature. In some cases, the exact nature of the consumed drug or drugs remains unclear, due to difficulties in the accessibility of the required laboratories.

Psychotic states, although can be severe, can be effectively treated with low doses of typical or atypical antipsychotics, though further research is needed, mainly in terms of safety and relative efficacy of antipsychotics. BZDs seem to be helpful, too.

SYNTHETIC CANNABINOIDS

Pharmacology

Synthetic cannabinoids show significant differences in their molecular structure. Classical molecules, such as HU-210, are analogues of THC and are based on its chemical structure, while other representatives have different structures. Still, their biological targets are the same. Unlike delta-9-tetrahydrocannabinol (THC), most synthetic cannabinoids are potent full agonists of cannabinoid receptors, and they bind not only CB1, but CB2 receptors as well. Being full agonists, the psychoactive effects (and side-effects) of these compounds can be more explicit than that of THC. Therefore, they have a greater potential for overdose and severe, sometimes life-threatening adverse effects (Jerry et al., 2012; Seely et al., 2012).

Psychoactive effects and complications

Although typical effects vary between compounds and individuals as well, the most frequently seen "desired" effects of these compounds are marijuana-like symptoms, relaxation, sedation, euphoria and perceptual alterations, which last for a few hours.

Beside these "desirable" effects, adverse psychological and physical reactions can be seen in many cases. Due to the higher receptor affinity and full-agonist mechanism of synthetic cannabinoid derivatives, these side-effects are more frequently seen and

more severe than those of THC, leading to emergency medical treatment in many cases.

Acute psychopathological symptoms related to consumption range from anxiety, agitation and irritability to alteration of time perception, memory and concentration disturbances, confusion or psychosis-like episodes characterized by paranoid delusions and hallucinations (Jerry et al., 2012; Seely et al., 2012).

Hurst et al. (2011) reported a case series of ten, otherwise healthy young men developing new-onset acute psychotic state as a consequence of synthetic cannabinoid use. This case report describes a set of psychotic symptoms, ranging from auditory and visual hallucinations to paranoid delusions, from thought blocking to disorganized speech, from anxiety and insomnia to stupor and suicidal ideation. There are several data on cannabinoids exacerbating psychotic symptoms of patients who had a history of former psychotic illness (Gunderson et al., 2012; Every-Palmer 2011, for examples).

Regarding long-term use psychological and somatic dependency and withdrawal symptoms were reported, while the existence of other long-term, marijuana-like neuropsychological consequences (like mood-regulation, personality and cognitive disturbances) is still unclear (Seely et al., 2012).

Somatic effects and complications

Aside from the quite common, tolerable somatic effects, like conjunctival injection, xerostomia and tachycardia, there are reports on more severe complications like hypertension, hyperventilation, diaphoresis, nausea, vomiting, tremor, muscle twitching in several cases (Gunderson, 2012), on generalized convulsion in one single case (Lapoint et al., 2011), and on cases of renal failure (Bhanushali et al., 2013).

CONCLUSIONS AND FUTURE PERSPECTIVES

Trends in drug usage patterns, worldwide and in Hungary, can be described by the explosion of designer drug use and subculture in recent years. This emerging phenomenon created a new and challenging situation for health care professionals working in psychiatry, addictology, toxicology or emergency units. Our knowledge on the somatic and mental health consequences of the abuse of these new compounds is very limited or missing, meanwhile new and formerly unknown (or old and forgotten) molecules are synthesized and marketed on a daily basis. By the time evidence is collected about the properties of a given

psychoactive agent and it gets scheduled, it is already replaced with more or less similar, potentially more hazardous molecules. The monitoring and scheduling of agents with similar molecule structures are thought to be helpful, but it seems to affect the designer drug industry only temporarily. Or, paradoxically, it can even speed up designer activity, leading to the appearance of brand new, maybe completely unknown compounds.

The easy and not always explicitly illegal availability of these compounds is more than appealing to drug consumers – talking about recreational drug users and patients with heavy using habits as well. Especially young population is in danger: the well known dangers (emphasized by prevention programs) and legal consequences of “classical” illicit drugs can withhold many of them from their use, but the misleading marketing of designer drugs might be tempting. In Hungary, the trend of new agents invading the market and drug users changing their abuse patterns is already visible.

Medical and social consequences of this trend are serious. From the point of view of health care professionals, lack of information is the source of most difficulties we face during everyday clinical work.

To manage this situation, monitoring of all possible information sources is inevitable – those being not only the “official” handbooks, journals or electronic data bases. Current information is available e.g. on the pages of early warning systems, National Drug Focal Point, European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and BSZKI. Data existing only on internet drug-forums can be useful as well, though their reliability can be questionable.

Abbreviations

4-MEC – 4-Methylethcathinone
 5-IT – 5-(2-Aminopropyl)indole
 APVP – alpha-pyrrolidinovalerophenone
 BSZKI – Bűnügyi Szakértői és Kutatóintézet
 BZD – benzodiazepine
 CB – cannabinoid
 CB1, CB2 – cannabinoid receptors 1,2
 EMCDDA – European Monitoring Centre for Drugs and Drug Addiction
 IDU – intravenous drug user
 LSD – Lysergic acid diethylamide
 MDMA – 3,4-methylenedioxy-N-methylamphetamine
 MDPV – 3,4-Methylenedioxypropylvalerone
 MPPP – 1-Methyl-4-phenyl-4-propionoxypiperidine
 NSP – needle and syringe programme
 STD – sexually transmitted disease
 THC – delta-9-tetrahydrocannabinol
 VMAT – vesicular monoamine transport

Corresponding author: István Bitter, Semmelweis University, Department of Psychiatry and Psychotherapy, H-1083 Budapest, Balassa utca 6.
 e-mail: bitter.istvan@med.semmelweis-univ.hu

REFERENCES

- Bhanushali, G.K., Jain, G., Fatima, H., Leisch, L.J., Thornley-Brown, D. (2013) AKI associated with synthetic cannabinoids: a case series. *Clin J Am Soc Nephrol*, 8(4): 523-6.
- Benzie, F, Hekman, K, Cameron, L, Wade, D. R., Miller, C, Smolinske, S, Warrick, B. (2011) Emergency department visits after use of a drug sold as “bath salts” –Michigan, November 13, 2010–March 31. *MMWR Morb Mortal Wkly Rep*, 60: 624-7.
- Bűnügyi Szakértői és Kutatóintézet: Monitoring hírlevél 2011. II. (http://www.bszi.hu/e107_files/downloads/MH2011II.pdf) Last visited: 1/5/2013.
- Castellanos, D, Singh, S, Thornton, G, Avila, M, Moreno A. (2011) Synthetic cannabinoid use: a case series of adolescents. *J Adolesc Health*, 49: 347-9.
- Coppola, M, Mondola, R. (2012) 3,4-methylenedioxypropylvalerone (MDPV): chemistry, pharmacology and toxicology of a new designer drug of abuse marketed online. *Toxicol Lett*, 5;208(1): 12-5.
- Coppola, M, Mondola, R. (2012) Synthetic cathinones: chemistry, pharmacology and toxicology of a new class of designer drugs of abuse marketed as “bath salts” or “plant food”. *Toxicol Lett*, 1;211(2): 144-9.
- Cozzi, N.V., Sievert, M.K., Shulgin, A.T., Jacob, P 3rd, Ruoho, A.E. (1999) Inhibition of plasma membrane monoamine transporters by beta-ketoamphetamines. *Eur J Pharmacol*, 381(1): 63-69.
- Durham, M. (2011) Ivory wave: the next mephedrone? *Emerg Med J*, 28: 1059-1060.
- European Monitoring Centre for Drugs and Drug Addiction: Hungary: drug-related information and data. <http://www.emcdda.europa.eu/countries/hungary> Last visited: 14/6/2013.
- Every-Palmer, S. (2011) Synthetic cannabinoid JWH-018 and psychosis: an explorative study. *Drug Alcohol Depend*, 1;117(2-3): 152-7.
- Farkas, K, Sirály, E, Szily, E, Csukly, G, Réthelyi, J. (2013) The decade of designer drugs in Hungary: Clinical characteristics of 5 hospitalized synthetic cathinone, 3,4-methylenedioxypropylvalerone (MDPV) users. *Psych Hung*, ahead of print.
- Fullajtár, M, Ferencz, C. (2012) Dizájner drog indukálta pszichózis. *Neuropsychopharmacol Hung*, 14: 137-140.
- Gunderson, E.W., Haughey, H.M., Ait-Daoud, N, Joshi, A.S., Hart, C.L. (2012) “Spice” and “K2” herbal highs: a case series and systematic review of the clinical effects and biopsychosocial implications of synthetic cannabinoid use in humans. *Am J Addict*, 21(4): 320-6.
- Gustavsson, D, Escher, C. (2009) Mephedrone – Internet drug which seems to have come and stay. Fatal cases in Sweden have drawn attention to previously unknown substance. *Lakartidningen*, 106(43): 2769-2771.
- Hadlock, G.C., Webb, K.M., McFadden, L.M., Chu, P.W., Ellison, J.D., Allen, S.C., Andrenyak, D.M., Vieira-Brock, P.L., German, C.L., Conrad, K.M., Hoonakker, A.J., Gibb, J.W., Wilkins, D.G., Hanson, G.R., Fleckenstein, A.E. (2011) 4-Methylmethcathinone (mephedrone): neuropharmacological effects of a designer stimulant of abuse. *J Pharmacol Exp Ther*, 339(2): 530-6.
- Hungarian National Focal Point. (2012) National Report

- to the EMCDDA by the Hungarian National Focal Point on the Hungarian drug situation. http://drogfokuszpont.hu/wp-content/uploads/HU_National_Report_2012.pdf Last visited: 18/5/2013.
17. Hurst, D, Loeffler, G, McLay, R. (2011) Psychosis associated with synthetic cannabinoid agonists: a case series. *Am J Psychiatry*, 168: 1119.
 18. Jerry, J, Collins, G, Stroom, D. (2012) Synthetic legal intoxicating drugs: the emerging 'incense' and 'bath salt' phenomenon. *Cleve Clin J Med*, 79(4): 258-64.
 19. Kalapos, M.P. (2011) 3,4-metilén-dioxi-pirovaleron- (MDPV-) epidémia? *Orv Hetil*, 152: 2010-2019.
 20. Kim, H.S., Aftab, A, Shah, M, Nayar, J. (2010) Physical and psychological effects of new legal high "Ivory Wave": a case report. *Br J Med Practition*, 3(4): a343.
 21. Kolli, V, Sharma, A, Amani, M, Bestha, D, Chaturvedi, R. (2013) "Meow meow" (mephedrone) and catatonia. *Innov Clin Neurosci*, 10(2): 11-2.
 22. Lapoint, J, James, L.P, Moran, C.L., Nelson, L.S., Hoffman, R.S., Moran, J.H. (2011) Severe toxicity following synthetic cannabinoid ingestion. *Clin Toxicol (Phila)*, 49(8): 760-4.
 23. Madras, B. (2012) Designer drugs: An escalating public health challenge. *The Journal of Global Drug Policy and Practice*, 2012 october. <http://www.globaldrugpolicy.org/Issues/Vol%206%20Issue%203/Designer%20Drugs%20FINAL%20V6%20formatted.pdf> last visited: 12/5/2013.
 24. Murray, B.L., Murphy, C.M., Beuhler, M.C. (2012) Death following recreational use of designer drug Bath salts containing 3,4-Methylenedioxypropylvalerone (MDPV). *J Med Toxicol*, 8(1): 69-75.
 25. Newcombe, R. (2009) Mephedrone: use of mephedrone (M-Cat, Meow) in Middlesbrough. *Lifeline*. <http://www.lifeline.org.uk/articles/the-use-of-mephedrone-m-cat-meow-in-middlesbrough/> last visited: 14/5/2013.
 26. Penders, T.M., Gestring, R. (2011) Hallucinatory delirium following use of MDPV: bath salts. *Gen Hosp Psychiatry*, 33: 525-526.
 27. Penders, T.M., Lang, M.C., Pagano, J.J., Gooding, Z.S. (2013) Electroconvulsive Therapy Improves Persistent Psychosis After Repeated Use of Methylenedioxypropylvalerone ("Bath Salts"). *J ECT*. [Epub ahead of print] PubMed PMID: 23609518.
 28. Prosser, J.M., Nelson, L.S. (2012) The toxicology of bath salts: a review of synthetic cathinones. *J Med Toxicol*, 8(1): 33-42.
 29. Seely, K.A., Lapoint, J., Moran, J.H., Fattore, L. (2012) Spice drugs are more than harmless herbal blends: A review of the pharmacology and toxicology of synthetic cannabinoids. *Prog Neuro-Psychopharmacol Biol Psychiatry*, 3;39(2): 234-243.
 30. Thornton, S.L., Gerona, R.R., Tomaszewski, C.A. (2012) Psychosis from a bath salt product containing flephedrone and MDPV with serum, urine, and product quantification. *J Med Toxicol*, 8(3): 310-3.
 31. Vandrey, R, Dunn, K.E., Fry, J.A., Girling, E.R. (2012) A survey study to characterize use of Spice products (synthetic cannabinoids). *Drug Alcohol Depend*, 1;120(1-3): 238-41.
 32. Warrick, B.J., Wilson, J, Hedge, M, Freeman, S, Leonard, K, Aaron, C. (2012) Lethal serotonin syndrome after methylone and butylone ingestion. *J Med Toxicol*, 8(1): 65-8.
 33. Watterson, L.R., Kufahl, P.R., Nemirovsky, N.E., Sewalia, K, Grabenauer, M, Thomas, B.F, Marusich, J.A., Wegner, S, Olive, M.F. (2012) Potent rewarding and reinforcing effects of the synthetic cathinone 3,4-methylenedioxypropylvalerone (MDPV). *Addict Biol*, Jul 11. doi: 10.1111/j.1369-1600.2012.00474.x.
 34. Winstock, A, Mitcheson, L, Ramsey, J, Davies, S, Puchnarewicz, M, Marsden, J. (2011) Mephedrone: use, subjective effects and health risks. *Addiction*, 106(11): 1991-6.
 35. Wood, D.M., Davies, S, Greene, S, L Button, J, Holt, D.W., Ramsey, J, Dargan, P.I. (2010) Case series of individuals with analytically confirmed acute mephedrone toxicity. *Clin Toxicol (Phila)*, 48(9): 924-927.
 36. Zaitsu, K, Katagi, M, Tatsuno, M, Sato, T, Tsuchihashi, H, Suzuki, K. (2011) Recently abused b-keto derivatives of 3,4-methylenedioxyphenylalkylamines: a review of their metabolisms and toxicological analysis. *Forensic Toxicol* 29(2):73-84.

„Designer” drogok a pszichiátriai gyakorlatban – Irodalmi áttekintés és a magyarországi helyzet elemzése

A magyarországi addiktológiai-pszichiátriai ellátórendszer az elmúlt néhány évben szembesült a designer drogok használatának drámai növekedésével. A pszichiátriai gyakorlatban talán első érzékelhető jele volt ennek a folyamatnak az MDPV (3,4-metiléndioxipirovaleron) nevű designer drog fogyasztását követően pszichotikussá vált, így akut hospitalizációra szoruló páciensek nagy száma. Jelenleg a hozzáférhető designer drogok száma és népszerűsége nagyobb, mint megelőzően bármikor. Köszönhető ez annak, hogy olcsók, a fogyasztók tudomása szerint nem illegálisak, nehezen kimutathatók, biztonságosak és „természetesek”. Ezzel szemben e termékek összetétele és biológiai hatásai legtöbbször ismeretlenek – nemcsak a fogyasztók, hanem az orvosok számára is, míg a lassan gyűlő irodalmi adatok arra utalnak, hogy fogyasztásuk szomatikus és pszichiátriai következményei gyakoriak, súlyosak, nemritkán életet veszélyeztetők lehetnek. Jelen cikkünk célkitűzése egyrészt a jelenleg rendelkezésre álló fontosabb irodalmi adatok összegzése néhány gyakrabban használt designer drog tekintetében (szintetikus katinonok és kannabinoidok). Ezen kívül szeretnénk felhívni a figyelmet a droghasználati szokások jelenlegi és jövőben várható változásaira. Végezetül, szeretnénk bemutatni e változások mindennapi klinikai gyakorlatban érzékelhető hatásait, bemutatva a leggyakrabban használt szerek használatának fontos pszichiátriai és szomatikus morbiditást jelentő szövődményeit.

Kulcsszavak: „designer” drogok, MDPV, kannabinoidok, pszichiátriai klinikai gyakorlat