Title: New psychoactive substances (NPS) – a challenge for the addiction treatment services

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Summary

In the last years hundreds of new psychoactive substances (NPS) have been observed in Europe. Apart from some herbal drugs, NPS are mainly new synthetic stimulants, e.g. cathinones, and synthetic cannabinoids. Synthetic NPS are often designer drugs developed by varying a basic chemical structure such as phenethylamine or tryptamine. The pharmacology and toxicology of most NPS is hardly known. Synthetic NPS are offered as "bath salts", "incense mixture" or under other concealing names especially on the internet. In addition, NPS are advertised as "Legal Highs" suggesting that trading with NPS is legal in contrast to substances regulated by national laws. The prevalence of the use of NPS is scarcely known. Especially regarding synthetic cannabinoids there is some evidence that NPS are more often associated with serious side effects, such as epileptic seizures or loss of consciousness than the drug, e.g. cannabis, which the user aims to replace.

Key words: new psychoactive substances – internet – cathinones – synthetic cannabinoids - Narcotics Law

1. Introduction

For decades the health care system for substance-related disorders has been focused on only a few psychoactive drugs, especially alcohol, amphetamines, cannabis, cocaine, MDMA (ecstasy) and heroin. Of course, experts in addiction medicine knew many more substances, especially several hallucinogenic drugs (LSD, psilocybe mushrooms, fly agaric mushrooms [Amanita muscaria] etc.). But even here the situation seems to be fairly stable. In the last years, however, the European Monitoring Centre for Drugs and Drug Abuse (EMCDDA) reported in its annual report about a rapidly increasing number of new psychoactive substances (NPS). In 2011, 41 new substances were already reported. This figure steadily rose to 79 (2013), 83 (2014) up to 101 (2015) and 98 (2016). These new substances are a challenge for the health care system as well for the legal system. In the following the most important classes of new psychoactive substance will be described regarding their chemical structure, their main effects and the related risks (overviews: Baumann et al., 2014; EMCDDA, 2015; Hohmann et al., 2014; Scherbaum et al., 2014). Further topics are the legal problems related to these drugs ("Legal highs") as well as the role of the Internet for the availability of information and for sale of the new drugs, respectively. Eventually, the risk assessment of NPS and the implications of the emergence of NPS for clinicians and drug prevention measures are discussed.

2. Chemical classes of new psychoactive substances

The NPS can be basically divided in synthetic drugs and herbal drugs (see table 1). The vast majority of NPS are synthetic drugs. They are designer drugs meaning that a given chemical basic structure, such as phenethylamine or tryptamine is systematically varied in their side groups creating hundreds of new substances.

2.1 Phenethylamines

Substances of the group of the phenethylamines are of high importance for the human organism (see figure 1). The neurotransmitters adrenaline, noradrenaline and dopamine are phenethylamines. In addition, drugs already known for a long time belong to the group of the phenethylamines such as amphetamine, methamphetamine or mescaline. Shulgin and Shulgin (1992) published a book "Phenethylamines I have known and loved". In this book they described the chemical synthesis as well as their personal experience with more than 170 drugs developed by the varying the basic structure of phenethylamine. For example, in this book MDMA (ecstasy), MDE (3,4-methylendioxy-N-ethylamphetamine) and MDA (3,4-methylendioxyamphetamine) are described. The other drugs listed in the book have mostly a stimulant or MDMA-like psychotropic effect. Other drugs derived from the basic structure of phenethylamine by Shulgin and Shulgin are the dimethoxyphenethylamines, such as 2C-B (4-brom-2,5-dimethoxyphenethylamine) and 2C-C (2,5-dimethoxy-4-chlorophenethylamine) producing visual hallucinations and synaesthesia (a sensory stimulus induces an experience in two systems of perception,

e.g. an auditive stimulus also induces the perception of colours; Luke and Terhune, 2013) an experience in second in higher doses.

In addition, on the basis of cathinone (benzoylethanamine), a substance naturally found in the plant Catha edulis (khat) (Rätsch, 1997), several other stimulating drugs such as mephedrone (Hadlock et al., 2011) or flephedrone were created. These NPS, in the slang of sellers and users named as "bath salts", are offered as legal substitutes for stimulants and ecstasy (MDMA). Cathinones are mostly taken orally or nasally, but can be injected as well. Similar to amphetamines, the side effects on physical health caused by cathinones can be partly explained by the strong activation of the noradrenergic system. In case series of emergency admissions of persons with recreational use of the cathinone MDPV (methylendioxypyrovalerone), tachycardia and agitation were the most common symptoms (Froberg et al., 2014). Of note, as other phenethylamines also cathinones can promote a potentially fatal serotonin syndrome due to their serotonergic action, especially if used in very high doses or in tandem with other serotonin receptor agonists (Rasimas, 2012). Deaths under the influence of cathinones, e.g. methylone (Barrios et al., 2016) and MDPV (Namera et al., 2013) were reported.

2.2 Tryptamines

Shulgin and Shulgin also published a book on the psychotropic effects of tryptamines (Shulgin & Shulgin, 1997). Like phenethylamines, trypta-

mines are substances which are physiologically present in the human organism (see figure 2), for example in shape of the neurotransmitters serotonin and melatonin. In addition, tryptamines with psychoactive effects have been known for decades, such as lysergic acid diethylamide (LSD), psilocybin/psilocin, the psychoactive compounds in psilocybe mushrooms, as well as bufotenine, the active substance in the aga toad (bufo marinus). A couple of synthetic tryptamine drugs have been known for a long time, especially dimethyltryptamine (DMT).

Characteristically, tryptamines are hallucinogens, based mainly on the stimulation of the HT2A-receptor in the serotonin system. Shulgin and Shulgin varied the basic tryptamine structure systematically, and described the psychotropic effects of their creations via self-using them. They published experiences with more than 50 tryptamine derivates. Besides them, few publications exist (e.g. 5-MeO-DALT (N,N-Diallyl-5-methoxytryptamine; see Corkery et al., 2011). In general, hallucinogenic drugs are assigned to have a low addictive liability, if at all. One hallmark of these drugs is the rapid development of tolerance to the hallucinogenic effect and a cross-tolerance between serotonergic hallucinogens.

2.3 Synthetic Cannabinoids

A few years ago, the story of "Spice" was reported even in lay media. "Spice" was sold in head-shops as well as on the internet as a herbal mixture to incense rooms. But this alleged application of "Spice" should only

deceive the public, especially the police, whereas initiated persons knew that these herbal mixtures were offered as legal substitute for cannabis. Initially, it was claimed by the sellers that the herbs composing "Spice" have the property to induce psychotropic effects similar to cannabis. However, chemical analysis identified synthetic cannabinoids (e.g. CP-47,497 or JWH-018) to be responsible for the psychotropic action of "Spice" (Atwood et al., 2010). Most likely, these synthetic compounds had been simply sprayed on the herbal preparations containing no psychotropic compounds themselves (Bonnet and Mahler, 2015). Currently, synthetic cannabinoids are increasingly offered purely as "research chemicals" (Werse and Morgenstern, 2015).

In the meantime, it became clear that synthetic cannabinoids come from different classes of chemical substances, e. g. bicyclic cyclohexylphenols (e. g. CP-55,940) and aminoalcylendols (e. g. JWH-018). Regarding their chemical structure, the synthetic cannabinoids are chemically not related to delta-9-tetrahydrocannabinol (THC), the main psychoactive ingredient of the cannabis plant. Synthetic cannabinoids are defined to bind to the cannabinoid 1 (CB1)-receptors. In comparison with THC, which represents a partial agonist at these receptors, the synthetic cannabinoids often bind much stronger to CB1-receptors.

Therefore, the health hazards of synthetic cannabinoids are difficult to predict, since many of the products emerging on the market even had not

been tested in animal experiments and were originally designed to be tools for investigating the endocannabinoid system in more detail. A couple of synthetic cannabinoids are reported to be more dangerous to humans than cannabis (Bonnet and Mahler 2015), and there is a mounting number of patients brought to emergency services with physical and behavioural complications associated with their use of synthetic cannabinoids. In this context, psychosis (Hurst et al., 2011), myocardial infarction (Mir et al., 2011), as well as epileptic seizures and loss of consciousness (Hermanns-Clausen et al, 2012) were described to be adverse effects of synthetic cannabinoids. Besides these acute side-effects, long-term use of synthetic cannabinoids is reported to cause cannabis addiction associated with signs of physical dependence such as tolerance and withdrawal symptoms (Zimmermann et al., 2009).

These reports are in sharp contrast to the long-standing experience regarding cannabis, that the use of cannabis is quite safe regarding its acute toxicity. The difference in toxicity between cannabis plant preparations and synthetic cannabinoids might have several reasons: synthetic cannabinoids are potent substances with psychoactive effects in much smaller doses than cannabis and THC, respectively. They are mostly full agonists in contrast to THC which is a partial agonist at the CB1-receptor. Full agonists show a linear increase in toxicity with increasing dosage, whereas partial agonists reach a plateau of toxicity at some point of dosage. In addition, in the cannabis plant there are more than 60 cannabinoids. Some

of these cannabinoids, especially cannabidiol (CBD), compensate effects of THC.

2.4 Herbal Drugs

There are comprehensive textbooks on the ethno-botany of psychoactive plants and mushrooms (e.g. Rätsch, 1997). However, the respective knowledge often originating already in the colonial era in the 19th century has been restricted to a small group of experts for a long time. This expert knowledge is now easily available on the internet. For example, there is the plant Mitragyna speciosa, which is indigenous in Thailand and Malaysia. It was already known in the 19th century that the dried leaves of this plant were used as substitute for opium under the name "Kratom". Nowadays, the indole alkaloid mitragynine has been identified as the main psychoactive ingredient of Kratom. Paradoxically, the effects of Kratom are described to be stimulating as well as sedating, resembling the complex effects of nicotine.

Today the entry "Kratom" in Google leads to the occurrence of search terms such as "Kratom kaufen" (to buy Kratom) and "Kratom bestellen" (to order Kratom). Taking into account the automatically generated search terms in Google being a reflection of often used search terms, this alone points to the amount of interest in this drug, which was largely unknown a few years ago. Other herbal drugs are related to various kinds of mush-

rooms with hallucinogenic properties ("magic mushrooms") such as Panaeolus cyanescens.

2.5 Other new psychoactive substances

Due to the limited space of this article, other NPS are mentioned merely cursorily (see table 1). These include stimulants with the basic structure of piperazines and benzofuranes, such as bromo-dragonFLY [Corazza et al., 2011]; 5-(2-amino-propylindole [Coppola and Mondola, 2012]; 2-aminoindanes such as 2-AI [Sainsbury et al., 2011]), as well as synthetic opiate-like and cocaine-like drugs. These NPS are considered to have similar effects to the already known drugs: cathinones are preferably stimulants, tryptamines belong to the hallucinogens and synthetic cannabinoids have sedating properties. However, there are remarkable differences in the severity of effects on mental and physical functioning (see above especially synthetic cannabinoids vs. cannabis).

3. Individual and environmental factors promoting the use of new psychoactive substances including the internet

The increasing number of NPS is partly an expression of the change of social life brought about by the internet (Corazza et al., 2011). The internet is a market place for several goods and services. The internet is also a market place for NPS. NPS are offered as "bath salts", "incense mixtures", "research chemicals", or under other concealing terms. Respective internet sites often have a disclaimer that the substances offered are not suit-

able for human consumption. However, it is implicit in the context of such internet sites, that especially the use by humans is obviously meant.

In addition, the internet is a medium for information. However, sources of information are not restricted to official sites of universities or institutions of health education. On the contrary, information is often given by head shops or sites linked to head shops in a way, that the use of NPS is advertised. Other sites (e. g. "erowid.org") give a comprehensive overview of different aspects of drugs. However, the attitude of this site is neutral regarding the use of drugs, comparable to information for the responsible and well-informed citizen who makes choices between different legitimate options regarding goods of daily living. Eventually, the chemical synthesis of NPS is described on the internet, especially by the publication of the two books of Shulgin and Shulgin (1992, 1997) about phenethylamines and tryptamines. Hitherto, the knowledge to what extent NPS are really sold via the internet is limited. This is also true for the assumption that the internet serves as a new sales channel, which recruits new groups of drug users who would not have engaged in substance use without it.

The intention of using NPS as substitutes of common psychoactive drugs might be mediated by risk taking, novelty seeking and niche effects in situations where individuals might be exposed to standard drug screens (e.g. penal institutions, road traffic, detoxification and opioid maintenance treatments, certain occupations).

4. Legal Aspects

The new psychoactive substances are also named “legal highs”. This term is clearly an advertisement slogan for these substances because it suggests that these drugs are legally available substitutes for illegal substances, such as cannabis or ecstasy (MDMA). According to the legal regulations in Germany, all substances which are not explicitly stated in the narcotics law (Betäubungsmittelgesetz) are not forbidden to sell or to buy. In order to classify a drug under the narcotics law, two requirements have to be fulfilled:

a) The substance has to be chemically defined.

b) There has to be evidence that the use of the substance can cause damage to the physical or mental health.

Given the situation that a new harmful drug is available on the market, it lasts several months at least to identify the new substance as well as its related adverse effects. After collecting data from different sources (police data of drug possession, chemical analysis, clinical surveys etc.), an expert board at the Federal Ministry of Health will make a recommendation which new substance should be regulated by the narcotics law. Following the recommendation there will then be a political decision about the inclusion of the new substance among the list of illegal drugs in Germany. The whole procedure from the appearance of a new drug on the market up to

the official listing of the drug in the narcotics law usually takes several months up to years. The whole circle will then start again when the recently listed substance is chemically changed, e.g. by exchange of a chemical side-group of a given basic chemical structure.

Some solutions to this legal problem have been discussed during the last years. Courts sentenced sellers of "legal highs" due to a violation of the German drug law (Arzneimittelgesetz), as these substances are able to influence the function of the organism. However, the European Court of Justice stated that "legal highs" are not medications (court decision of July 10th, 2014). It is proposed to regulate simply the whole substance classes, such as phenetylamines, tryptamines, synthetic cannabinoids, piperazines, benzofuranes, arylamines, and ketamine derivates, in an annex of the German Narcotics Law. Accordingly, drugs showing the backbone of e.g. phenethylamines or tryptamines are forbidden to sell. This legal discussion has not yet come to an end in Germany, whereas other countries, e.g. Austria, have already taken this way (Neue-Psychoaktive-Substanzen-Gesetz, NPSG).

5. Epidemiology of the use of new psychoactive substances

Regarding the prevalence of the use of new psychoactive substances there are only limited epidemiologic data. In the last German survey on the use of psychoactive drugs (Pabst et al., 2013), 0.2% of adult persons (up to

64 years of age) of the general population stated that they used "Spice" at least one time in the last 12 months. Among persons in the age of 18 to 20 years, 0.7% stated the use in the last 12 months. There might be higher prevalence rates of NPS use in specific subgroups such as in specific youth groups (Bernard et al., 2013), especially using so-called club drugs (Weaver und Schnoll, 2008), as well as in the MSM (men who have sex with men)-community (Dirks et al., 2012). It is assumed that the pattern of use of NPS is mostly sporadic and recreational. Basically however, cannabis is by far the most commonly used illegal substance in Germany (Pabst el., 2013) and in the EU (EMCDDA, 2016). In Germany 12-months prevalence rates for cannabis use are 4.5% (adult population) and 16.7% (persons 18-20 years of age), respectively.

In principle, it has to be assumed that it is difficult to acquire valid epidemiological data about the use of NPS, because this group of drugs consists of several hundred single substances with a change of availability of single substances in time and locally. According to clinical experience, patients with substance-related disorders in hospitals are rarely addicted to NPS. In contrast, there is a strong increase of patients addicted to methamphetamine ("Crystal Meth"), especially in the eastern federal provinces of Germany (Härtel-Petry, 2014). In addition, the prescription rates of opioid analgesics in Germany (and to a much higher degree in the USA) appeared to be markedly increased within the last 10-15 years (Schubert et al., 2013). Especially in the USA it is well documented, that the group of

patients addicted to opioid analgesics is a significant problem of the health care system (Dart et al., 2015).

6. Discussion

Up to now, it is difficult to estimate the future prevalence of the use of NPS and their real challenges for the health care system. For decades, there have been much more psychoactive substances than the currently used ones. Regarding the long-term demand and appreciation of specific drugs, one might assume some kind of selection with the result that among them, merely a few substances found a user group of a relevant size. For example, aversive effects of atropine containing hallucinogenes (e.g. different varieties of brugmansia or "angels trumpet"), such as tachycardia, hyperthermia, and severe agitation, might limit the frequency of use or prevent a later use once for all. A similar selection is assumed to result from the intake of NPS with a strong activation of CB1-receptors, which make them not attractive enough to replace cannabis sustainably.

The risk assessment regarding NPS is quite difficult. Pharmacological research on the pharmacodynamics, pharmacokinetics, and toxicity of all NPS is an overwhelming task given the massive increase of new substances during the last ten years. According to Nutt et al. (2007), different dimensions of risks have to be differentiated, such as

a) acute hazards for mental and physical health in the state of intoxication, such as serotonin syndrome using "bath salts".

b) hazards for mental and physical health as a consequence of chronic use, such as the development of an addiction or the infection with hepatitis C in the context of intravenous drug application.

c) acute and chronic social risks, such as inability to drive a car, high risk sexual behaviour and aggressiveness during the intoxication.

Up to now, most reports on the risks of NPS relate to acute somatic risks. It is a difficult task to keep the users and medical personnel, particularly of emergency units informed on the current development of the availability of NPS and their already recognized acute adverse effects. Currently, there exists less conclusive information, whether a frequent use of NPS is associated with specific long-term sequelae. For example, frequent use of ketamine increased the risk of developing an ulcerative cystitis (Lieb et al., 2012). Ketamine differs from NPS in that it is broadly used in human and veterinary medicine, while most NPS have little or no history of medical use. In contrast to licensed medication, NPS are not systematically evaluated regarding safety and toxicity before entering the market. Therefore, the use of NPS is associated with incalculable risks regarding possible side-effects of substance use.

From the user´s perspective is worth noting that using an unknown synthetic drug is definitely a self-experiment, whose outcome is hardly predictable. This may serve as a preventive message to the users. Most NPS are characterized by missing or markedly limiting scientific and less user

knowledge. In addition, the user has to be sceptical whether the offered substance is at all a defined drug or perhaps a chemically related substance, however with different effects and risks. For so called "psychonauts", however, risk taking and novelty seeking might be principle intentions to use NPS in addition to the avoidance of the use of illegal substances. It is emphasized, that the fact, that a NPS is not regulated by narcotic laws does not imply that this substance is harmless.

Regarding clinical psychiatry, it is necessary to know the phenomenon of NPS and their (by now) main substance classes. Especially for intoxication psychosis, a wide range of substances (with different side effects on physical health) has to be taken into account. As production of textbooks cannot keep up with the yearly appearance of new drugs, current knowledge can easily be available only on the internet. For example, the EMCDDA as (off:well as official institutions in Germany) offer this information on their websites (www.emcdda.europa.eu (off www.drugcom.de). In addition, in the project NEPTUNE (Novel Psychoactive Treatment: UK Network) clinicians and researchers from the United Kingdom published a guidance on the clinical management of side-effects of NPS, e.g. intoxications, in the Internet (NEPTUNE, 2015). By websites such as NEPTUNE, information about on NPS, their toxicity and side-effects as well as treatment issues are easily available for clinicians. However, such websites need a frequent updating.

Moreover, most NPS are currently not quickly identifiable by standard urine drugs screens, which usually based on enzyme-immuno-assays. They can be verified validly with gas chromatography and mass spectrometry (GC/MS) (Dresen et al., 2010), which, nevertheless, is more expensive and provides no immediate result. Meanwhile, the first enzyme immune-assays for the determination of synthetic cannabinoids have been introduced, however, with the peculiarity to be adjusted to ongoing changes in the chemical structure of the provided drugs. Also the cathinones are not detectable as amphetamines in standard urine screens.

In a possible case of a NPS-related dependence the common treatment steps (motivation – detoxification – rehabilitation) are assumed to be indicated.

[raus: The intention of using NPS as substitutes of common psychoactive drugs might be mediated by risk taking, novelty seeking and niche effects in situations where individuals might be exposed to standard drug screens (e.g. penal institutions, road traffic, detoxification and opioid maintenance treatments, certain occupations zu S. 10).

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