

# New Psychoactive Substances - Challenges

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## SUMMARY

**Introduction:** The United Nation Office of Drugs and Crime (UNODC) defines „new psychoactive substances” (NPS) as substances for abuse that are not under the control of the 1961 Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but may constitute The definition of a group of different substances, which have been developing very rapidly since 2000 and are difficult to identify due to frequent changes in pharmacological and toxicological properties. The health risk assessment of consumers has been insufficiently researched. The use of NPS is reaching epidemic proportions worldwide and poses an increasing danger to the individual and public health. There are several basic groups of NPS, according to their chemical composition and pharmacological properties. All NPS cannot be safely differentiated according to these groups, and their effects, potency and risk profile are not similar to the substances from which they are derived. The highest percentage of abused NPS is from the group of synthetic cathinones and synthetic cannabinoids. Clinically, NPS abuse is categorized as acute intoxications, which is more common, because NPS is most often used on certain occasions (outings, musical events) or as an addiction. Acute intoxications with different types of NPS are severe, with numerous mental and physical symptoms, often life-threatening and with fatal outcomes. Adequate diagnosis is uncertain, diagnostic laboratory tests for drugs are generally not applicable to NPS. Symptomatic internal medicine and psychiatric therapy are used in the treatment because there are no specific antidotes, except for the group of synthetic opioids, (naltrexone). Patients with more serious complications are taken care of in intensive care units. Addiction to certain types of NPS is diagnosed and treated according to the principles of treatment of addiction to already known drugs.

**Methods:** The paper presents an overview of available foreign and domestic literature and experiences of various authors on the topic of NPS from the previous 10 years, as well as the latest reports of regulatory bodies in the USA and Europe, in charge of monitoring epidemiological data on NPS.

**Topic:** The main goal of the paper is to draw the attention of the professional public to the problem of the epidemic wave of new psychoactive substances in the world, as well as significant amounts of knowledge and experience and developing new strategies for registration, monitoring, diagnosis and treatment of abuses and dependence on these substances.

**Conclusion:** These facts impose the need to raise the vigilance of the health and legal system according to the presence of NPS on the market and the prevalence of use in the population, their health risks, as well as connecting with European organizations for monitoring NPS and developing new strategies for their control and prevention.

**Keywords:** New Drugs, Treatment, Public Health

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## INTRODUCTION

Human beings have been exploring the effects of various psychoactive substances on their psyche since ancient times. Numerous drugs have changed in the social milieu of their users, and during the last decade, that scene has completely changed, with the development of the so-called new psychoactive substances (NPS) [1]. The number of newly registered NPS is constantly growing, and their global distribution and prevalence of users is becoming alarming and poses an increasing threat to the public health of many countries [2]. They are known by various street names - „legal highs”, „herbal highs”, bath salts, party pills, aphrodisiac tea, HyperDrive, NeuroBlaster, synthetic drugs / synthetic cocaine, herbal ecstasy /, air fresheners, etc. They are easily available, cheap, procured online, or in body shops, regulatory control is usually lacking, because their legal status is undefined. Their production takes place in unregistered laboratories, mostly in Asian countries and in India, their chemical composition is unregulated, they are often altered molecules of already known drugs, or even toxic synthetic compounds, with frequent changes in structure. They are not detectable by available toxicological tests. All this contributes to numerous unknown facts regarding their pharmacological and toxic effects, clinical picture and therapeutic guidance for treatment of either acute intoxications, or addiction and abstinence syndromes from these substances. Clinicians are usually not sufficiently familiar with the existence or action of NPS, and they are often faced with life-threatening effects and complications, especially among the adolescent population [2]. These facts impose the need to raise the vigilance of the health and legal system according to the presence of NPS on the market and the prevalence of use in the population, their risks and health hazards, connecting with European organizations for monitoring and prevention of NPS, as well as developing new prevention strategies.

## METHODS

The paper presents an overview of available foreign and domestic literature and experiences of various authors on the topic of NPS from the previous 10 years, as well as the latest reports of regulatory bodies in the USA and

Europe, in charge of monitoring epidemiological data on NPS. The paper presents the facts collected so far from epidemiological research, clinical experiences and observations and neuropharmacological studies of NPS, within the chapter on the definition of NPS, types (categories) and pharmacological characteristics of so far known NPS, epidemiology, clinical pictures of acute intoxications and NPS dependence, as well as treatment options.

## TOPIC

The main goal of the paper is to draw the attention of the professional public to the problem of the epidemic wave of new psychoactive substances in the world, as well as significant amounts of knowledge and experience and developing new strategies for registration, monitoring, diagnosis and treatment of abuses and dependence on these substances.

In our country, the problem has been recognized in general and the first steps have been taken to connect with the centers in Europe, in charge of monitoring and early detection of NPS.

Based on the experiences and actions taken by other countries for control and adequate diagnostic, therapeutic, legal and other aspects of this complex problem, possible next steps are proposed, which would enable this in our environment as well.

### Definition and types (categories) NPS

According to the definition of the United Nation Office of Drugs and Crime (UNODC), the term NPS means „a substance for abuse, whether pure or altered, which is not controlled by the 1961 Narcotics Convention” or the 1971 Convention on Psychotropic Substances, but may pose a danger to public health [2]. This definition includes a group of very different substances, which have developed very quickly since 2000. and especially after 2010. and whose identification is very difficult, given the frequent changes in pharmacological and toxicological properties. Also, consumer health risk assessment is also one of the unknowns. There are several basic groups of NPS, according to their chemical composition - aminoindans, synthetic cannabinoids, synthetic cathinones, tryptamines, phenylamines,

piperazines, phencyclidines, synthetic opioids, plant-based substances / kratom, khat / and others. This division is also simplified and approximate, because not all NPS can be differentiated with certainty according to these groups, nor are their effects, potency and risk profile completely similar to the substances from which they are derived [3].

According to the latest UN drug report, 2018, there are the most registered synthetic cannabinoids - 251 species and synthetic cathinones - 148 species [3].

UNODC recently classified NPS into six categories, according to their basic action: sedatives / hypnotics (e.g. NPS benzodiazepine type), dissociative (e.g. deschloroketamine), hallucinogens (e.g. N-Methylbenzylmethoxyphenylamine-25I-NBOMe), stimulants (e.g. dimethylcathinone), a synthetic cannabinoid receptor agonist (e.g. AB-PINACA) and synthetic opioids (fentanyl and non-fentanyl opioids) [4].

### Epidemiology

Epidemiological data are unsystematized, as insufficiently detailed studies have been conducted.

Depending on the time period of observation, the prevalence of NPS use is in the period from 2000-2010, higher in countries with lower economies, while from 2010-2017, the picture is changing, and their use is becoming significant in countries with richer economies. According to recent data from the European Monitoring Center for Drugs and Drug Addiction (EMCDDA) from 2019, in the adult population, the prevalence of NPS use is lower - about 1% than in the youth population, where it ranges from 1-8% [5]. The situation in Serbia, given in the report from 2017, within the EMCDDA project, is not presented numerically, but it is stated that during the previous years there has been an increase in the prevalence of synthetic stimulants and other NPS, whose use occurs in nightclubs and large music festivals [6]. Since the NPS began to be monitored by world and European monitoring centers, from 2004 until now, about 50 to as many as 100 new substances are recorded each year. In the period from 2009 to 2017, 803 NPS were registered [3].

According to UNODC data, as of December 2018, in the largest percentage (36%) of all NPS, synthetic stimulants (cathinones)

are used, followed by synthetic cannabinoids 39%, hallucinogens 15%, synthetic opioids 7%, while dissociatives and sedative-hypnotics are 3%, least represented. It is pointed out that the number of registered synthetic opioids in use has doubled, 62, as well as the percentage of users compared to the previous report from 2016, which corresponds to the current opioid crisis [3].

### Chemical composition and pharmacological activity of NPS by categories

#### Phenylamines

Phenylamines are stimulants and hallucinogens, they are similar in chemical structure to amphetamines and catecholamines. They are classified into classic, psychoactive with the addition of mescaline products and new, with added or modified molecules [7].

#### Piperazines

According to the chemical structure, they are benzylpiperazines (BZP), dibenzylpiperazines, phenylpiperazines. Some of them (BZP) are similar to amphetamines, but with less potent stimulatory effects. They act on the release of dopamine and norepinephrine, as well as the monoamine inhibition of reuptake in general. They are often advertised as herbal products, but they are actually synthetic, with a stimulating effect, but of lower intensity [7].

#### Phencyclidines

The chemical structures are similar to ketamine, with the so-called dissociative effect. In small doses, they have a stimulating effect, in larger doses they are hallucinogenic and dissociative. It is popular as a „safe substitute for ketamine”, with numerous street names („Special K”, „M ket”, „legal ketamine”) or is sold as ecstasy [7].

#### Tryptamins

Synthetic tryptamines are produced by modifying natural tryptamines, which are derivatives of the amino acid tryptophan. They act hallucinogenic and abuse many of their variants - AMT, 5-methoxy-AMT, N-diisopropyltryptamine, with street names „foxy”, „foxy methoxy” [8].

### Benzodiazepine type NPS

The most famous among them is GHB, it belongs to fatty acids by chemical structure, it is a GABA-B receptor agonist by its pharmacological action, and it also increases levels of dopamine by inhibiting reuptake. It is approved by the FDA for the treatment of narcolepsy, and is used due to the effect of euphoria and increased sexual drive. Phenazepam is a benzodiazepine with GABA-A receptor agonist activity, synthesized and approved for the treatment of anxiety and alcohol dependence in Russia, abuse often leads to fatal acute overdoses, especially in combination with other substances [7].

### Synthetic cannabinoids

They are similar in chemical structure to THC, with similar pharmacological effects, i.e. cannabinoid receptor agonists, but with much more potent effects, which often leads to numerous side effects - insomnia, memory defects, dizziness and a pronounced risk of developing psychosis. They are often sold as spices, „spice”, mixed with other herbal product [7].

### Synthetic cathinones

According to their chemical structure, they are analogs or derivatives of natural cathinone (one of the active components of the khat plant). The pharmacological action of cathinone is an agonist of monoamine transport on the cell membrane and an increase in the action of all monoamines. Synthetic cathinones have not been sufficiently studied and their effect on the brain has not been sufficiently studied, so that in addition to the basic stimulating effect, they often have numerous side effects - panic attacks, hallucinations, paranoid ideas. Also, cathinone intoxications often lead to death. They are often sold as „bath salts”, as a cheap substitute for other stimulants and cocaine [8].

### Synthetic opioids

Produced as fentanyl and non-fentanyl derivatives of opioids, often as legal painkillers, the basic pharmacological action is opioid receptor agonists their use and abuse are reaching epidemic proportions, especially in the United

States. Due to a very potent effect, multiple in relation to heroin, these often lead to intoxications, addictions and deaths [9].

### Neuropharmacological studies of NPS

The need to broaden and better understand the effects and health implications of NPS has guided preclinical and clinical research in recent times. Groups of synthetic cannabinoids and synthetic cathinones, as the most common substance of abuse, have been the subject of several studies focused on the role of NPS in modulating the action of CNS neurotransmitters [1]. The results of several preclinical studies, which dealt with the action of synthetic cannabinoids on the serotonergic system, indicated that they stimulate the 5HT 1A receptor response, causing hypothermia and catalepsy in experimental animals, while the effect on the dopaminergic system is manifested through dopamine release in the ventrostriatal region of CNS and psychostimulant effects [2,8].

Recent studies of synthetic cathinones have indicated that they are rapidly absorbed and cross the blood-brain barrier, acting on the dopaminergic system similar to the effects of MDMA, as typical stimulants, with additional hyperthermic and psychomimetic effects. It has also been shown that there is a higher risk of causing serotonin syndrome, with the use of these substances in experiments [2,8].

The results of the research indicated that side effects of medical and psychiatric effects with these substances occur more often than with the original cathinones and THC.

A study of 3,4-dichloromethylphenidate (3,4-CTMP), which is advertised and abused due to its cocaine-like effects, showed that its effects on dopamine release are significantly more potent than methylphenidate (a drug used to treat ADHD), with simultaneous release of norepinephrine [1].

Reports of new synthetic opioids - fentanyl and non-fentanyl analogues, which have recently flooded the illegal market, warn of their acute toxic effects and frequent deaths [3,9].

Encouraging basic and other research of NPS and education of experts are becoming a significant goal of many research centers and groups, which deal with prevention and treatment in the field of addiction, but also public

health.

### Clinical features and treatment

#### Acute intoxications

Clinically, acute intoxications vary depending on the underlying action of the substance, but other symptoms, mental or physical, have been observed, which can lead to numerous complications and serious risks to the health of consumers, and fatalities are not uncommon, especially when taking several different substances [2,4].

NPS from the group of sedatives/hypnotics act as CNS depressants and after the initial euphoria, they can cause various disorders of consciousness from sedation to coma, mental confusion, anxiety, agitation, aggression, psychosis, delirium, as well as various physical complications - tachycardia, hypertension, nausea and vomiting, respiratory arrest [2].

Hallucinogens and dissociatives cause states of altered reality, accompanied by various sensory deceptions and unpredictable and uncritical behavior, which can progress to psychosis, with homo and hetero aggression, agitation, delirium. Physical complications, such as tachycardia, hypertension, hyperthermia, headache, nausea, and vomiting, are very common, and severe toxic events have been reported, with rhabdomyolysis, renal failure, and death [8].

Stimulants cause euphoria, increase in energy, general activation, but this is often accompanied by agitation, aggression, paranoid ideas or complete psychosis, anxiety, panic attacks, later insomnia, depression, suicidal ideas. Also, accompanying physical complications are regular - hypertension, tachycardia, headache, nausea and vomiting, and heart attacks and sudden cardiac death have been reported [8].

Synthetic cannabinoids cause euphoria, hallucinations, states of altered consciousness, with the possible development of frightening hallucinations, crazy ideas of persecution, psychosis, anxiety and panic attacks, with consequent depressive syndromes and amotivation syndromes. Tachycardia, palpitations, hypertension, epileptic seizures, stroke or the most severe - rhabdomyolysis, renal failure, deaths also occur.

Synthetic opioids cause initial eu-

phoria, states of ecstasy, later disorders of consciousness, disorientation, mental confusion, psychosis, and in the most severe cases, respiratory arrest and death. Due to their high potency, they often cause severe intoxications and over-dose [9,10,11].

Adequate diagnosis in patients, who are seen in emergency units and centers, is often very difficult [12,13]. Patients usually come to the state of altered consciousness or are not ready to give detailed information, followers are usually not present. Diagnostic laboratory tests are not helpful, because currently existing tests for original types of drugs are not usable for NPS. There are no specific antidotes, except for opioids, and symptomatic internal medicine and psychiatric medication are most often used in therapy, depending on the clinical picture [12,14]. In case of severe complications, patients are taken care of in intensive care units. Acute synthetic opioids intoxication are treated with naltrexone, an opioid receptor blocker, and later methadone or buprenorphine are included, in addition to the already mentioned symptomatic therapy [9,10].

#### NPS addictions

It is less often described than acute intoxications, since NPS are usually abused occasionally, during socializing, going out, music events, and various other gatherings of young people [15]. Addiction has characteristics related to a certain type and effects of the substance, but significantly higher risks of intoxication and overdose are emphasized, given the variable composition of substances, mixing with other substances and unknown, often high potency compared to the original substance.

They usually occur in the groups of NPS with the highest percentage of abuse, such as synthetic cannabinoids and synthetic cathinones [15].

Diagnostic and therapeutic protocols do not differ from those applied to addicts of original substances, taking into account the special characteristics of NPS and the risks that are characteristic of them. Both diagnostics and treatment emphasize adherence to the principles defined by current international classifications and national guides to good clinical practice [4,13].

## Challenges in monitoring and control of NPS

The increased motivation for NPS abuse is stimulated by numerous factors - their easy availability, low price, non-detectability by routine drug-screening tests, hidden presence in supposedly safe herbal and cosmetic products, uncomplicated way of consumption - pills, sprays, etc. Drug monitoring and surveillance agencies are recording a steady increase, as well as an increase in the number of consumers around the world, especially in the youth population. There are more and more reports of serious health complications, which accompany the abuse of NPS, especially severe intoxications, with damage to vital organs and often with fatal outcomes [2,16].

The conventional approach to monitoring and control of NPS does not give adequate results for several reasons [13].

Questionnaires, which test potential users, are standardized for a relatively small number of known drugs and should be adapted and improved, so that they can be used in the population of NPS users.

Laboratory tests used to detect known drugs in blood or other biological material are not useful for NPS, due to their difference from the original drugs, variability, constant appearance of new substances, variability of their pharmacokinetic and pharmacodynamic properties. Their analysis implies special equipment and knowledge, which for now can only be provided by specialized laboratories [17].

The dynamic nature of the NPS market requires a monitoring system, which will quickly and proactively register signals - the so-called events of significance, which may present a potential risk to public health and be reported with minimal delay, within a few hours or days. This would allow for the timely identification of the substance causing the greatest damage, the formation of priorities for decisions and risk reduction interventions. Some organizations have already accepted the features of this new approach in their work, e.g. EMCDDA- Early Warning System [5].

NPS are also a challenge for the international drug control system, as well as for national and regional control.

At this point, efforts are focused on identifying NPS, which would be a priority to consider, due to their prevalence of use and

potential health risk. In Europe, a three-tier legal framework has been established, which includes early warning, risk assessment and rapid control measures, which should enable the detection, consideration and response to threats to public health by the NPS. These steps are aimed at regulation, rather than the criminalization of NPS consumption. Some countries (Denmark, Great Britain, Israel) have resorted to the law on the temporary ban, in order to examine a certain NPS and determine its potential health risks and possibly include it in the list of dangerous drugs (substances). The legislation is not always clearly defined and is different, often varying from country to country [5,18].

The public health and clinician response is predominantly motivated by acute intoxications with NPS and an increase in overdose and NPS-related deaths in different countries. Due to the lack of specific tests for NPS, clinical diagnosis and treatment guides (eg Novel Psychoactive Treatment UK Network- NEPTUNE) have been developed, the principles of which are presented in the chapter Clinical picture and treatment. It is recommended to develop centralized laboratories, capable of successful detection of NPS or use of toxicological laboratories [18]. Given the often sensationalist media reports about certain cases of intoxication and death related to NPS, it is proposed to educate the public and raise awareness about the nature of the dangers of using NPS, the specific needs of their consumers and their focus on existing services or health organizations dealing with drug users [13].

## CONCLUSION

The future development and prevalence of NPS are difficult to predict. It is possible that the number of newly discovered psychoactive substances will decrease in developed countries thanks to the developed system of supervision and control, but there are indicators of worsening the risk of developing harmful health complications related to NPS abuse. There is an increase in NPS-type benzodiazepines and opioids, which can suppress the already identified illegal drugs on the market, and synthetic cannabinoids and cathinones, as cheaper and more affordable, can increase abuse among the marginalized population. It is also possible to spread NPS abuse in coun-

tries with middle and lower developed economies, which have less capacity for adequate control and where more severe health implications may occur.

The current situation requires a social response more focused on improving health outcomes, associated with the risks of using NPS, than on the legal status of NPS. Therefore, supporting the development of national and regional oversight systems and networking of national and international organizations is a key mechanism for controlling the abuse of NPS and the risks associated with them.

Although the processes of globalization, the possibilities of fast communication on the Internet can be accused of encouraging the production, transport and diffusion of NPS in different parts of the world and society, in a way that is difficult to control and regulate, they can be used to combat them by proactively detecting new substances and make rapid changes in the information on their possible health damage and the establishment of a coordinated response - local, national and international to identified risks.

Difficulties in finding an adequate response to NPS may motivate a change in our way of thinking and acting, in order to respond to much more dynamic and complex models of drug use and addiction than they have been in the past.

## CONFLICT OF INTEREST

All authors declare no conflict of interest.

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## Nove psihoaktivne supstance - izazovi

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### KRATAK SADRŽAJ

**Uvod:** United Nation Office of Drugs and Crime (UNODC) definiše „nove psihoaktivne supstance” (NPS) kao supstance za zloupotrebu koje nisu pod kontrolom Konvencije o opojnim drogama iz 1961.g. ili Konvencije o psihotropnim supstancama iz 1971.g., ali mogu predstavljati pretnju zdravlju osobe koja ih uzima. Definicija obuhvata grupu različitih supstanci, koje se veoma brzo razvijaju, počev od 2000. godine, i teško identifikuju, zbog čestih izmena farmakoloških i toksikoloških svojstava. Procena rizika po zdravlje konzumenata je nedovoljno istražena. Upotreba NPS dostiže epidemijske razmere na svetskom nivou i predstavlja sve veću opasnost za pojedinca i javno zdravlje. Postoji više osnovnih grupa NPS, prema njihovom hemijskom sastavu i farmakološkim osobinama. Sve NPS se ne mogu sa sigurnošću diferencirati prema ovim grupama, a njihovi efekti, potentnost i profil rizika nisu slični supstancama od kojih su izvedeni. U najvećem procentu se zloupotrebljavaju NPS iz grupa sintetskih katinona i sintetskih kanabinoida. Kliničke slike, povezane sa zloupotrebom NPS, se kategorišu kao akutne intoksikacije, što je češće, jer se NPS najčešće koriste u određenim prilikama (izlasci, muzički događaji) ili kao zavisnost. Akutne intoksikacije različitim vrstama NPS su teške, sa brojnim psihickim i telesnim simptomima, često životno ugrožavajućim i sa fatalnim ishodom. Postavljanje adekvatne dijagnoze je neizvesno, dijagnostički laboratorijski testovi za droge u glavnom nisu primenjivi na NPS. U tretmanu se koristi simptomatska internistička i psihijatrijska terapija jer ne postoje specifični antidoti, sem za grupu sintetskih opioida, (naltrexone). Pacijenti sa težim komplikacijama se zbrinjavaju u jedinicama intenzivne nege. Zavisnost od pojedinih vrsta NPS se dijagnostikuju i leče prema principima tretmana zavisnosti od već poznatih droga.

**Metode:** Rad predstavlja pregled dostupne strane i domaće literature i iskustava različitih autora na temu NPS iz prethodnih 10 godina, kao i najnovijih izveštaja regulatornih tela u SAD i Evropi, zaduženih za praćenje epidemioloških podataka o NPS.

**Tema:** Osnovni cilj rada je skretanje pažnje stručne javnosti na problem epidemijskog talasa novih psihoaktivnih supstanci u svetu, kao i već prikupljene značajne količine znanja i iskustava i razvijanja novih strategija registrovanja, praćenja, dijagnostike i tretmana abususa i zavisnosti od ovih supstanci.

**Zaključak:** Navedene činjenice nameću neophodnost podizanja budnosti zdravstvenog i legalno-pravnog sistema prema prisutnosti NPS na tržištu i raširenosti upotrebe u populaciji, njihovim zdravstvenim rizicima, kao i povezivanje sa evropskim organizacijama za praćenje NPS i razvijanje novih strategija njihove kontrole i prevencije.

**Ključne reči:** nove droge, lečenje, javno zdravlje

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