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An Overview of Novel Psychoactive Substances

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Abstract:

New psychoactive substances (NPS) are a variety of chemical compounds that are often marketed as "legal" alternatives to controlled substances. In recent years, in response to market dynamics and regulatory pressures, these categories of drugs have emerged in pharmaceutical markets worldwide. The production and sale of these unknown compounds on the black market creates a very complex situation. New psychotropic drugs are synthetic drugs that have been made by modifying traditional drugs and have similar pharmacological properties, are used to treat various disorders, or are subject to sanctions due to their use in religion or culture. The incidence of health problems related to NPS use is rapidly increasing, and there is a need for a better understanding and timely identification of their physiological effects.

Keywords: Novel psychoactive, Neuropsychiatric, Immune disorder.

Introduction:

Novel Psychoactive Substances (NPS) are an inhomogeneous group of substances which are typically sold as “legal” alternatives to the classical scheduled drugs of abuse, such as heroin, cocaine, amphetamines, benzodiazepines, marijuana, Lysergic acid diethylamide (LSD) and others ***(1).***

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) defines "novel psychoactive substance" (NPS) as a new narcotic or psychotropic drug, whether in pure form or as a preparation, that is not regulated by the Single Convention on Narcotic Drugs and Psychotropic Substances (1961and1971) and is not monitored by the United Nations Office of Drugs and Crime (UNODC), posing a threat to public health when compared to substances listed in the conventions ***(2).***

The United Nations Office of Drugs and Crime (UNODC) defined NPS as “novel chemical substances with psychoactive properties, designed based on the chemical structure of a given parent drug and synthesized specifically for sale on the illicit market and to by-pass regulations on controlled substances” ***(3).***

According to applicable legislation, an NPS is any new psychotropic or neurotic substance that is not controlled by the international drug conventions but may have similar threatening consequences as traditional drugs (***4)***.

The phrase novel doesn’t not necessarily refer to innovations, but to substances that have just become available. As a result, the term novel can refer to a failed medication or an old parent that has been rediscovered and marketed for prospective recreational use ***(5).***

Conversely, the term novel can also express something newly created or a compound that has come back into fashion on the scene or being used in an unusual way, thus having a fresh and appealing quality (***6).***

Epidemiology

Substance abuse is a growing problem in the world as the estimated number of people who use drugs in 2006 was around 200 million. In 2017, it was around 300 million with annual prevalence about 6% (***7***).

The illicit drug market of novel psychoactive substances (NPSs) is expanding and has been described as a 'growing worldwide epidemic', becoming an alarming threat due to increasing intoxication cases and insufficient knowledge of their effects. Convenient availability of illegal drugs at affordable prices and absence of reliable methods for regular testing for new psychoactive substances (NPS) have led to a quick rise in their consumption ***(8).***

The main drives for consuming NPS are the reported "safety" and "natural origin" by the supplier. Even so, the "legality" of these compounds still represents one of the main attractions for consumers. These concepts have led to an extraordinary growth in popularity of NPS since 2007, especially among younger users browsing the Internet (***9).***

Novel psychoactive substances were not covered by the International Drug Control Conventions (IDCC). Nowadays, since many of the compounds have been later introduced, they are included in the list of scheduled substances at a national or international level. More than 1000 NPS have been reported to the United Nations Office on Drugs and Crime (UNODC) and 830 NPS being reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) by the end of 2020. At the end of 2020, 830 NPSs were subjected to monitoring, and 46 of these were reported for the first time in Europe (***10***).

In the time interval 2015–2021, 68 NPSs were placed under international control, and synthetic cannabinoids were the most common, followed by synthetic opioids and stimulants. Phenethylamines and synthetic cathinones are also very common, as confirmed by recent wastewater studies. Most NPSs in the market called legal Spice are named bath salts, kryptonite, herbal highs, legal highs, synthetic drugs, research chemicals, party pills, and so on. Egypt's substance abuse rate has exceeded 10% or double the global average. Despite significant efforts to reduce their usage, the number of NPSs continues to rise with the number of users ***(11).***

Strox and Voodoo, synthetic cannabinoids, are seen as the top choices of new psychoactive substances in the drug market in Egypt. substantial variation in the types and concentrations of NPS chemical constituents and adulterants contribute to the variation in clinical presentation. Although many NPS are being identified and closely monitored, their usage in the general population remains low compared to other illegal drugs. In the past 5 years, usage has decreased due to factors like legal regulations, market changes, evolving substance trends, and variations in the accessibility of other controlled substances (12).

Clinical importance

There is a worldwide health concern toward NPS, due to their serious risks to public health and safety. A variety of psychological and physiological effects on human health was obvious with NPS ***(8).***

These novel psychoactive substances may have abuse potential that may lead to dependence and induce toxic effects of unpredictable severity. Their emergence has challenged the traditional approaches to drug monitoring, surveillance, control, and public health responses to reduce drug related harm. Challenges are the rapid growth of those substances, lack of awareness of the contents of substances and the diverse unknown potency, effects, and risk profile ***(13).***

In Egypt, the social acceptance and tolerance of natural cannabis contribute to the abuse of its potent synthetic counterpart. In addition, unlike natural cannabis, strox is inexpensive, quickly produced, and highly substitutable, allowing it to avoid routine toxicological testing. Novel psychoactive substances prevalence in the general population was highest among Adolescence (young adults aged between 16 and 24 years old), which is a critical developmental period ***(14)***.

Nevertheless, NPS use is not limited to the general public; it also occurs among vulnerable groups like the homeless, who are unaware of the negative effects of these substances, homosexual men, and people with severe mental illnesses, who may be more likely to engage in suicidal or self-harming behavior and imprisoned. Novel psychoactive substances (NPS) are characterized by geographic heterogeneity, their transient nature and other characteristics that do not meet the criteria required by international control. However, many of them have been associated with hospital admissions and death ***(15).***

Numerous behavioral, neurochemical, and electrophysiological studies have been conducted to elucidate the pharmacological action of NPS, with a majority of them concentrating solely on the immediate toxic effects. The scheduling of specific substances typically functioned effectively. The system needs regular updates for the list of controlled substances, so the government has allocated extra resources to ensure suitable action, minimizing harm and creating a relevant legal framework for the situation ***(16).***

Classification of novel psychoactive substances

Novel psychoactive substances may be categorized by chemical structure, by psychoactive properties, by biological targets, or by source (plant, synthetic, or combined) ***(17).***

→ On the basis of their origin, they are divided into natural and synthetic psychoactive drugs ***(18).***

→ Functionally, NPS can be categorized into three broad categories (stimulants, hallucinogens and depressants) based on the features seen with acute toxic effects ***(19)***.

→ These substances can be grouped depending on the chemical structure into

- Synthetic Cannabinoids, - Synthetic Cathinones
- Phenethylamines -Arylcyclohexylamines,
- Tryptamines - Indolalkylamines,
- New Synthetic Opioids (Ketamine) -Piperazines
- Designer Benzodiazepines, - Plant-Based Substances
- Miscellaneous substances (***20).***

Recently with their evolution, they have often been considered in four: stimulants, cannabinoids, depressants and hallucinogens, together with substances of natural origin, slightly overlapping functional categories related to their chemical structure, and psychopharmacological desired and unwanted effects (***21).***

Undetermined mixtures with similar names can differ in constitution from one country to another and even between two packages. This can lead to inaccurate dose calculation and hazardous adulterants resulting in a wide range of physical symptoms which can be life-threatening ***(19).***

New Psychoactive Substances (NPS) classes:

Novel psychoactive substances (NPS) with stimulant and psychedelic properties include a rich number of compounds that shape the illicit designer drug market together with synthetic cannabinoids, synthetic opioids, and dissociatives ***(22).***

I. Synthetic cannabinoids

According to the UNODC, cannabis has been reported to be the most widely used drug. They were first synthesized in the 1960s for cannabinoid research regarding the endocannabinoid system and its receptors inside and outside the CNS**.** This was done in an attempt to develop pharmaceutical products with analgesic or anti-inflammatory properties without being psychoactive. Synthetic cannabinoids were first formally identified in Europe in the early 2000s and reported to the EMCDDA in 2008, initially they were used as alternatives to herbal cannabis (particularly to avoid detection in forensic drug testing regimes such as prisons, sports programs and the military) ***(23).***

Currently they represent the largest and most structurally diverse class of NPS. The UNODC have reported approximately 280 synthetic cannabinoids had been identified by the end of 2019. Despite their good intentions, several synthetic cannabinoids with greater psychoactivity than natural cannabis were invented and quickly gained popularity as recreational drugs, especially among youth (***24).***

The variety of SCRAs that are currently available on the market indicates that they are perceived as a legal alternative to cannabis. New synthetic cannabinoids are regularly developed by both reliable and underground chemists as bulk powders, then dissolving into acetone or methanol, sprayed onto inert plant or paper and either mixed with tobacco or smoked directly as a main route of use ***(25).***

The presence or absence of substituent groups can complicate the prediction and monitoring of the pharmacological profiles of new compounds ***(26)***.

Chemical structures of synthetic cannabibinoids:

The compounds classified as SCRA have relatively large and complex chemical structures (many structurally unrelated to tetrahydrocannabinol [THC]), providing a variety of options for SCRA structural analogues. The remarkable difference between THC and SCRAs is that THC has only one metabolite mediated by Cytochrome P450 (CYP_{450}), which is 11-OH-THC with reduced cannabinoid receptor (CB1) receptor affinity ***(27)***.

However, at least nine monohydroxylated metabolites of SCRAs have been found to maintain a high level of binding affinity and activity at CB1 receptors. Based on their molecular structures, thirteen different synthetic cannabinioid receptor agonists are categorized as follow; benzoylindole, naphthoylindole, phenylacetylindole, indazolecarboxamide, cyclohexylphenyl, naphthylmethylindole, naphthyoylpyrrole, naphthylmethylindene, aminoalkylindole, adamantoylindole, tetramethylcyclopropylketoneindole, quinolinyl ester indole, and dibenzoprane**.** Although the chemical structures of SCRAs differ from those of phytocannabinoids, their pharmacological properties are similar. They are marketed as herbal mixtures, sprayed on dried plants or herbs, and masking them as a blend of natural products ***(28***).

Mechanisms of action of synthetic cannabinoids:

Synthetic cannabinoids interact with the endo-cannabinoid system CB1 and CB2 receptors which are known to be responsible for various psychoactive function such as appetite, mood, sedation, cognition, spasticity, and analgesia rather than cardiovascular and respiratory performance, gastrointestinal motility and immune-regulation ***(29).***

The CB1 receptor is widespread throughout the brain, with particular concentration in the neocortex, basal ganglia and hippocampus**.** CB1 receptors are G-protein coupled and reduce cyclic adenosine monophosphate concentrations when stimulated, indicating that they mediate the inhibition of neurotransmitter release. The CB2 receptor, initially thought to be confined to immune cells and peripheral tissues, has recently also been found in cerebellum and brain stem neurons that may also play a role in endocannabinoid retrograde neurotransmission (30).

Synthetic cannabinoids are full agonists at CB1 and CB2, predominantly with the cannabinoid receptor type-1 (CB1) and, less frequently with the cannabinoid receptor type-2 (CB2). They also have a significantly greater affinity compared with partial agonism of THC, making them much more potent 10–200 times greater and potentially more toxic ***(31).***

Synthetic cannabinoids do not contain cannabidiol (the main neuro-protective compound found in natural cannabis which predominantly acts on CB2 receptors) and this may be related to the increased toxicity observed with these compounds compared with natural cannabis (***32)***

Cannabinoid receptors can also activate inwardly, rectifying potassium channels and mediating an inhibition of N- and P/Q-type calcium currents. These differences likely fortify the emerging greater incidence of major psychiatric complications and other adverse effects compared with traditional cannabis (***33)***.

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