



Current challenges and future research areas for New Psychoactive substances

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ABSTRACT

New psychoactive substances (NPS) are a heterogeneous group of synthetic substances that aim to imitate the symptoms of existing illegitimate psychoactive substances. They are associated with several health and social harms on an individual and societal level. NPS toxicity and dependence syndromes are recognized in primary care, emergency departments, psychiatric inpatient, and community care settings. One pragmatic classification system is to divide NPS into one of four groups: synthetic stimulants, synthetic cannabinoids, synthetic hallucinogens/dissociative and opioid like compounds. The current challenges and future research area for NPS are explored, in the context of the diverse range of NPS currently available, rate of production and emergence of new substances, the different formulations, and methods of acquisition and distribution.

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INTRODUCTION

The competence to produce stimulation of CNS (Central Nervous system) upon the consumption of any substance, preparation, fungus or living organism is known as Psychoactive substances.

The symptoms that result from the intake of such substances includes behavior changes, aggression, anxiety, sleeping disorder, fatigue, dizzy, hallucinations, depressing stage or cause a state of dependence. There could be possibility of experiencing balance issues, overall confusion & blurry vision.[1]

The condition called nystagmus may also take place which is the involuntary eye movements due to the intake of Psychoactive substances.

These drugs have been abused throughout the world & thus there are certain acts that have been formulated to control the regulation of such substances.[2]

In India such psychoactive substances have been prohibited or considered illegal to manufacture, cultivate, sell, possess, purchase, store, transport, and/or consume under the Narcotic Drugs and Psychotropic Substances Act, 1985. This act is also known as NDPS Act.[3]

As per the rules or orders of NDPS act, these drugs can be manufacture, cultivate, sell, possess, purchase, store, transport, and/or consume for medical & scientific purposes with the prior issuance of license.

There is a list of controlled substances that are regulated by NDPS Act. The name of drugs that are mentioned in the NDPS list are following the standard of International Nonproprietary Name (INN) format of the drugs. Any formulation or mixtures of the substances that are enlisted in NDPS Act are also prohibited.[4]

NEW PSYCHOACTIVE SUBSTANCES (NPS)

NPS are synthetic drugs that aim to imitate the symptoms of existing illegitimate psychoactive substances. i.e., the effects upon administration of these New psychoactive substances are like that of the drugs that are prohibited by NDPS. As these synthetic drugs are not regulated or enlisted in the list of controlled substances under NDPS, thus these synthetic drugs are also traded with the name as **legal highs**. [3,5]

New psychoactive substances (NPS) or Synthetic drugs, or, are also traded by a no. of different names like new and emerging drugs (NEDs), herbal highs, herbal incense, bath salts, aphrodisiac tea & monkey dust.

The most popular forms of substance were powders, crystals, or tablets (31.0%); herbal smoking mixtures (24.1%); liquids (17.9%); or 'another substance' (31.0%). Prevalence of nitrous oxide ('laughing

gas') has remained relatively high and stable over the past few years (despite legal control in 2016), and 2.3% of 16–59-year-olds and 8.7% of 16–24-year old's report use in the previous year. Amongst 16–24-year old's, nitrous oxide is now the second most prevalent drug after cannabis (reported by 17.3% of 16–24-year old's).[6-7]

CLASSIFICATION OF NEW PSYCHOACTIVE SUBSTANCES

NPS interface with CNS in the similar way as that of conventional medications to create the required psychoactive impacts. NPS produce psychoactive impacts practically equivalent to those of customary drugs.

The New psychoactive drugs classified into two categories based on their usage:

1. Drugs that are designed in such a way that the people whosoever are going to abuse will not be caught for drugs legislation.
2. Drugs that are designed for research work. This incorporates materials that are exclusively synthesized for potential pharmaceutical items & investigate studies that were never completely discharged to the commercial center.

TYPES OF PSYCHOACTIVE SUBSTANCES

Considering the range of their activities on intellectual procedures, mind-set and conduct, NPS are typically classified into basic categories:

- Synthetic Cannabinoids (e.g., Delta-9-THC)
- Stimulants (e.g., Amphetamine and Ecstasy)
- Opioid-Like Compounds (e.g., Fentanyl)
- Hallucinogens/Dissociatives (e.g., Phencyclidine)

HOW WIDESPREAD ARE NPS

NPS have brought a huge change in synthetic drug market by showing up in huge numbers and assorted variety over a wide geographic spread.

The utilization of NPS has quickly developed in the most recent time and reports of the accessibility and assembling of such substances expanded. These new psychoactive drugs are multiplying at an unusual rate and presenting critical general wellbeing challenges. The quantity of NPS revealed overall rose from one hundred and twenty-six to four hundred and fifty in the year 2009 to 2014 respectively. [8,9]

- ▶ NPS have become a worldwide drug that have been traded & reported in one hundred and nineteen countries.
- ▶ By the year 2019, 888 substances (NPS) have been reported by UNODC Early Warning Advisory (EWA).
- ▶ Most substances that have been reported by UNODC Early Warning Advisory (EWA) were stimulants which are preceded by cannabinoid & then by hallucinogens.[10]

While in 2009, just 32 diverse manufactured cannabinoids were known to be accessible on tranquilizer markets, this number expanded to more than 250 substances by the year 2017. In 2010, reports of substances, for example, methoxetamine (MXE), which delivered dissociative impacts, synthesize in Europe. [11,12]

New NPS develop each year at a normal pace of around one substance for every week. The NPS advertise is additionally profoundly powerful as this market experiences both development and stagnation. Despite a huge developing number of substances revealed by different countries every year, a few NPS are transient in their temperament; new substances keep on rising; a few NPS have been in the market for a considerable length of time; and others vanish after some time. [13,14]

THE SYMPTOMS AND SYMPTOMS OF NEW PSYCHOACTIVE SUBSTANCES

The symptoms of these NPS have been reported by users or by the aid of their medical report as a result of new psychoactive substance toxicity.

Very few researches have been done on New psychoactive substances till date. [15,16]

Some few researches have been conducted on the drugs that are designed for medical purpose or for research purpose itself. As the research is yet to be done on NPS, it would be better if each substance is consider as exclusive in its symptom, effect & action, and thus the precaution need to be taken based solely on their structure relationship. The reports of subjective users are ample, yet should be translated with alert.[17,18]

Some researches uncovered the accompanying key discoveries:

- Most often the substances were being utilized in huge amounts & the mode of administration that has been practiced by users is intravenously. This pattern of intake of drug by an individual will elevate the social & health risk. Specifically, the utilization of NPS among individuals has been related with vein & skin harm, expanded event of ulcers & abscesses, and the fast beginning of psychosis.[19-20]
- In a survey conducted on NPS, the use of BZP & mephedrone was most widely reported by survey respondents whereas the use of ethnobotanical substances was reported by very few respondents.[21]

•The individual who use to have a record of drug abuse (particularly cannabis, cocaine &ecstasy) are tend to incline more for the use of NPS comparatively.[22]

•The users of new psychoactive substances use to blend NPS with different substances, particularly ecstasy, cannabis, & cocaine before uptake of such substances.[23]

The negative impacts upon intake of NPS are more pronounced in powder form of NPS as compare to tablet form of NPS. Powders were related with memory symptom like amnesia or blackout specifically. Palpitations (an unpleasant awareness of one's own heartbeat) were related with both tablet-form NPS & powder-form. These symptoms of palpitations appear to have been particularly stressing for certain individuals. [24-26]

Powder form of NPS has been consumed by snorting, baking into a cake bombing, & mixing in the tea. Drug user generally avoids snorting of NPS because of the discomfort caused in nasal passage. Mixing in tea is to prevent the damage that may cause to stomach due to some harsh substance like 'Amplified'. None of the users had ever injected these substances. [27-29]

Potential risk

They are traded as legal high as they are not prohibited by any legal authority yet.

Some points are featured with regards to considering the potential dangers related with the utilization of NPS as follows:

- There is huge difference in the content of NPS that has been advertised & the content which is present & this absence of uniformity may elevate the probability of overdose & abuse. Additionally, a lack of uniformity of the active substance in an individual product may put user in danger of abusing the substance, or of overdosing.
- There are no quality control guidelines for new psychoactive substances & thus their composition is not yet known. [5,30]
- New psychoactive medications/substances (NPS) are not recognized by conventional detection techniques making them famous substitute for controlled substances, expanding difficulties to research centers and legitimate framework that includes the task need to be performed by forensic scientist. Moreover, there is no as such reference standard for NPS imply that toxicological examination can be troublesome. [31,32]
- There are very few data accessible on the security or lethality of NPS. Additionally, no as such guidelines for the dosage are mentioned over the drugs therefore possibly improving the probability of overdose.
- Due to inadequate knowledge of new psychoactive substances, it is quite hard to advice the precaution or cure to be taken while administration of such substances. Thus, it is suggested to take precautionary measures relating to the use of cannabis & stimulants. [33]

CURRENT CHALLENGES

Over the time, the synthetic drug market has changed at an amazingly quick rate, making it especially hard to foresee future improvements with any level of sureness. Specifically, the ongoing remarkable development of countless NPS of various compositions has fundamentally challenged our comprehension of the synthetic/designer drug market. The evolution of broad and consistently expanding NPS from moderately few numbers of structurally comparable substances have been marketed over several years. [34-35]

INSTRUMENTAL ANALYSIS OF NEW PSYCHOACTIVE SUBSTANCES

- High resolution mass spectrometry (HRMS) has been recognized as the strategy for wide screening of New Psychoactive Substances in a wide scope of analytical contexts as a result of its capacity to quantify exact masses utilizing data-independent acquisition (DIA) procedures. Furthermore, it has demonstrated guarantee for non targeted screening methodologies that have been created to recognize and distinguish novel analogs without the requirement for certified reference materials (CRMs) or without the need of comprehensive mass spectral libraries. The increasing popularity of HRMS has also prompted the exploration of new ways to screen for NPS, including broad-spectrum wastewater analysis to identify usage trends in the community and metabolomic-based approaches to examine the effects of drugs of abuse on endogenous compounds.[36]
- Gas chromatography mass spectrometry (GC-MS): It is a hyphenated scientific strategy in which 2 techniques are joined to enable a scientific expert to investigate an analyte containing various synthetic compounds quantitatively & qualitatively. This hyphenated method will provide better identification than it would be conceivable from either framework when used independently. GC-MS is a procedure utilized in medicinal, pharmaceutical & also in Forensic science laboratories.

Gas chromatographic mass spectrometry is the absolute most significant apparatus for the ID and quantization of unpredictable and semi-unstable synthetic substances like NPS.[34]

- The differentiation of cathinone and phenethylamine-type NPS analogues based on their NIR spectrum recorded in 2 seconds on a portable 1350 – 2600 nm spectrometer. In 51 mixtures and 22 seized casework samples, the correct isomeric form was detected in all cases except for a few mixtures with an active ingredient content of 10 wt%. These results show the feasibility of on-site NPS detection as presumptive test performed directly at the scene of crime with a small size NIR-spectrometer. Additionally, in the illicit drug analysis laboratory the combination of NIR and GC-MS analysis might be suitable for robust identification of NPS isomers and analogues.[37]
- Ultra-performance liquid chromatography-mass spectrometry (UPLC-MS) method with good specificity, accuracy and high precision was developed for qualitative and quantitative analysis of six new psychotropic substances (diazepam, chlorpromazine, clozapine, triazolam, alprazolam and estazolam). Under optimized chromatographic conditions and positive ionization mode of UPLC-MS technology, all substances show good linearity in the range of 0.01–10 µg L⁻¹. The detection and quantification limits can reach 0.001 and 0.005 µg L⁻¹, respectively. [38]
- A qualitative screening approach for serum samples by means of liquid chromatography--quadrupole time-of-flight mass spectrometry. Samples were measured in data-dependent auto tandem mass spectrometry mode and identified by fragment spectra comparison, retention time and accurate mass. Approximately 500 NPS, including 195 synthetic cannabinoids, 180 stimulants, 86 hallucinogens, 26 benzodiazepines and 7 others were investigated. Samples were extracted using solid-phase extraction with non-encapped C18 material and elution in two consecutive steps. Benzodiazepines were eluted in the first step, while substances of other NPS subclasses were distributed among both extracts. To determine LOIs, both extracts were combined. Ninety-six percent (470/492) of investigated NPS were detected in 10 ng/mL samples and 88% (432/492) were detected in 1 ng/mL samples. [39]
- Analyzing these large numbers of NPS and other associated substances often relies on liquid chromatography coupled to triple quadrupole mass spectrometry (LC-QqQ-MS) with multiple-reaction monitoring (MRM) mode. However, the differentiation of critical pairs, coeluted isobaric and/or isomeric species, is one of the challenges for this analytical platform. Transitions selected by Transition Finder showed much better accuracies than those selected only by fragment abundance in some mixtures of critical pairs. Using the proposed analytical strategy, a method that can simultaneously determine 219 NPS and 65 other substances across a variety of NPS classes in urine samples was developed, validated, and applied to analyze clinical urine samples. [40]
- A gas chromatograph (GC) has been coupled to a drift tube ion mobility spectrometer (IMS) in order to develop an analytical procedure for the determination of psychoactive substances in oral fluids. Working parameters, including the GC-IMS interface ones, were adjusted in order to obtain sensitive and robust signals. [41]
- A liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF-MS) method was used for screening and identification of 40 target compounds. Method validation including limits of detection, recovery, matrix effect, and precision was performed for all 40 -target compounds. The limits of detection (LOD) of the 40 analytes were between 0.002 and 0.084 mg/L. Extraction recovery ranged from 36.9% to 110.6% (average 87%). Matrix effects ranged from -29.0% (ion suppression) to 9.8% (ion enhancement). Both intra- and inter-day precision values were less than 27.5% (RSD%).[39]

CONCLUSION

The fast evolvement of new psychoactive substances (NPS) which are not constrained by worldwide conventions, however that may represent a general wellbeing danger or are reported as equally dangerous as those substances that have been enlisted in such conventions.

These New psychoactive drugs advertised by the name smart drug, plant feeder, bath salt, or legal high are normally sold by means of Internet & consume it as legitimate options in contrast to controlled substances for utilization particularly among youngsters.

NPS have been misinterpreted as the safest drug due to its trading name as legal high. Many of the NPS has been not been analyzed yet & several cases of lethal outcome upon administration of these drugs have been reported.

Furthermore, the exceptional speed of appearance and circulation of the NPS throughout the world will make it way more difficult for one to analyze these substances efficiently and hazard evaluation in real time.

The procedure of recognition and evaluation of these new substances is hard to achieve on the grounds that a significant number of them display indistinguishable compound, spectral and chromatographic properties. Moreover, the nonappearance of good quality guidelines, reference samples & reference library data will build the difficulty in analysis, being scarcely accomplished through routine logical conventions.

As there is no as such defined analytical procedure for new psychoactive substance, it is stating a very severe problem in the cases that would be reported in the forensic science laboratory due to the overdose of such new psychoactive substance. Moreover, as these synthetic drugs are growing with such a high pace that it would be quite difficult to attain distinguish analytical procedure for each type of drug.

However, a recent advancement in the analysis of New psychoactive substance by High resolution mass spectrometry (HRMS) have surpass many hurdles that have been faced for the analysis. Instruments like GC-MS, NIR-spectrometer, UPLC-MS, liquid chromatography--quadrupole time-of-flight mass spectrometry, liquid chromatography coupled to triple quadrupole mass spectrometry have also been used by many researchers for the analysis of NPS.

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