WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.453
Volume 15, Issue 1, 403-420. Review Article ISSN 2277–7105

THE EVOLVING THREAT OF NEW PSYCHOACTIVE SUBSTANCES (NPS)

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Article Received on 03 Dec. 2025,
Article Revised on 23 Dec. 2025,
Article Published on 01 Jan. 2026,

https://doi.org/10.5281/zenodo.18093715

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How to cite this Article: Tanishka Jain1*, Aditya Pant2, Nayan Gupta3, Karan Salvi4, Tushar Salvi5. (2026) THE EVOLVING THREAT OF NEW PSYCHOACTIVE SUBSTANCES (NPS). "World Journal of Pharmaceutical Research, 15(1), 403–420.

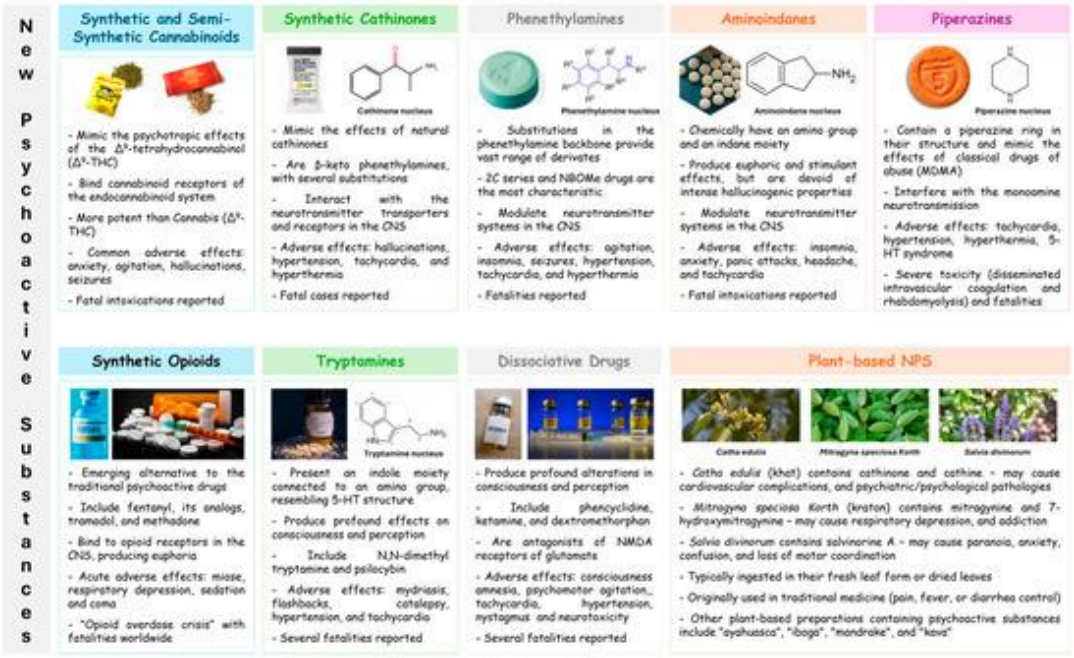
ABSTRACT

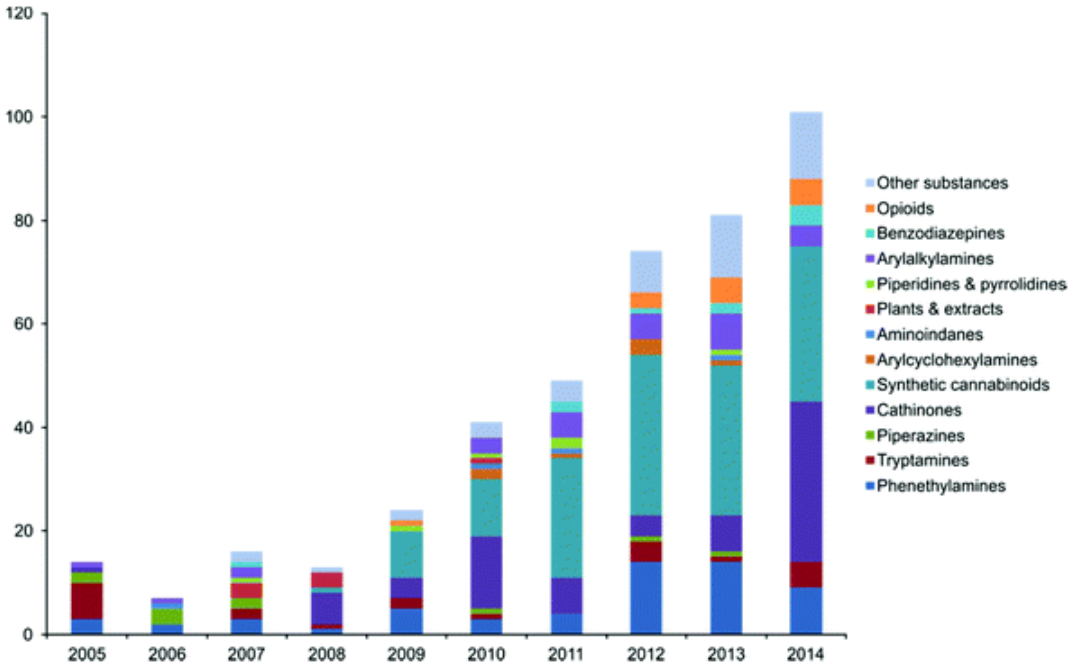
New psychoactive substances (NPS) have become a worldwide phenomenon, and there are now over 134 countries and territories that have reported NPS worldwide. Since December 2021, there have been confirmations made by the UNODC Early Warning Advisory concerning EWA of NPS of more than 1124 substances. NPS into one of four groups: synthetic stimulants, synthetic cannabinoids, synthetic hallucinogens and synthetic depressants. NPS epidemiology is under-developed, and differences in definition and methodologies means that it is difficult to gain accurate estimate with some research suggests that NPS are associated with harms in key populations such as people who are homeless or prisoners. An unprecedented increase in the number of NPSs in the last 5 years. NPSs are a new multi-disciplinary research field with the main emphasis in terms of forensic identification due to their adverse health effects, which can range from minimal to life threatening experiences.

New psychoactive substance

New psychoactive substances (NPS) are a complex and diverse group of substances often known as either designer or synthetic drugs, or by the more popular but misleading colloquial term of ‘legal highs’.[1] NPS pose significant challenges for drug consumers, clinicians – both in drug services and, more broadly, researchers, forensic toxicologists, healthcare systems and drug control policy globally – and have been described as a ‘growing worldwide

epidemic.[2] The United Nations Office for Drugs and Crime (UNODC) has defined NPS as 'substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat'.[3] In the United Kingdom (UK), for example, the Psychoactive Substances Act 2016 introduced legislation that made it an offence[1] to produce, supply, offer to supply, possess with intent to supply, possess on custodial premises, import or export psychoactive substances, but did not make it an offence to possess for personal use outside of a custodial setting.[4] The United Nations Office for Drugs and Crime (UNODC). By 2018, a total of 892 individual NPS, reported by 119 countries, were being monitored by the UNODC[5] early warning system,15, and by the end of 2018, over 730 NPS had been notified. Despite a large number of NPS being detected and actively monitored, estimates of general population use are relatively low compared with other type of controlled drugs, and use has fallen over the previous 5 years as result of factors such as legal control, market dynamics, substance trends and fashions, and changes in the availability of other controlled drugs. The 2018/2019 Crime Survey for England and Wales (CSEW) reported around 0.5% of adults aged 16–59 years[6] Traditionally established recreational drugs and NPS have been functionally categorised into three broad categories (stimulants, hallucinogens and depressants) based on the features seen with acute unwanted effects; more recently with the evolution of the NPS they have often been considered in four, somewhat overlapping functional categories related to their chemical structure, and psychopharmacological desired and unwanted effects: stimulants, cannabinoids, hallucinogens and depressants.[7]





A graphical representation of new psychoactive substances notified to the EWS between 2005–2014.[8]

Synthetic stimulants

Synthetic stimulants comprise of a diffuse group of base compounds, which include cathinones, aminoindanes, phenethylamines, piperazines and tryptamines, of which synthetic cathinones are by far the largest group and the most studied[9] They are designed to replicate the effects of traditional stimulant controlled drugs, such as cocaine, MDMA and amphetamines and one of the most studied group in UNODC and EMCDDA.[10] They can be

made into a variety of formulations and be insufflated, swallowed (often wrapped in paper, known as 'bombing'), inhaled, smoked, injected or used rectally, the most common route being taken in pill/tablet form. Increase in synaptic availability of neurotransmitters, mainly dopamine (DA) plays an important role in motivation, arousal, learning and reward and whereas 5-HT is a contributor to feelings of happiness and a sense of emotional connectedness.[11] These include sought-after experiences such as euphoria, increased feelings of empathy and compassion, sense of inner peace and relaxation, enhanced self-confidence, sociability and libido, and boosted energy and alertness with adverse effects like high addiction potential, severe intoxications linked to cardiac, metabolic, neuropsychiatric and neurological complications.[12]

Chemical structures

first generation synthetic cathinones include methcathinone, 4-methylmethcathinone, 3,4-methylenedioxy-N-methylcathinone and 3,4-methylenedioxypyrovalerone whereas, second generation consisting of 4-methyl-N-ethylcathinone, 4-fluoromethcathinone, and α-PVP (α-pyrrolidinopentiophenone).[13] Synthetic cathinones have similar structure to amphetamine type stimulants and are chemically referred to as β-ketone analogues because of the carbonyl (=O) group in β carbon. 3,4-methylenedioxypyrovalerone (MDPV) are highly lipophilic compared with other synthetic stimulants, and so have a high blood–brain barrier penetration and volume of distribution, resulting in longer plasma and tissue half-lives. Buyers or users who want to experience the ultimate new 'party drug' which is more potent, longer acting and delivers a better 'high'.[14-16]

Mechanism of action

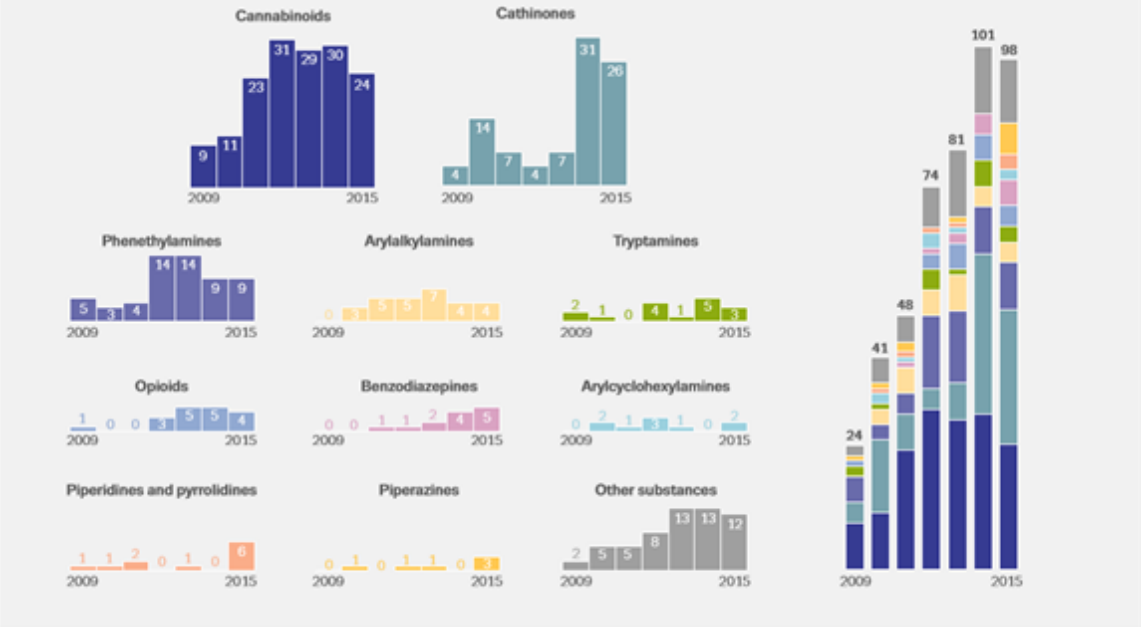
Monoamine neurotransmitters DA and 5-HT and to a lesser extent, noradrenaline (NE) concentration in the synaptic cleft, which then mediate the stimulatory effect which they are responsible for the increase in monoamine concentration in the synaptic cleft. Firstly, there is stimulation of non-exocytotic neurotransmitter release by inhibiting the vesicular monoamine transporter-2 (VMAT2) and reversing the transporter influx, thereby stimulating neurotransmitter release from the cytosolic pool or synaptic vesicles.[17,18] Then, there is inhibition of the uptake of neurotransmitters from the synaptic cleft by inhibiting the plasma membrane transporters, which are responsible for the uptake of DA, 5HT and NE.[19,20]

Craze in rave in INDIA

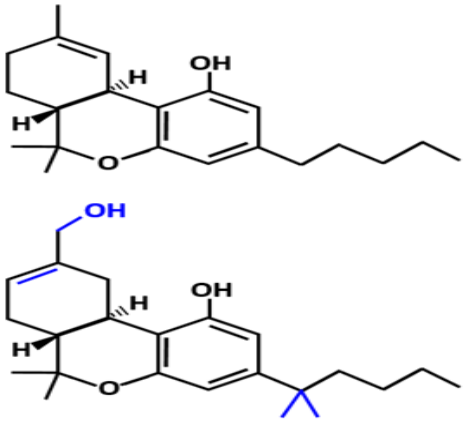
NPSs are not novel to Indian market, although the data are limited but continuous media reports about the seizure under the name of Meow Meow (mephedrone) in many metropolitan cities in India.[21] Mephedrone has gained tremendous popularity among Indian teenagers, they are cheaper than cocaine, selling for Rs. 150/g versus Rs. 3000/g for cocaine. Mephedrone, manufactured in India and China, is marketed as plant feed or bath salts on the internet. According to the report, almost 8 out of 10 drug users in Mumbai city are using this cheap party drug.[22] The first nationwide survey indicated new emerging trend of substance use in India, with amphetamine-like substances (ATS) are being more used in specific regions like Goa and Ahmedabad. In Goa rave parties they begun in mid-seventies known as Hippi culture, and in North, kullu is very famous for full-moon jungle rave parties. In recent years, the craze had been tried extensively in clubs at Goa, and there are also structured or unstructured channels for ketamine, according to Goa police. Locally widely available pills called CK1 pills that are now in trend in clubs as party drugs in which the pills are combined cocaine and ketamine sold under the street name as Blizzard and Calvin Klein.[3,23,24]

Manufacturing and Production Line

In Orange County of California, two overdose deaths were reported, Both the victims had a consistent history of heroin abuse, but when toxicological analysis was conducted, the results have no trace of drugs. After these deaths, in 1980 a total of fifteen deaths were recorded but, similarly their was no trace of drug use.[25] As a result the law of enforcement officials seized street samples sold as heroin, and found the substance was absent and the drug identified as alpha-methyl fentanyl, a potent narcotic that had not undergone scientific evaluation. substance produced very similar effects to fentanyl. The global increase: According to the European Monitoring Centre for Drugs and Drug Addition (EMCDDA), in the last five years, 368 NPS have been recorded, with 98 new substances alone accounting for 2015.[26,27] On a European scale, there were ~50,000 seizures in 2014 in relation to new substances across Europe, with the majority being synthetic cannabinoids 30,000 followed by synthetic cathinones (8,000) and other groups such as fentanyl and benzodiazepines. On a global scale, information by the United Nations Office on Drugs and Crime (UNODC) in 2012 based on the global spread of NPS, received 240 responses from 80 countries.



Number and categories of NPS notified to the EU Early Warning System for the first time, 2009-2015.[2,3,28] The laboratories are primarily found in the Far Eastern nations of China and Indonesia, and in Holland and Israel. China, was originally the country in which the ‘research chemicals’ were exported for the manufacturers. Turning specifically to the production of the synthetic cannabinoids, the ‘main’ active ingredient is copied and named THC. The first ‘classical’ cannabinoid analogue of THC synthesized in Israel in 1988 was ‘HU-210’; ‘a whole series of ‘cannabinoid’ families structurally dissimilar to THC was generated, in both ‘non-classical’ and ‘aminoalkylindoles’.[29] Dr. Zee is an Israeli chemist and has the ‘status’ of ‘the godfather’ of ‘legal highs’, he controls the ‘chemical structure’ and ‘manufactures’ of the substances, as he tests his substances in order to establish what ‘effect’ they give in ‘the human body and the brain. He says, “I make molecule after molecule and try them without prejudice”. ‘You have to keep an ‘open mind’. And that ‘said I have a great deal of knowledge that allows me to disqual potential dangers.”[30]

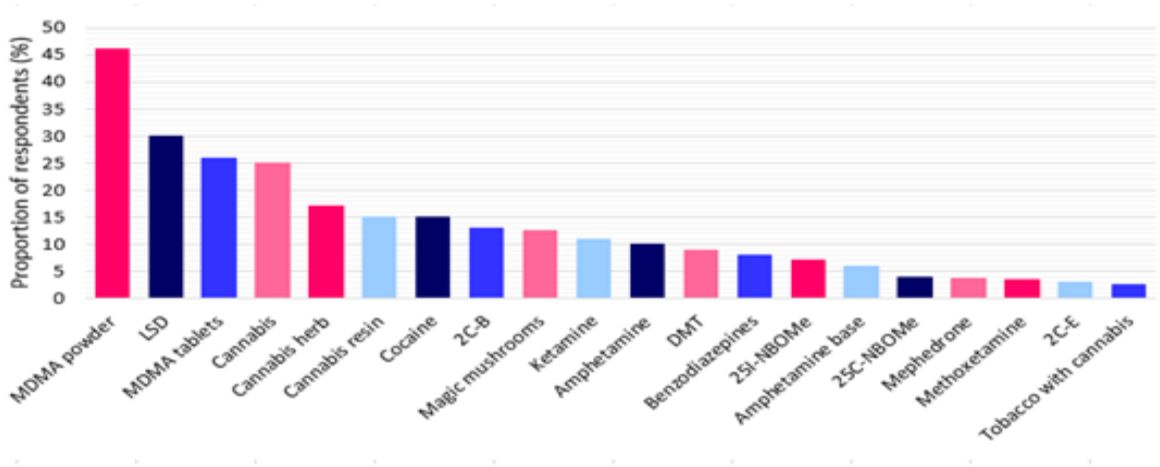


Chemical structure of classical cannabinoids delta-9-tetrahydrocannabinol (top), and of the synthetic cannabinoid HU-210 (bottom). The differences between the synthetic cannabinoid and the controlled substance tetrahydrocannabinol are highlighted in blue. Modified from United Nations Office on Drugs and Crime, 2013.[31]

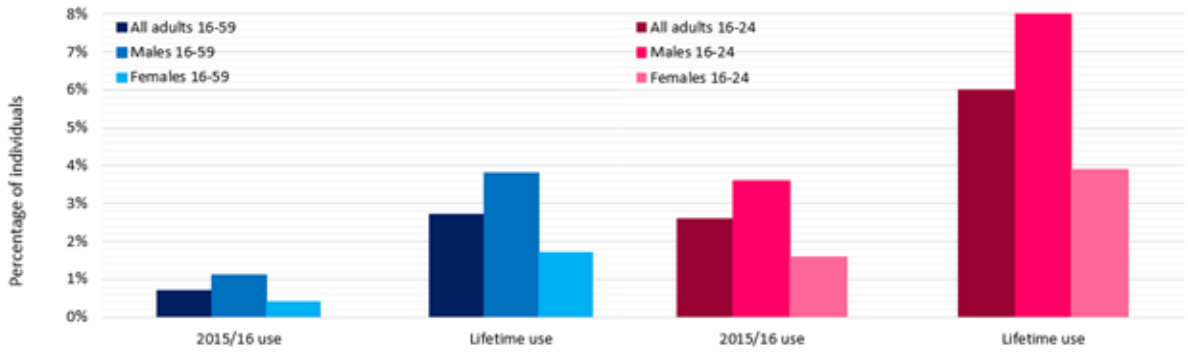
Online Marting

Chinese laboratories and to a lesser extent, India, supply large quantities of final products and intermediate chemicals required for the manufacture of NPS. When they reach their destination, commonly countries in the EU or America, they are either repackaged and redistributed by retailers using online or offline services, or are delivered to the UK directly.[32,33] The emergence and growth of this community is becoming concerning for control agencies, with number of online shops selling NPS increasing from 170 in 2010 to 693 in 2012. The National Crime Agency (NCA) has estimated that in the UK there are between 100 and 150 websites on the ‘clear net’ that sell non-controlled NPS, After introductions of control measures such as legislation, in an effort to regulate their supply, the transfer of sales onto the ‘dark net’ has erupted and creates a further platform for the increase in sale and availability. Global Drug Survey 2015 (GDS)certain types of drugs on the ‘dark net’ between November and December 2014 was recorded majority of the drugs purchased on the ‘dark net’, as expected, were traditional illegal drugs, illegal NPS substances still contributed to a portion of the market. The ‘dark net’ supplies a further ‘security blanket’ as it allows customers[34] to purchase illegal substances with anonymity and personal safety, by hiding identities.[35] ‘The Onion Router’, which conceals computer IP addresses of those accessing the site, and leaves them relatively untraceable. The encrypted payment methods, better known in the drug community as ‘cryptocurrencies’, used by these services like bank transfers, e-money and virtual currencies including, bitcoin and Litecoin. Arguably, offenders

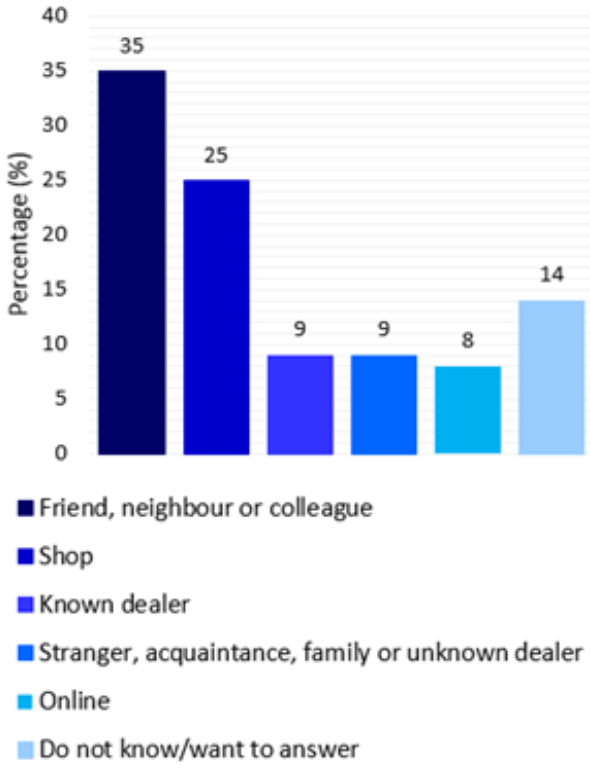
claim they show no interest in moving to the 'dark net' to advertise their products, as their risk of being caught on the 'clear net' is slim.[36]



Drugs purchased on the 'dark net', by types of drug, 2014. Modified from the New psychoactive substances review report of the expert panel. Home Office 2014.



Prevalence of NPS use in 2015/16 and the adult's lifetime, by sex and age. Modified from the 2015/16 Crime Survey for England and Wales.[37]

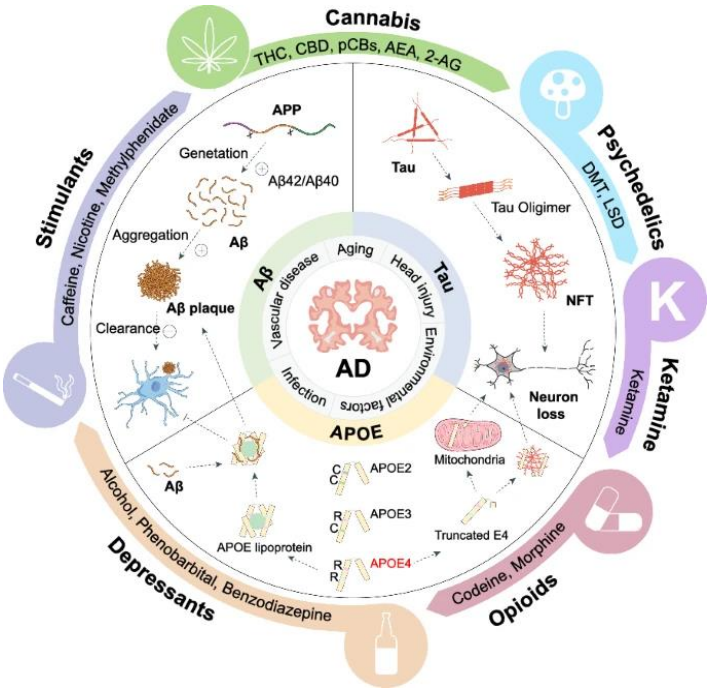


Source of NPS used on the last occasion, by adults aged 16-59. Modified from the 2015/16 Crime Survey for England and Wales.[38]

Therapeutic potential in cases of Alzheimer's and Depression

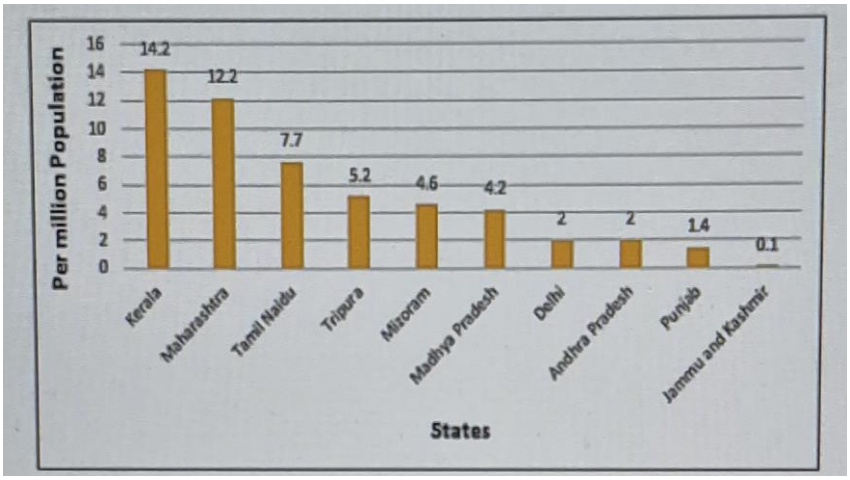
A neurotransmitter involved in mood regulation, perception, anxiety, aggression, and appetite. "The 5-HT2A receptor, highly expressed in such brain areas as the prefrontal cortex and hippocampus, particularly affected in AD, plays a crucial role in these processes," including "such substances as D-lysergic acid diethylamide (LSD), dimethyltryptamine (DMT), mescaline, and cannabis (especially tetrahydrocannabinol – THC), act on these serotonin receptors, mainly 5-HT2A."[39] Although they can be classified among "hallucinogens," the impact of these substances cannot be reduced to "hallucinatory effects." Indeed, they significantly affect various cognitive processes. Neuroplasticity has an extremely crucial role in cognitive functions, particularly within AD, when lost connections between neurons and corresponding atrophy evoke cognitive impairments.[40,41] Psychedelics' activation of these receptors, Neuroplasticity, presenting "remarkable adaptability of the nervous system," has an extremely crucial role in cognitive functions, particularly AD, when lost connections between neurons evoke cognitive impairments. Psychedelics' activation of these receptors In addition to cognitive functions, certain psychedelic effects also appear to

be extremely crucial in modulating mood, particularly through "serotonergic system activation." Indeed, these substances significantly modulate glutamate system functions through activation of these receptors. Serotonergic system activation can be particularly useful in reducing AD symptoms such as anxiety, depression, or agitation. In this regard, these substances can significantly improve patients' "psychological well-being," boosting "quality of life." An increasing number of studies confirm that these substances can be extremely useful in dealing with "mood, anxiety, or depression," particularly for patients who did not get adequate assistance from available treatments. In terms of current That is, at present, amongcurrent.[42,43]



India's challenge with NPS

Indian data on the use of NPS and use-related health hazards are limited, Majority of information is available through newspapers .Direct indicators such as seizure data have also raised concern over the growing use of NPS in India.[44] As per data from the Narcotics Control Bureau, 1003 kg of mephedrone and 10 kg of ketamine were seized in-between January and March 2015 in which India is also reported to be a major producer of NP S under Section 27 of the Narcotic Drugs and Psychotropic Substances Act of 1985 and/or under Section 294 of the Indian Penal Code. However, the government has recently placed ketamine under Schedule X of Drug and Cosmetics Act, 1940.[45]



Drug abuse (or) Drug addiction related suicides in some Indian states.[46]

What 2016 law says

The act has made it illegal to produce, supply, or offer to supply any of these materials. Exempt from this act are substances such as nicotine, alcohol, caffeine, and medication. The penalties for this crime are such that a person can face a maximum of 7 years in prison if they are caught committing this offense The government reported that by fining producers and distributors a maximum of 7 years, it would convey the seriousness of NPS and the number of people using it would eventually fall from a survey conducted by the National Youth Charity YMCA on >1,000 16-24-year-old 16-24 year olds, that no matter the new law introduced, 64% of them are still likely to take them.[47]

Offence	Summary (Magistrates Court)	Indictment (Crown Court)
Possession	Not an Offence	Not an offence
Possession in a custodial institution	Up to 12 months and/or a fine	Up to 2 years and/or a fine
Possession with intent to supply	Up to 12 months and/or a fine	Up to 7 years and/or a fine
Supply/offer to supply	Up to 12 months and/or a fine	Up to 7 years and/or a fine
Production	Up to 12 months and/or a fine	Up to 7 years and/or a fine
Importation/exportation	Up to 12 months and/or a fine	Up to 7 years and/or a fine
Failure to comply with a prohibition/premises notice	Up to 12 months and/or a fine	Up to 2 years and/or a fine

Penalties under the Psychoactive Substances Act 2016.[47,48]

CONCLUSION

There is a need to be aware of the health as well as social implications of these drugs and also to recognize effective demand reduction measures. These measures would be implemented by

spreading awareness regarding NPS in schools and colleges. Treatment-related information and help in case of emergencies would be delivered through helpline numbers. Web-based harm reduction and prevention plans would be developed and implemented. NPS has created a serious crisis in the field of public health. There has been a sudden explosive outbreak of NPS. This has resulted in a toxic exposure epidemic. Unfortunately, this field has not been explored much as a research study yet. There has been a lack of relevant information regarding its nature as well as its potential threats. The health professionals need to be extremely alert regarding NPS as well as its potential mental impacts on vulnerable groups of people. The issue of NPS demands a multi-disciplinary research in the field of epidemiology studies, pharmacology studies, and preventive studies. Research-driven preventive education would help tackle the current global health crisis effectively.

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